Narrative review

Extended-spectrum β-lactamases (ESBL), AmpC β-lactamases and carbapenemases in Enterobacterales of human origin: A comparative analysis in the Sri Lankan and global context

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Abstract

Extended-spectrum β-lactamase (ESBL), AmpC β-lactamase, and carbapenemase-producing bacteria greatly threaten human health. Resistance rates in Enterobacterales vary across regions. ESBL rates range from 2% in the USA to 70% in India, AmpC rates from <10% in the USA and Europe to >30% in India and carbapenemase rates from <1% in Europe to a staggering 65% in India. In Sri Lanka, ESBL rates are as high as 50%, AmpC β-lactamase rates are around 19%, and carbapenemase producers comprise 9%-11% of clinical isolates. The predominant ESBL types locally are CTX-M and SHV, for AmpC, CMY and DHA, and for carbapenemases, OXA-48-like, and NDM. Porin mutations contributing to β-lactam resistance include premature stop codons in ompF in *Escherichia coli* and the Iaa134-135GD insertion mutation in ompK36 in *Klebsiella pneumoniae*. The spread of β-lactamase resistance occurs through clonal expansion and horizontal gene transfer mediated by mobile genetic elements. Some well-known resistant clones reported from Sri Lanka are *K. pneumoniae* ST14, ST147 and ST340 and *E. coli* ST131. The ColKP3 plasmid with IS*Ecp1*, which promotes rapid dissemination of carbapenem resistance, and a cluster of *aac* (6c)-Ib-cr, *bla*$_{\text{OXA-1,}}$ and *cat*B3 genes associated with an IS26 composite transposon have been identified. Standard methods for detecting β-lactamase production in Enterobacterales have limitations. Multiple β-lactamases and other resistance mechanisms have resulted in false test results in Sri Lankan isolates. Despite the cost, molecular methods have shown promising results. Some important data from Sri Lanka is available in the literature. However, there remains much to investigate.

Key words: *Beta-Lactamases, Enterobacteriaceae, Sri Lanka, Porins, Microbial Sensitivity Test*

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Introduction

Enterobacterales with β-lactamase-mediated resistance to third-generation cephalosporins and carbapenems are identified as priority pathogens that pose threats to human health (World Health Organisation).[1] Rapid dissemination of ESBL, AmpC and carbapenemase-mediated resistance via clonal expansion and horizontal gene transfer has become a global and local challenge. Both phenotypic and genotypic epidemiological data on antimicrobial resistance (AMR) are important to guide empiric antibiotic treatment, track the emergence and dissemination of AMR and design effective infection control strategies.[1] Although a range of phenotypic and molecular tests are available for detecting β-lactamase production in Enterobacterales, they all have limitations.[2,3] This review reports on the phenotypic and genotypic epidemiology, porin mutations, role of mobile genetic elements (MGE) and methods for detection of extended spectrum β-lactamase (ESBL), AmpC β-lactamase and carbapenemase-producing Enterobacterales, in the global and Sri Lankan context.

A Boolean strategy was used to identify studies on antimicrobial resistance in Enterobacterales of human origin. A comprehensive literature search was conducted in PubMed, Google Scholar, and Sri Lankan Journals Online, including abstracts of conference proceedings for local data, to identify relevant English-language studies. Grey literature was obtained through institutional libraries and direct author contact, with no restrictions on publication dates. The search, initiated on May 15, 2023, was updated on December 30, 2023. Reference lists of relevant articles were also screened.

Functional classification of β-lactamases

β-lactams are a group of antibiotics that act on the bacterial cell wall. These include penicillins, cephalosporins, carbapenems and monobactams. β-lactams inhibit cell wall synthesising enzymes [penicillin-binding proteins (PBPs)], thus weakening the cell wall.[4] PBPs play a crucial role in bacterial cell wall synthesis by catalysing glycosyltransferase reactions, which form the glycan chains, and transpeptidase reactions, which cross-link peptide chains for structural integrity.[5] β-lactam resistance occurs through production of β-lactamases, porin loss, efflux and PBP modification.[4,6] Enzymes that hydrolyse the β-lactam ring i.e. β-lactamases, notably ESBLs, AmpC β-lactamases and carbapenemases, are prevalent in Enterobacterales.[4] ESBLs hydrolyse third-generation cephalosporins and monobactams and are inhibited by clavulanic acid, sulbactam and tazobactam.[4,6] AmpC enzymes also hydrolyse third-generation cephalosporins and cephamycins but are not inhibited by β-lactamase inhibitors.[6] Carbapenemases are inhibited to a lesser degree by traditional β-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam and vary in their substrate hydrolysis.[6]

Functional classification categorises β-lactamases based on hydrolytic properties.[6] Group 1 cephalosporinases include AmpC enzymes belonging to Ambler molecular class C, which are capable of conferring carbapenem resistance when combined with additional mechanisms.[6,7] Group 2 serine β-lactamases, the largest, comprise Ambler molecular classes A and D, and include penicillinases, ESBLs and KPC carbapenemases. OXA type enzymes are class D.[6,7] Group 3 comprises metallo-β-lactamases (MBL) requiring zinc ions for activity and inhibited by the metal ion chelators, EDTA, dipicolinic acid and 1,10-*o*-phenanthroline. This group includes plasmid-mediated enzymes like IMP (imipenemase) and VIM (Verona integron-encoded metallo-β-lactamase), as well as chromosomally and plasmid-coded enzymes such as NDM (New Delhi metallo-β-lactamase).[6,7]

Diversity of common ESBL, AmpC β-lactamase and carbapenemase types

Some TEM and SHV types, such as TEM-3, TEM-12, SHV-2, as well as all CTX-Ms types, are classified as extended-spectrum beta-lactamases (ESBLs) and belong to Ambler class A.[7,8] CTX-M types have high cefotaxime hydrolytic activity.[8] Some OXA types, such as OXA-10 and OXA-45 also exhibit ESBL activity.[8] Most ESBLs are plasmid-encoded.[9]

While chromosomal genes encoding Amp C β-lactamases are common in some species like *Enterobacter* sp. and *Citrobacter* sp., others like *E coli*, *Klebsiella* sp. and *Salmonella* sp. may produce plasmid-mediated Amp C β-lactamases.[9] Examples of prevalent plasmid-mediated AmpC β-lactamases include CMY-2 and DHA-1, whereas ACT/MIR are chromosomally encoded types.[9] CMY-33 and CMY-69, derived from CMY-2, exhibit increased resistance.[10] These enzymes are sometimes referred to as extended-spectrum AmpC (ESAC) β-lactamases that efficiently hydrolyse penicillins, cephamycins and third-generation cephalosporins but are inactive against carbapenems.[9]

The main carbapenemases that occur in Enterobacterales are KPC of Ambler class A, NDM, IMP, and VIM of class B, and OXA-48 type of class D.[9] Other carbapenemases such as SME (*Serratia marcescens* enzyme), Nmc-A (non-metallo-carbapenemase-A), IMI (IMIpenemase) and GES types also belong to Ambler class A. These enzymes may be chromosomally encoded (SME and Nmc-A), plasmid-encoded (KPC and GES) or both (IMI). There are five recognised groups of class D OXA carbapenemases: OXA-23, OXA-24/40, OXA-51, OXA-58 and OXA-48-type. Of these, the OXA-48-type is the most common.[9]

Global and local epidemiology of ESBL, AmpC β-lactamase and carbapenemase-mediated resistance in Enterobacterales

Global epidemiology

The prevalence of ESBL-producing Enterobacterales is low in countries like United Kingdom, Europe (3% to 6%), USA (2%) and Australia, Sweden, Japan, Korea and Singapore (less than 15%)[8,10-12], but exceeds 30% in Portugal, Italy and Turkey[8] and surpasses 50% in China and Thailand.[13] In India, the prevalence is around 70%.[14,15] The distribution of ESBL types varies, with CTX-M-15, CTX-M-14 and SHV-12 reported as common in the Asia Pacific region[10] and TEM and SHV variants are common in Europe and the Americas.[11,12]

Plasmid-mediated AmpC β-lactamases show varying prevalence globally, with notable rates in countries like China (>15%) and India (>30%).[15,16] The prevalence in the USA and Europe is <10%.[17,18] CMY-2, CMY-7, CMY-21, CMY-2, DHA-1 and ACT/MIR are the dominant AmpC-type β-lactamases reported in Asia, while CMY-23, DHA-1, FOX-5, and ACC types are common in the UK.[19,20]

The carbapenemase rates reported in India range from 27%-65%[21], while in China, the rates are around 18%.[22] In contrast, the rates in Western Europe are less than <1%.[23] Carbapenemase gene types exhibit regional differences.[24] The most common carbapenemases reported in Asia are NDM-1, followed by OXA-48-like.[20,24] NDM is less commonly reported in the United States, Canada and Europe but found in Romania, Poland, Denmark, Spain, Italy and Hungary. OXA-48-like enzymes have spread in Asia, the Middle East, Africa and South America. KPC-producing Enterobacterales have been reported in the United States, Mediterranean countries and in Asia, with the highest prevalence in Italy and Greece. The VIM type is commonly reported in Mediterranean countries and India.[24]

Table 1: Reported β-lactamase gene variants in Enterobacterales from Sri Lankan studies

β-lactamase Type	Reported gene types and gene variants	Species	References
ESBL	*bla*$_{\text{CTX-M}}$: *bla*$_{\text{CTX-M-14}}$, *bla*$_{\text{CTX-M-15}}$	*E. coli, Klebsiella sp, Enterobacter* sp	28, 29, 31, 32, 33
AmpC	*bla*$_{\text{CMY}}$: *bla*$_{\text{CMY-2}}$, *bla*$_{\text{CMY-42}}$, *bla*$_{\text{DHA}}$: *bla*$_{\text{DHA-1}}$, *bla*$_{\text{DHA-7}}$	*E. coli, Klebsiella sp*	29, 33
	bla $_{\text{ACT}}$: *bla*$_{\text{ACT-1}}$, *bla* $_{\text{ACT-7}}$	Enterobacter sp	29
Carbapenemase	*bla*$_{\text{OXA-48-like}}$: *bla*$_{\text{OXA-181}}$, *bla*$_{\text{OXA-232}}$	*E. coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*	29, 30, 31, 32, 33
	bla$_{\text{NDM}}$: *bla*$_{\text{NDM-1}}$, *bla*$_{\text{NDM-4}}$	*K. pneumoniae*, *K. aerogenes, C. freundii, Providencia rettgeri, E. cloacae*	29, 30, 31, 33
	bla$_{\text{KPC}}$	*K. pneumoniae*	30

Local epidemiology

In Sri Lanka, a high rate (85%) of multidrug-resistant coliforms was reported from the Central Province as far back as 2008.[25] Later, studies on uropathogens at a tertiary care hospital in the Western Province revealed that the presence of ESBL producers was significant (32.87%).[26] The Antimicrobial Resistance Surveillance Project (ARSP) Working Group simultaneously reported a high rate of ESBL-producing *E. coli* and *K. pneumoniae* in blood cultures (22.5%).[27] More recently, ESBL rates in uropathogenic Enterobacterales have risen to 40.2% in southern Sri Lanka[28] and 50.2% in the Western Province.[29] This trend possibly reflects evolving resistance dynamics due to continued selective pressure and differing regional prescribing patterns. The reported rates of AmpC β-lactamase production in uropathogenic Enterobacterales is 19%, and carbapenemase production is 9%-11%.[29,30]

There have been only a few Sri Lankan studies exploring the β-lactamase gene variants in Enterobacterales (Table 1).[28-33] Enterobacterales co-producing multiple β-lactamase types are becoming increasingly common. Combinations of ESBL, AmpC beta-lactamase and carbapenemase genes are seen, with some isolates harbouring up to six separate *bla* genes.[29-32] Similar findings have been reported in India and other countries.[34-36]

Structure of the main porins and their mutations leading to carbapenem resistance in *E. coli* and *Klebsiella* sp.

Porins in Gram-negative bacteria occasionally act as barriers, restricting the entry of certain molecules, including antibiotics. On the other hand, OmpF and OmpC in *E. coli* and OmpK35 and OmpK36 in *K. pneumoniae* are non-specific porins facilitating β-lactam antibiotic entry. Loss or modification of porins, particularly large-channel ones, due to mutations increases resistance to β-lactams.[37] Studies have identified that decreased porin expression correlates with cephalosporin and carbapenem resistance in *E. coli*, while in *K. pneumoniae*, alterations in OmpK35 and OmpK36 result in carbapenem resistance. A common mutation associated with

*omp*K36, leading to carbapenem resistance, is Iaa134-135GD.[31] Mutations in loop L3 of the *omp*K36 gene can prevent antibiotic influx by channel constriction, leading to carbapenem resistance.[37]

Studies from Sri Lanka demonstrated insertions, deletions and substitutions in *omp*K35 and *omp*K36 in *K. pneumoniae* and *omp*F in *E. coli*.[29,31] Of these, some significant porin mutations are the insertion Iaa134-135GD encoding glycine and aspartic acid at amino acid positions aa134 and aa135 in *omp*K36 and a premature stop codon in *omp*F.[29,31] These mutations were associated with carbapenem resistance in Enterobacterales isolates lacking carbapenemase genes.[29,31]

Dissemination of β-lactamase resistance: horizontal gene transfer and clonal expansion

The spread of β-lactamase-mediated resistance occurs through clonal dissemination and/or horizontal gene transfer (HGT) via mobile genetic elements (MGE) like plasmids and transposons.[24] Examples of clonal dissemination of "fit" clones are *K. pneumoniae* ST258 and *E. coli* ST131 which propagate resistance genes within specific lineages.[24] AMR genes can move between species and strains of Enterobacterales via MGE, accelerating local and global spread of AMR.[38,39]

In Sri Lanka, *K. pneumoniae* ST14, ST147, ST340, and ST437 (which is a single locus variant of the globally prevalent ST258) have been reported among carbapenem-resistant isolates. These genotypes have been associated with the intercontinental spread of carbapenemases.[31,32,39] *E. coli* ST131, bearing ESBL genes, has also been reported.[39]

MGE, such as insertion sequences (IS), transposons (Tn), and integrons (In) play crucial roles in horizontal gene transfer, aiding the spread of resistance genes. These elements mediate gene mobilisation, contributing to the dissemination of antibiotic resistance. IS typically contains transposase genes and facilitates gene movement via copy-paste or cut-paste mechanisms.[38] *ISEcp1* is one such commonly reported IS (including in Sri Lanka) that facilitates the dissemination of $bla_{\text{CTX-M-15}}$ ESBL genes and $bla_{OXA48\text{-}like}$ carbapenemase genes.[32,38,39] Non-composite transposons, like the Tn3 commonly carry resistance genes. Composite transposons associated with AMR gene clusters facilitate the co-transmission of AMR.[38,39] In Sri Lanka, a cluster of *aac* (6c)-Ib-cr, $bla_{\text{OXA-1}}$ and *cat*B3 genes, associated with an IS26 composite transposon conferring co-resistance to quinolones, aminoglycosides, β-lactams and chloramphenicol has been identified.[39] Integrons facilitate the mobilisation of gene cassettes containing AMR genes. Class I integrons can harbour multiple cassettes, conferring multi-resistance. Integrons captured by transposons can further facilitate the dissemination of co-resistance.[38]

In Enterobacterales, both conjugative plasmids (which are self-transmissible) and mobilisable plasmids (which are not self-transmissible but mobilise with assistance of helper conjugative plasmids) facilitate horizontal AMR gene transfer.[38] Plasmids of the IncF group are some of the most frequent conjugative resistance plasmids found in Enterobacterales. IncF plasmids identified in Sri Lankan isolates carried both virulence genes and AMR genes.[32,39] High rates of such plasmids conferring both virulence and AMR have been reported in China. ColKP3 plasmids are mobilisable plasmids reported globally, including in Sri Lanka, that promote rapid dissemination of carbapenem resistance.[32,39-41]

Risk factors for colonisation and infection with β-lactamase producers

Risk factors for colonisation and infection with β-lactamase producers vary, but commonly include prior antibiotic use, chronic illnesses, the presence of invasive devices, and increased length of stay (LOS) in the hospital.[24] Third-generation cephalosporin use is strongly associated with the emergence of ESBL-mediated resistance, along with quinolones and aminoglycosides.[8] Elderly individuals with comorbidities are particularly vulnerable to colonisation and infection with β-lactamase producers.[24] In the local setting, recurrent urinary tract infections, previous use of antibiotics, older age, diabetes, and the presence of indwelling urinary catheters are risk factors for community-acquired infections with AMR organisms.[26,29]

Detection of ESBLs, AmpC β-lactamases and carbapenemases in the clinical microbiology laboratory

Detection of ESBLs, AmpC β-lactamases and carbapenemases in Enterobacterales in the clinical microbiology laboratory poses challenges such as false positive or negative results caused by co-occurrence of multiple *bla* genes and/or other resistance mechanisms in a single isolate.[2,3,33] Both CLSI and EUCAST offer standard tests for detecting *bla*-mediated resistance, with slight differences. Various manual and automated methods are available, but all have limitations.[2,3]

For ESBL detection, CLSI and EUCAST screening and confirmatory methods differ in their approach and interpretation.[2,3] The double disc synergy test (DDST) and modified double disc synergy test (MDDST) are traditional manual methods that are still used in low resource settings, while the Vitek ESBL test and Microscan panels offer expensive automated options. The CLSI does not provide a recommended method for detecting AmpC β-lactamases, whereas EUCAST recommends screening for cefoxitin resistance, followed by confirmation using the cloxacillin synergy test. However, molecular confirmation is recommended due to limitations in phenotypic testing.[3] Commercial discs are also available for ESBL and AmpC detection[3]. Carbapenemase detection methods, such as the modified carbapenem inhibition method with or without EDTA (mCIM/e-mCIM), the CarbaNP test (recommended by CLSI), and meropenem combination discs (recommended by EUCAST) are used to identify various types of carbapenemases. These methods often incorporate carbapenemase inhibitors to detect different carbapenemase types. For example, the mCIM test utilises EDTA(e-mCIM) to identify MBLs, and meropenem combination discs use boronic acid to detect KPC-producing organisms. However, both CLSI and EUCAST guidelines advise molecular confirmation.[2,3] MALDI-TOF MS, Cepheid Xpert Carba-Rβ-CARBA test and several other tests are commercially available to detect carbapenemase production, but they come at a high cost.[42]

Detecting ESBL, AmpC, and carbapenemase producers in the clinical microbiology laboratory by routine phenotypic testing is increasingly challenging due to geographic variation in prevalent enzymes.[43] A study conducted in Sri Lanka showed further challenges due to the presence of multiple β-lactamases and the effect of coexisting resistance mechanisms such as porin mutations. MDDST was identified as the better test for detecting ESBLs. Screening with cefoxitin and the AmpC disk test showed good sensitivity, although low specificity, in identifying AmpC production. Meropenem was found to be a better substrate for screening carbapenemases. The mCIM test was the most effective for confirming carbapenemase production, with minimal interference from other β-lactamases and porin changes.[33]

Combining phenotypic and genotypic methods may provide a solution for the accurate detection of *bla*-mediated resistance in Enterobacterales. However, the incorporation of

molecular methods for AMR surveillance in the local setting is a challenge due to the high cost. Detection of β-lactamase genotypes in Enterobacterales in Sri Lanka has therefore been confined to individual research studies, which are limited in time and space.[28-32, 44-46]

Application of whole genome sequencing to identify antibiotic resistance

Whole genome sequencing (WGS) predicts phenotypic traits based on genetic determinants.[47] WGS revolutionises the identification of antibiotic resistance by providing extensive data on species, serotypes, virulence and antibiotic resistance using a single technique. However, data analysis demands bioinformatics expertise and curated databases.[48] At present, WGS is used to aid surveillance and infection control, exemplified by the CDC-coordinated Antibiotic Resistance Laboratory Network (ARLN) and the National Antimicrobial Resistance Monitoring System (NARMS) projects.[49] Despite global adoption, WGS use in Sri Lanka is sparse due to high cost and limited bioinformatics expertise, evidenced by the presence of only two studies using this technique. These studies reported data related to mechanisms of AMR, pathogen identity, virulence and ancestry.[32,39] Decreasing costs and the increasing availability of user-friendly, open-access, curated databases may make WGS routine, even in resource-limited nations like Sri Lanka.[47]

Limitations of the study

This review focuses exclusively on data from human isolates. While these data provide valuable insights into antimicrobial resistance patterns, it does not account for potential contributions from environmental, animal, or food sources. This limitation should be considered when interpreting the findings, as broader surveillance would offer a more comprehensive understanding of resistance trends.

Conclusion

In conclusion, resistance rates and mechanisms of AMR in Enterobacterales vary across regions. MGE-associated AMR dissemination, limitations in the accuracy of routine phenotypic detection methods and prohibitive cost of molecular methods are some of the major challenges to the detection and control of the spread of these priority pathogens. Some important data from Sri Lanka exists in the literature in this regard. However, there remains much to investigate.

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