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REVIEW

CTX-M-Producing *Escherichia coli*: History, Molecular Epidemiology and Laboratory Detection

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Abstract: From being a curiosity in the 1990s, CTX-M-producing *Escherichia coli* invaded most parts of the globe during the 2000s and 2010s, with multidrug-resistant (MDR) clone ST131 and CTX-M-15 leading the charge. The most widely distributed CTX-M types, with the highest global frequencies (up to 70% in certain lower- and middle-income countries), are CTX-M-15, CTX-M-14 and CTX-M-27. *E. coli* isolates with $bla_{\text{CTX-M-27}}$ are currently emerging globally. The worldwide ascendancy of *E. coli* with $bla_{\text{CTX-M}}$ genes occurred via the spread of IncF plasmids between isolates and the existence of certain successful clones (eg, ST131) that acted as repositories for these genes. This is an impressive "gene survival strategy" that aided with the endurance of $bla_{\text{CTX-M}}$ in different environments, including the community and hospitals. The detection of extended-spectrum β-lactamase (ESBL)-producing *E. coli* (including CTX-M isolates) in clinical laboratories is reasonably straightforward. However, different methodologies (eg, immunogenic and genomic) have recently become available to specifically identify CTX-Ms in bacterial isolates as well as human specimens. The role of such tests is currently unclear. *E. coli* with CTX-M β-lactamases have indirectly been driving the carbapenemase pandemic and are forces to be reckoned with.

Keywords: *Escherichia coli*, CTX-M β-lactamases, MDR high-risk clones, ST131

Introduction

Antimicrobial resistance (AMR) is one of the most pertinent threats to human health.[1] During 2019, approximately 5 million global deaths were associated with bacterial AMR infections, including over 1 million deaths directly linked to bacterial AMR.[2] There is a global shortage of cost-effective antimicrobial agents for treating multi-drug-resistant (MDR) Gram-negative bacterial infections, especially in lower- and middle-income countries.[3]

Escherichia coli is divided into three pathotypes,[4] namely i) normal gastrointestinal tract flora of humans and animals, ii) *E. coli* isolates that cause gastrointestinal infections, and iii) extraintestinal pathogenic *E. coli* (ExPEC), which are responsible for infections outside the gastrointestinal tract. For the remainder of this article, *E. coli* will specifically refer to ExPEC.

E. coli is the most frequent cause of community urinary and bloodstream infections worldwide.[5] Therefore, *E. coli* will evade specific hospital-designed infection control and prevention measures.[6] *E. coli* isolates are common global causes of sepsis and deaths, particularly among the elderly.[7] Bloodstream infections caused by cephalosporin-resistant *E. coli* are linked with mortalities, extended hospital stay and increased healthcare expenditures.[8] In 2019, AMR *E. coli* caused just over 800,000 global deaths.[2] *E. coli* is an important One Health source for AMR genes and is often utilized to check the movement of such genes across different environments.[9]

Before the 2000s, *E. coli* isolates causing human infections were mainly susceptible to a variety of antimicrobial agents, especially the fluoroquinolones and third generation cephalosporins that are often used to treat serious infections.[10] During the latter 2000s and early 2010s, fluoroquinolone- and third generation cephalosporin-resistant *E. coli* escalated.[11] This worldwide increase in MDR *E. coli* has led to the utilization of the carbapenems, leading to increased carbapenem resistance.[12,13] Resistance to carbapenems will be devastating for clinical practice.[13] Carbapenems are effective treatment options for critical MDR Gram-negative infections.[14] The World Health Organization added *E. coli* to its global MDR watchlist in 2017.[15]

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Clinically Important β-Lactamases Among Escherichia coli

The first report of an *E. coli* enzyme that inactivated penicillin was published during the 1950s.[16] β-Lactamases are enzymes that hydrolyze β-lactams, resulting in ineffectual compounds.[17] β-Lactamases differ in their substrate profiles, inhibitor profile and sequence homology.[17] β-Lactamases are divided into classes (ie, Ambler classes A, B, C and D, based on amino acid sequence similarities) and into groups (ie, Bush–Jacoby–Medeiros groups 1, 2, 3 and 4, based on substrate and inhibitor profiles.[18,19] β-Lactamases that belong to classes A, C and D have serine in their respective active sites, while the class B β-lactamases (also known as metallo-β-lactamases or MBLs) contain zinc ions in their active sites.[20] Carbapenemases, which inactivate the carbapenems, belong to Ambler class A (eg, KPC types), class B/MBLs (eg, VIM, IMP and NDM types) and class D OXA β-lactamases.[21]

β-Lactam agents (especially cephalosporins and carbapenems) are the mainstay of treating serious *E. coli* infections.[10] These include the following: third generation cephalosporins (eg, cefotaxime, ceftriaxone and ceftazidime), fourth^{h} generation cephalosporins (eg, cefepime), β-lactam/β-lactamase inhibitors (eg, amoxicillin/clavulanic acid and piperacillin/tazobactam) and the carbapenems (eg, ertapenem, imipenem and meropenem). Among *E. coli*, β-lactamases remain the most clinically important causes of resistance to β-lactam agents.[22] These include the following enzymes: extended-spectrum β-lactamases (ESBLs), AmpC β-lactamases and carbapenemases.[23] ESBLs are the most common cause of cephalosporin resistance, and CTX-M enzymes are by far the most common ESBL types identified in *E. coli*.[24] AmpC β-lactamases are also responsible for cephalosporin resistance within *E. coli*, but are less often encountered than CTX-Ms.[10] OXA-48-like, NDMs and KPCs are the most common carbapenemases among *E. coli,* while VIM and IMP carbapenemases tend to be rare.[25] The global expansion of CTX-M-producing *E. coli* during the 2000s and 2010s had led to the increased use of carbapenems, hence creating selection pressures for the emergence of Enterobacterales with carbapenemases.[26] *E. coli* with OXA-48-like carbapenemases are spreading silently "beneath the radar" in community settings in certain parts of the world.[27,28]

During the late 1990s, 2000s and early 2010s, *E. coli* with CTX-Ms changed the face of global antimicrobial resistance forever, and are the focus of this narrative review article. We review the emergence of *E. coli* that produce CTX-Ms during the late 1990s to 2000s, and provide updates on the molecular epidemiology and laboratory detection of *E. coli* with these β-lactamases. *E. coli* with other important β-lactamases (eg, OXA-48-like, NDMs and AmpCs) have recently been reviewed in detail.[27–31]

Overview: Molecular Epidemiology

The dispersion of AMR genes within bacterial populations is due to the perseverance of successful global MDR clones and/or the interchange of AMR genes within and between various isolates, strains or clones.[32,33] MDR bacterial clones are non-sensitive to at least one antibiotic in three or more classes.[34] Such clones (known as high-risk, super, epidemic, eminent, special or problem clones) are indirectly responsible for the spread of AMR genes. They act as essential hosts and repositories of AMR genes.[35] Among *E. coli*, such high-risk MDR clones have been central to the global spread of AMR genes, specifically for CTX-Ms and certain OXA-48-like carbapenemases (eg, OXA-181 and OXA-244).[36]

The capture and intracellular dispersion of AMR genes take place via mobile genetic elements (MGEs), such as insertion sequence elements, transposons and integrons.[37] The intercellular movement of AMR genes occurs via structures such as plasmids, integrative conjugative elements and bacteriophages.[37] Plasmids are important media for horizontal AMR gene transfer.[38] Plasmids transfer genes between bacterial cells via conjugation.[38,39] The IncF type of plasmids are the most plentiful plasmid types among *E. coli*.[40] IncF plasmids are examples of low copy number, conjugative, narrow host range and epidemic plasmids.[41] These plasmids are frequent in various global *E. coli* clonal complexes (including AMR and non-AMR isolates) obtained from One Health environments, and have been detected since the 1950s.[40] IncF plasmids contain different replicons (eg, RepFIA, RepFIIA, RepFIB and RepFIC).[40] pMLST (multilocus sequence typing) has identify individual IncF replicons (eg, F1:A1:B1). IncC, IncL, IncM and IncX3 types of plasmids have also been found among *E. coli*.[41]

Overview: Laboratory Detection of ESBLs

Clinical microbiology laboratories are timely warning systems, notifying the medical community of novel, emerging and increasing AMR mechanisms found in clinically important bacteria.[42] Some clinical laboratories are always wise to the

importance of detecting ESBL-producing bacteria.[42] This has resulted in the spread of MDR Gram-negative bacteria, leading to treatment failures and hospital outbreaks.[43]

The Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Testing (EUCAST) do not currently advocate routine ESBL testing for clinical management, but do endorse mandatory testing for infection control and public health purposes.[44] The detection of ESBLs in cultured isolates involves a screening step (ie, non-susceptibility to ceftazidime, aztreonam, cefotaxime or ceftriaxone), followed by confirmation tests (eg, phenotypic, genotypic or proteomic methods).[44] Using defined antimicrobial susceptibility testing (AST) screening cut-offs set for ESBL detection (eg, minimum inhibitory concentrations [MICs] for cefotaxime and ceftazidime >1 μg/mL, according to EUCAST), suspicious strains can be evaluated with further phenotypic confirmatory tests that implement clavulanic acid (eg, combination-disk test or double-disk synergy test). Overall, this process is time consuming, and the turnaround time (TAT) from bacterial colonies is usually ≥48 h.[44]

Methods for the detection of ESBLs (specifically those with CTX-M genes) directly on clinical specimens have recently become available to clinical laboratories.[45] These methodologies do not involve a screening step and are therefore expensive for routine clinical use. They often consist of genotypic procedures (eg, real-time polymerase chain reaction [PCR], loop-mediated isothermal amplification [LAMP] and matrix-assisted laser desorption ionization–time of flight mass spectrometry) to detect CTX-M genes and proteomic methods (eg, immunochromatographic assays) to detect CTX-M-β-lactamases.[46]

CTX-M-Producing Escherichia coli

Overview: CTX-M β-Lactamases

A cefotaxime-resistant and ceftazidime-sensitive *E. coli* isolate was obtained from the ear exudate of a 4-month-old German child during 1989, which contained a non-TEM and non-SHV β-lactamase that was inhibited by clavulanic acid.[47] This enzyme was named CTX-M, which stands for active on CefoTaXime, and was first isolated in Munich. CTX-M β-lactamases belong to Ambler class A and include more than 250 different enzymes that are divided into five clusters based on their amino acid identities (clusters CTX-M-1, -2, -8, -9 and -25) (Table 1).[48] Certain CTX-M enzymes

Table 1 Different CTX-M Clusters Based on Amino Acid Homologies

Cluster	Parent Enzymes	Origin	Most Frequent	Other Examples
CTX-M-1	Unknown	CTX-M-1	CTX-M-15	CTX-M-3, -10, -12, -22, -23, -28, -29, -30, -32, -33, -34, -36, -37, -42, -52, -54, -55, -58, -60, -61, -62, -64, -66, -68, -69, -70, -71, -72, -79, -80, -82, -88, -96, -101, -103, -114, -116, -117, -123, -127, -132, -136, -138, -139, -142, -143, -144, -150, -153, -154, -155, -156, -157, -158, -162, -163, -164, -166, -167, -169, -170, -172, -173, -175, -176, -177, -178, -179, -180, -181, -182,-183, -184, -186, -187, -188, -189, -190, -193, -194, 197, -199, -202, -203, -204, -206, -207, -208, -209, 210, -211, -212, -216, -218, -220, -222, -224, -225, -226, -227, -228, -230, -231, -232, -234, -236, -237, -238, -244, -245, -246, -251, -254, -256, -257, -258, -259, -260, -261, -262, -263, -264, -265, -266, -268, -271, -273, -274, -275, -276, -279, -280, -281, -282
CTX-M-2	KLUA-5, -6, -8, -9, -10, -11	CTX-M-2	CTX-M-2	CTX-M-4, -5, -6, -7, -20, -31, -35, -43, -44, -56, -59, -74, -75, -76, -77, -92, -95, -97, -115, -124, -141, -165, -171, -200, -229, -253, -270, -272, -283
CTX-M-8	KLUG-1	CTX-M-8	CTX-M-8	CTX-M-40, -63
CTX-M-9	KLUY-2, -3, -4	CTX-M-9	CTX-M-14 CTX-M-27	CTX-M-13, -14, -16, -17, -19, -21, -24, -27, -38, -45, -46, -47, -48, -49, -50, -51, -65, -67, -73, -81, -83, -84, -85, -86, -87, -0, -93, -98, -99, -102, -104, -105, -110, -111, -112, -113, -121, -122, -125, -126, -129, -130, -134, -137, -140, -147, -148, -159, -161, -168, -174, -191, -192, -195, -196, -198, -201, -213, -214, -215, -219, -221, -223, -233, -235, -239, -240, -241, -242, -243, -247, -248, -249, -252, -255, -267, -269, -277, -278
CTX-M-25	Unknown	CTX-M-25	CTX-M-25	CTX-M-26, -39, -41, -78, -89, -91, -94, -100, -152, -160, -185, -205, -217

Notes: CTX-M-14, -15 and -27 are currently the most common global CTX-Ms among *E. coli*. This table was compiled from reference 48.

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(especially CTX-M-1, -9 and -14) are more active against cefotaxime and ceftriaxone than against ceftazidime and cefepime.[49] Single-nucleotide point mutations around the active sites of CTX-M-3 and CTX-M-14 genes lead to CTX-M-15 and CTX-M-27 genes, respectively, with enhanced ceftazidime inactivation abilities.[50] The CTX-M enzymes originate from KLUA-like genes found on different *Kluyvera* species chromosomes.[49]

CTX-M genes have also been detected in non-human sources.[51–53] These sources include environmental (surface water, rivers, lakes, wastewater treatment plants, soils and plants), animal reservoirs (food-producing, companion and wildlife) and food-chain reservoirs (meat, seafood, raw vegetables, fruit and herbs).

During the 1990s, $bla_{\text{CTX-M}}$ genes were reported from various Gram-negative bacteria (eg, *Klebsiella pneumoniae* and *Salmonella* spp.) from South America and Europe.[49] Global reports of CTX-Ms then escalated during the early 2000s, and *E. coli* was the main driver of this "CTX-M pandemic".[54] From being a mere curiosity in the 1990s, CTX-M-producing *E. coli* invaded most parts of the globe during the 2000s and 2010s, with CTX-M-15 leading the charge.

The History of CTX-Ms During the 1990s: Japan, Germany, Argentina

In 1986, Matsumoto et al described a non-TEM, non-SHV type of ESBL, named FEC-1 (fecal *E. coli*) from the fecal flora of a laboratory dog (that was exposed to β-lactam antibiotics) in Osaka, Japan.[55] FEC-1 hydrolyzed cefuroxime, cefotaxime and ceftriaxone, and was inhibited by clavulanic acid, sulbactam and imipenem. Several years later, the $bla_{\text{FEC-1}}$ gene was sequenced, and it was shown that FEC-1 was nearly identical to CTX-M-3.[48]

In 1995, Ishii et al identified a different non-TEM, non-SHV type of ESBL, named Toho-1 (after Toho University School of Medicine) in a cefotaxime-resistant *E. coli* isolate (TUH12191) obtained from the Toho University Omori Medical Center in Tokyo.[56] TUH12191 was responsible for lower urinary tract infection, and sequencing of $bla_{\text{Toho-1}}$ during the 2000s identified Toho-1 as CTX-M-44.[57] The same investigators described *E. coli* with Toho-2 in 1998,[58] which was later sequenced and identified as CTX-M-45.[48]

Bauernfeind et al, from Munich in Germany, obtained a cefotaxime-resistant and ceftazidime-sensitive *E. coli* isolate (GR1) from the ear exudate of 4-month-old child during 1989.[47] GR1 contained a non-TEM, non-SHV cefotaxime-hydrolyzing enzyme with a pI of 8.9, which was inhibited by clavulanic acid and was named CTX-M. This was the first use of the abbreviation "CTX-M" (ie, active on cefotaxime, first isolated in Munich). After the discovery of CTX-M-2 (see the next paragraph for details), the CTX-M enzyme in GR1 was named CTX-M-1.[59] Bernard et al, in France, obtained a cefotaxime-resistant *E. coli* during 1990, with a non-TEM, non-SHV enzyme CTX-M enzyme similar to that within GR1 (also with a pI of 8.9). That enzyme was named MEN-1 after the patient, who originated from Italy.[60]

Argentinian investigators characterized β-lactamases of MDR *Salmonella* spp. obtained from two hospitals in Buenos Aires, Argentina.[59] The patients presented with meningitis, septicemia or enteritis. The isolates contained non-TEM, non-SHV cefotaxime-hydrolyzing enzymes (with pI of 7.9) and were named CTX-M-2. During the 1990s, Argentina experienced several hospital outbreaks due to various Gram-negative bacteria with CTX-M-2.[61,62]

Which are the Most Common CTX-Ms Among E. coli?

The switch from TEM/SHV types of ESBLs to CTX-M enzymes among *E. coli* was especially evident in Calgary, Canada, a healthcare region with a centralized microbiology laboratory system, which enabled investigators to perform population-based studies. All Calgary hospital and community patients with bloodstream infections due to ESBL-producing *E. coli* were studied over a period of 10 years (2000–2009).[63] By 2003, CTX-M enzymes dominated the *E. coli* ESBL population. Of interest, TEM/SHV variants of ESBLs were found among *E. coli* during 2000–2005, but disappeared from 2006 onwards.[64] On a global scale, the same patterns emerged, in that the CTX-M "invasion" occurred earlier (ie, late 1990s to early 2000s) among *E. coli* with ESBLs, while the switch occurred later (ie, late 2000s) among ESBL-producing *K. pneumoniae*.[65–67]

Currently, the most frequent causes of third generation cephalosporin non-susceptibilities in *E. coli* are the CTX-M enzymes.[10] *E. coli*-producing CTX-M enzymes emerged in the 2000s as important causes of global community-onset urinary tract and bloodstream infections.[68] The following CTX-M variants emerged globally.[69] In the early 2000s, CTX-M-14-producing isolates (especially in Asia and Canada) were followed by CTX-M-15 in the mid- to late 2000s (especially in the Indian subcontinent, Europe and Canada). *E. coli* with $bla_{\text{CTX-M-15}}$ quickly became the most dominant

CTX-M variant in most areas worldwide.[70] The exception was in some Southeast Asian countries (especially China and Japan), where CTX-M-14 remained the most common CTX-M variant during the 2000s.[71] The CTX-M-27 gene is a single-nucleotide variant of $bla_{\text{CTX-M-14}}$, leading to an enzyme with enhanced activity against ceftazidime. *Enterobacterales* with $bla_{\text{CTX-M-27}}$ emerged in the early to mid-2010s in countries such as China, Japan, Vietnam and Canada.[12] By the late 2010s and early 2020s, *E. coli*-producing CTX-M-27 had spread across the globe and is increasing at a rapid rate, replacing CTX-M-14 and CTX-M-15 producers.[44]

Reports from the mid- to late 2010s showed that CTX-M-producing *E. coli* (mainly with $bla_{\text{CTX-M-15}}$ but also with other CTX-M types, depending on the region) have high frequencies (more than 50% of all *E. coli* isolates) in developing countries.[44] It is likely that limited access to basic sanitary provisions, combined with human migration, has contributed to the spread and high prevalence of *E. coli* with $bla_{\text{CTX-M}}$ genes in several developing countries.[71] The most widely distributed CTX-M genes with the highest global frequencies among *E. coli* are CTX-M-15, followed by CTX-M-14 and CTX-M-27.[71,72]

Which Mobile Genetic Elements (MGEs) are Responsible for the Spread of CTX-M Genes Among E. coli?

MGEs (eg, insertion elements, transposons and integrons) have captured (from *Kluyvera* spp.) and then disseminated CTX-M-encoding genes. This was a result of the insertion element IS*Ecp1,* which mobilized KLUA-like genes onto plasmids (Figure 1).[73–75] IS*Ecp1* also served as a strong promoter for the expression of $bla_{\text{CTX-M}}$ genes. Insertion elements such as IS*26*, class 1 integrons and IS*CR1*, IS*Ecp1* have also moved CTX-M-encoding genes into different plasmid platforms.[70] The capture and underlying molecular epidemiology of CTX-M-15 genes (the most common ESBL among *E. coli*) are shown in Figure 1.

CTX-M-encoding genes in *E. coli* are mainly harbored on IncF plasmids (Figure 1).[76] Moreover, various IncF pMLST subtypes are linked with certain CTX-M enzymes:[77] eg, F1:A2:B20 and F2:A-:B- plasmids with $bla_{\text{CTX-M-14}}$ and $bla_{\text{CTX-M-27}}$, and F2:A1:B1 and F31:A4:B1 plasmids with $bla_{\text{CTX-M-15}}$.[78] Other plasmid types were also essential for the global dispersion of CTX-M genes: $bla_{\text{CTX-M-14}}$ is also harbored on IncK and IncI1 plasmids, $bla_{\text{CTX-M-1}}$ on IncN and IncI1 plasmids, $bla_{\text{CTX-M-3}}$ on IncL, IncM and IncI1 plasmids, and $bla_{\text{CTX-M-9}}$ are often harbored on IncHI2 plasmids.[79]

Which MDR Clones are Responsible for the Spread of CTX-M Genes Among E. coli?

Several MDR *E. coli* high-risk clones (eg, ST10, ST38, ST315, ST393, ST405 and ST648) were pivotal for the global dispersion of CTX-M genes.[80] However, the greatest MDR high-risk clone of all time (ie, ST131) was crucial in the global appearance, spread and expansion of CTX-Ms during the mid-2000s and early 2010s.[81] This is shown with the appearance of ST131 in Calgary, Canada. Studies stretching from 2000 until 2010 showed that CTX-M-producing *E. coli* causing bacteremia were scarce during the early 2000s, (ie, 0.3%).[64,82] However, by 2010, the frequency of CTX-M-producing isolates escalated to 14%.[64,82] This was mainly due to the expansion of ST131. During 2000, CTX-M-producing *E. coli* tested negative for ST131.[64,82] During 2010, 78% of CTX-M-producing *E. coli* tested positive for ST131.[64,82] Subsequent studies highlighted the Calgary results and illustrated that the expansion of ST131 with $bla_{\text{CTX-M}}$ genes occurred from the late 2000s to the early 2010s across the world.[80]

ST131 is currently the most universal clone among human *E. coli*.[78] It causes millions of human infections and thousands of deaths annually. ST131 belongs to three clades (ie, A, B and C) and four subclades (ie, C0, C1, C1-M27 and C2) (Table 2).[83] There are different ST131 clade and CTX-M combinations.[81] Overall, CTX-M β-lactamases are still rare in clades A, B and C0. CTX-M-14 genes are frequent within C1, CTX-M-27 genes with C1-M27 and CTX-M-15 genes with C2.[84,85] The ST131 C clades (especially C1 and C2) are frequent within global ST131 isolates.[36]

Within the ST131-C subclades, different IncF subtypes are associated with specific clades and CTX-M enzymes.[77] For instance, F1:A2:B20 plasmids containing $bla_{\text{CTX-M-14}}$ and F1:A2:B20 plasmids with $bla_{\text{CTX-M-27}}$ are found mainly within C1 and C1-M27, respectively. F2:A1:B1 and F34:A4:B1 plasmids with $bla_{\text{CTX-M-15}}$ have high frequencies with C2.[78] These specific ST131-C and CTX-M IncF type plasmid combinations are templated for successful clone/plasmid strategies.[33,77,86]

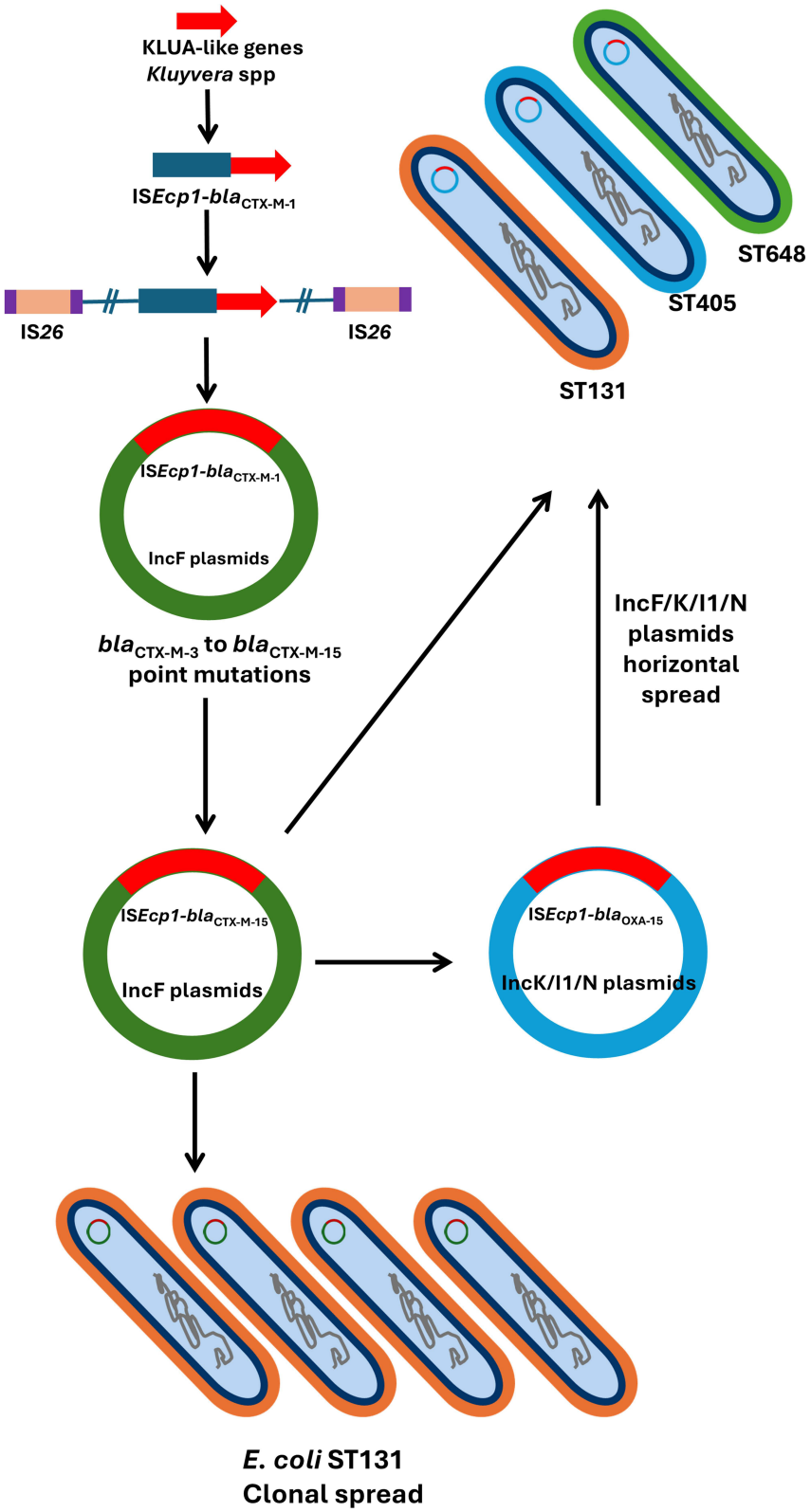

Figure 1 The capture and underlying molecular epidemiology of CTX-M-15 genes.

Table 2 Characteristics of *Escherichia coli* ST131 Clades and Subclades

Clade/ Subclade	Evolution	Serotype Type I Pilli	Population Structure*	CTX-M (%)	IncF pMLST	Other AMR Determinants	Comments
A	Ancestral, emerged in mid- to late 1800s	O16:H5 *fimH*41	5–10%	Rare CTX-M-55 (<1%)	F29:B10	QRDR mutations Certain AMEs, dfrA, sul, tet genes	Clade A with $bla_{CTX-M-15}$, bla_{OXA-48}, $bla_{OXA-244}$ is emerging rapidly and increasing in frequency in some European countries
B	From clade A, emerged in early to mid-1900s	O25b:H4 *fimH*22/27/32	5%	Rare	Various	Rare	Rare clade that was more frequent in the early 2000s
C0	From clade B, emerged in late 1970s	O25b:H4 *fimH*30	<1%	Rare	Various	Rare	Very rare clade
C1-nonM27	From subclade C0, emerged in mid-1990s	O25b:H4 *fimH*30	30–40%	CTX-M-14 (30–40%)	F1:A2:B20	QRDR mutations bla_{TEM-1} Certain AMEs, dfrA, sul, tet genes	C1-nonM27 was very common in the 2000s and early 2010s
C1-M27	From subclade C1-nonM27, emerged in early 2000s	O25b:H4 *fimH*30	10%	CTX-M-27 (80–90%)	F1:A2:B20	QRDR mutations Certain AMEs, dfrA, sul, tet genes	C1-M27 with $bla_{CTX-M-27}$ is emerging globally and replacing C1-nonM27 in certain regions
C2	From subclade C0, emerged in mid-1990s	O25b:H4 *fimH*30	40–50%	CTX-M-15 (60–70%)	F2:A1:B1 F34:A4:B1	QRDR mutations *aac(6')-Ib-cr* Certain AMEs, dfrA, sul, tet genes	C2 is the most common and most AMR subclade. Increasing in frequency since the late 2000s

Notes: *Frequencies with global ST131 population.
Abbreviations: AMR, antimicrobial resistance; QRDR, quinolone-resistant determining regions; AME, aminoglycoside-modifying enzyme.

A global collection of ST131 with CTX-Ms and carbapenemases showed that bla_{CTX-M} genes were harbored mainly on IncF plasmids, while the carbapenemase genes were present on different plasmid platforms, including IncU, IncF, Col-like, IncN, IncR, IncX3, IncC, IncL. and IncM1.[87] This suggested that the global spread of carbapenemase and CTX-M genes among ST131 was driven by different underlying plasmid platforms.

Currently, ST131 clades A and C producing CTX-M-15 and OXA-48 or 244 are responsible for community outbreaks in several European countries, such as Ireland (ie, Clade C with bla_{OXA-48}) and France, Germany and Denmark (ie, Clade A with $bla_{OXA-244}$).[88] The sudden emergence of carbapenemase genes among ST131 is a significant public health concern.

How Do Clinical Laboratories Detect CTX-M β-Lactamases Among E. coli?

The laboratory confirmation of ESBL-producing *E. coli* isolates (including those expressing CTX-Ms) has traditionally relied on phenotypic approaches based on MIC determination or disk diffusion methods.[89] Phenotypic confirmation tests, for the most part, involved clavulanic acid inhibitor-based procedures using the criteria of EUCAST or CLSI.[90] Overall, these processes are accurate and cost effective but unfortunately time consuming, with TATs ranging from 24 to 48 h.

To overcome these TAT issues, various semi-automated and rapid commercial AST systems have been developed for quicker testing within isolates (eg, Vitek-2 or Phoenix systems).[91] Rapid colorimetric (eg, NDP test) and biochemical (eg, β-LACTA test) assays for ESBL detection have also been reported.[91] Very rapid AST systems for direct implementation on positive blood culture samples have recently appeared in the market, and include the Accelerate Pheno system and the LifeScale Biosensor system.[91]

Phenotypic-based assays cannot distinguish between CTX-M and non-CTX-M types of ESBL (eg, TEM and SHV types). Such differentiation can only be achieved by methods that identify specific CTX-M proteins or CTX-M genes.

These methods have more rapid TATs but are significantly more expensive than phenotypic tests. Proteomic methods include the following: commercial lateral flow immunoassays (immunochromatographic) such as the NG-Test CTX-M MULTI (NG-Biotech Laboratoires), RESIST CTX-M (Coris) and TRURAPID RESIST CTX-M (3B BlackBio Dx Ltd).[92] Genotypic methods include several in-house[93,94] and commercial microarray-, PCR- and LAMP-based methodologies, including, but not limited to, Check-Points Microarrays (Check-Points Health), Verigene system (Diasorin), Check-Direct ESBL screen (Check-Points Health), Acuitas AMR Gene Panel (OpGen) and BioFire FilmArray (bioMérieux).[91] PCR- and LAMP-based in-house tests are also available for the detection of ST131 on isolates and specimens.[81,95,96]

The implementation of rapid, user-friendly CTX-M diagnostics could improve clinical outcomes in infected or colonized patients.[46] However, their widespread adoption in routine clinical microbiology laboratories remains limited. Several factors have contributed to this restriction, including the high assay costs. Moreover, the integration into existing laboratory workflows is further constrained by the requirement for additional trained personnel and validation processes. In addition, their clinical utility is sometimes perceived as limited, as robust evidence demonstrating a clear impact on healthcare costs and patients' morbidity and mortality is still lacking. Therefore, we propose that all clinical laboratories serving tertiary-care hospitals should at least perform rapid CTX-M assays on positive blood cultures that contain Gram-negative bacteria (on Gram stain). This would be especially prudent for specialized wards caring for critically ill patients.

Summary

CTX-M-1-producing *E. coli* was first described in the mid-1990s, and during the late 1990s Argentina experienced several hospital outbreaks due to various Gram-negative bacteria with CTX-M-2. Global reports of CTX-M enzymes then escalated dramatically from the mid-2000s onwards, and became known as the "CTX-M pandemic". Even though during the 1990s and early 2000s $bla_{\text{CTX-M}}$ genes were reported from various members Gram-negative bacteria, it quickly became apparent that *E. coli* with CTX-M was the main driver of the 2000 global CTX-M pandemic. The CTX-M *E. coli* pandemic started in the early 2000s with CTX-M-3/CTX-M-9 in Europe and CTX-M-14 in Asia, followed during the mid- to late 2000s by CTX-M-15, and CTX-M-27 in the late 2010s. When cost-effective PCR tests for ST131 identification became available, several studies showed that *E. coli* ST131 was mainly responsible for the global dissemination of $bla_{\text{CTX-M-15}}$ during the late 2000s and early 2010s. From being a mere curiosity in the 1990s, CTX-M-producing *E. coli* invaded most parts of the globe during the 2000s and 2010s, with ST131 and CTX-M-15 leading the charge. *E. coli* with CTX-M-15 remains one of the all-time greatest examples of global pandemics due to β-lactamase-producing bacteria and rivaled the *E. coli* with $bla_{\text{TEM-1}}$ pandemics that occurred during the 1950s and 1960s.

Evidence of the impact of rapid CTX-M detection, which could improve patient outcomes and aid with the implementation of effective antimicrobial stewardship and infection control, is currently lacking.[46] Undertaking large, randomized international studies to address these issues is essential to encourage uptake by clinicians and healthcare institutions. The inclusion of these assays in clinical guidelines and their integration into surveillance programs could further strengthen their epidemiological and therapeutic relevance. In parallel, educating laboratory personnel and clinicians on the benefits and interpretation of rapid diagnostics could enhance acceptance, support appropriate utilization and emphasize their role in optimizing antimicrobial therapy while limiting the spread of MDR pathogens.

The global proliferation of CTX-M-producing *E. coli* during the mid-2000s and early 2010s has indirectly fueled the carbapenemase pandemic. *E. coli* with CTX-M enzymes are a force to be reckoned with, and the appearance of carbapenemase genes among this successful clone is a significant public health concern.

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Disclosure

The authors report no conflicts of interest in this work.

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