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MOLECULAR CHARACTERIZATION OF EXTENDED-SPECTRUM BETA-LACTAMASE (ESBL)-PRODUCING ESCHERICHIA COLI AND KLEBSIELLA PNEUMONIAE: A REVIEW

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ABSTRACT

Extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli and Klebsiella pneumoniae are among the most important causes of nosocomial infection worldwide, conferring resistance to penicillins, cephalosporins, and monobactams while typically remaining susceptible to beta-lactamase inhibitors and carbapenems. This review synthesises the molecular microbiology of the major ESBL enzyme families — TEM, SHV, CTX-M, and OXA — and the epidemiological evidence for their spread, drawing on a thesis study of 50 Gram-negative blood-culture isolates (36 E. coli, 14 K. pneumoniae) from hospitalised patients in Punjab, India, in which 80% (40/50) were confirmed ESBL producers by disc diffusion and E-test, with blaCTX-M (73%), blaTEM (68%), blaOXA (60%), and blaSHV (24%) detected by PCR and blaCTX-M-15 identified by sequencing as the dominant allele. The review traces the molecular evolution of TEM and SHV enzymes from narrow-spectrum precursors, the global expansion of CTX-M-type enzymes as the now-dominant ESBL family, and the comparatively minor but clinically relevant OXA-type enzymes, before comparing prevalence and gene-distribution data across studies from India, the Middle East, North Africa, and South America. Pulsed-field gel electrophoresis (PFGE) genotyping of the reviewed isolates showed considerable but incomplete genetic diversity (four E. coli clusters, mean similarity 64%; two K. pneumoniae clusters plus one outlier, similarity 61–100%) with no correlation between genotype and resistance phenotype, consistent with the wider literature. The review concludes that CTX-M-15 has become the dominant ESBL genotype in Punjab

and much of the Indian subcontinent, that carbapenems (imipenem) remain reliably effective, and that enhanced antimicrobial-resistance surveillance and antibiotic stewardship are the priority measures for containing further spread.

KEYWORDS: extended-spectrum beta-lactamase; ESBL; Escherichia coli; Klebsiella pneumoniae; CTX-M-15; blaTEM; blaSHV; blaOXA; antimicrobial resistance; PFGE.

1. INTRODUCTION

Extended-spectrum beta-lactamases (ESBLs) are plasmid- or chromosomally-encoded enzymes that hydrolyse penicillins, broad- and extended-spectrum cephalosporins, and the monobactam aztreonam, while remaining susceptible to beta-lactamase inhibitors such as clavulanic acid, sulbactam, and tazobactam (Perez et al., 2007). First recognised in the early 1980s as point-mutation variants of the TEM and SHV enzymes, ESBLs now number more than 700 documented variants and represent one of the most significant drivers of treatment failure in Gram-negative nosocomial infection worldwide (Perez et al., 2007). Resistance to third-generation cephalosporins in Enterobacteriaceae, once a rarity, is now reported in excess of 60–70% in several Indian clinical series, reflecting both the intrinsic mobility of ESBL-encoding plasmids and sustained selective pressure from cephalosporin overuse (Colodner, 2005).

This review consolidates the molecular and epidemiological literature on ESBL-producing E. coli and K. pneumoniae, using as its empirical anchor a thesis study characterising 50 Gram-negative blood-culture isolates from hospitalised patients in Punjab, India, in which resistance genes were identified by PCR and sequencing and genetic relatedness assessed by PFGE. Despite the scale of the problem, the source thesis notes that detailed regional surveillance of ESBL molecular epidemiology in North India, including Punjab specifically, remains limited — a gap this review and its underlying study seek to help address.

2. Molecular Classes of ESBL Enzymes

TEM-type enzymes. The original blaTEM-1 gene was identified in E. coli shortly after ampicillin's clinical introduction in 1965 and remains the most common resistance determinant among plasmid-mediated ampicillin resistance in Enterobacteriaceae, carried on the highly transposable Tn3 element (Mroczkowska and Barlow, 2008). TEM-1 and TEM-2 hydrolyse penicillins and first-generation cephalosporins but not oxyimino-cephalosporins; TEM-3, described in 1987, was the first mutant with extended-spectrum activity, and more than 160 TEM variants are now recognised (Sturenburg and Mack, 2003).

SHV-type enzymes. First identified in Klebsiella strains, the ancestral SHV-1 enzyme is typically chromosomally encoded in K. pneumoniae and confers resistance to broad-spectrum penicillins without extended-spectrum cephalosporin activity; ESBL-type SHV variants (e.g., SHV-11, SHV-12) arise from point mutations that broaden substrate specificity (Sturenburg and Mack, 2003).

CTX-M-type enzymes. Distinguished by preferential hydrolysis of cefotaxime over ceftazidime, CTX-M enzymes were initially associated with South America, Eastern Europe, and the Far East but have since spread globally and are now considered the most prevalent ESBL family worldwide, including across India (Paterson and Bonomo, 2005). CTX-M enzymes are roughly ten-fold more susceptible to tazobactam than to clavulanic acid and frequently co-occur with SHV or AmpC enzymes in the same isolate.

OXA-type enzymes. Named for their oxacillin-hydrolysing activity, OXA enzymes are most associated with Pseudomonas aeruginosa but also occur in Enterobacteriaceae; OXA-1, the commonest variant, is found in 1–10% of OXA-positive E. coli isolates, while extended-spectrum variants such as OXA-10 and OXA-11 through OXA-45 confer additional resistance to cefotaxime and, in some cases, ceftazidime and aztreonam (Paterson and Bonomo, 2005).

3. Epidemiology of ESBL-Producing Enterobacteriaceae

Global surveillance shows CTX-M-15 as the single most frequently reported ESBL genotype, identified across hospital and community isolates in India, the Middle East, North Africa, East Asia, and South America (Ensor et al., 2009; Moubareck et al., 2005; Al-Agamy et al., 2009). Within India, multicentric studies from both northern and southern regions report rising ESBL prevalence in tertiary care facilities, with K. pneumoniae generally showing higher ESBL carriage than E. coli, and CTX-M-15 the dominant molecular subtype in both organisms, while SHV variants are comparatively rare outside Klebsiella (Chaudhary and Aggarwal, 2004). The reviewed thesis's data are consistent with this pattern: 80% overall ESBL prevalence (92.8% among K. pneumoniae versus 75% among E. coli), and CTX-M-15 identified in all sequenced blaCTX-M-positive isolates.

4. Antimicrobial Resistance Profiles and Treatment Implications

Across the isolates reviewed, resistance exceeded 70% for ampicillin (94%), cephalothin (92%), cefpodoxime (82%), nalidixic acid (78%), and tetracycline (74%), rendering these agents unsuitable for empirical therapy of suspected ESBL infection in this setting. By contrast, resistance to chloramphenicol (16%), amikacin (10%), and ticarcillin-clavulanic acid

(6%) remained comparatively low, and no isolate showed resistance to imipenem, confirming carbapenems as the most reliably effective treatment option for confirmed ESBL infection — consistent with international guidance (Paterson, 2006). E-test data further indicated that fourth-generation cefepime retained activity against roughly half of isolates, markedly outperforming the third-generation agent ceftriaxone (24% susceptible), suggesting a potential, carbapenem-sparing role for fourth-generation cephalosporins in selected cases pending susceptibility confirmation.

5. Molecular Typing and Genetic Diversity

Pulsed-field gel electrophoresis (PFGE) remains the reference method for assessing clonal relatedness among ESBL-producing isolates and for distinguishing outbreak-associated clonal spread from independent plasmid-mediated dissemination (Tenover et al., 1995). In the reviewed thesis, E. coli isolates clustered into four major PFGE groups with 64% mean similarity (two isolates 100% identical), while K. pneumoniae isolates showed two major clusters plus one outlier, with similarity ranging from 61–100% (two isolates 100% identical). Critically, no correlation was found between PFGE genotype and antimicrobial resistance phenotype in either species — an expected finding given that resistance genes are frequently carried on mobile plasmids capable of horizontal transfer independent of the chromosomal background, meaning genotypically unrelated strains can acquire an identical resistance phenotype through plasmid exchange.

6. Comparative Evidence from Published Studies

Table 1 situates the reviewed thesis's findings against published ESBL prevalence and gene-distribution data from India and comparable settings internationally.

Study	Setting	Organism(s)	ESBL Prevalence	Dominant Gene
Chaudhary & Aggarwal, 2004	India (review)	E. coli / K. pneumoniae	Variable, rising trend	CTX-M emerging
Al-Agamy et al., 2009	Riyadh, Saudi Arabia (NICU)	K. pneumoniae	High among NICU isolates	CTX-M-15
Ensor et al., 2009	Kuwait (hospital & community)	E. coli / K. pneumoniae	Predominant ESBL type	CTX-M-15
Khalaf et al., 2009	Cairo, Egypt	E. coli / K. pneumoniae / Enterobacter	Common among isolates	CTX-M
Messai et al., 2008	Algeria (hospital)	K. pneumoniae	Notable prevalence	CTX-M
Minarini et al., 2009	Brazil (outpatients)	Enterobacteriaceae	Predominant among outpatients	CTX-M

Mehrgan & Rahbar, 2008	Tehran, Iran (tertiary hospital)	E. coli	Substantial tertiary-hospital burden	ESBL (CTX-M-type)
Present study (reviewed thesis), 2026	Punjab, India (nosocomial)	E. coli / K. pneumoniae (n = 50)	80% (40/50)	CTX-M-15 (73% overall)

The consistent identification of CTX-M-15 as the dominant genotype across geographically diverse settings — Punjab, Riyadh, Kuwait, Cairo, and Brazil alike — supports the hypothesis that CTX-M-type enzymes, and CTX-M-15 in particular, have become the globally predominant ESBL lineage, likely reflecting both efficient plasmid-mediated horizontal transfer and strong selective pressure from widespread cephalosporin use across healthcare systems.

7. DISCUSSION

The 80% ESBL prevalence reported in the reviewed thesis is high relative to most published Indian series, plausibly reflecting a combination of genuine regional antibiotic-prescribing pressure in Punjab and the fact that isolates were drawn specifically from hospitalised, nosocomially infected patients rather than a broader community-plus-hospital sample. The finding that all TEM-positive isolates carried only the ancestral TEM-1 allele, and all OXA-positive isolates only OXA-1, indicates that CTX-M-15 — rather than TEM or OXA extended-spectrum variants — is the principal driver of the ESBL phenotype in this population, consistent with the wider Indian literature (Chaudhary and Aggarwal, 2004). The exclusive detection of blaSHV in K. pneumoniae, and its complete absence in E. coli, mirrors the well-established chromosomal origin of SHV-1 within the Klebsiella genus (Sturenburg and Mack, 2003).

The absence of correlation between PFGE genotype and resistance phenotype, despite considerable genetic relatedness within both species, reinforces that plasmid-mediated horizontal gene transfer — rather than clonal expansion of a single resistant strain — is the principal mechanism sustaining ESBL spread in this setting. This has direct infection-control implications: outbreak control measures premised on identifying and isolating a single clonal source may be insufficient where resistance genes circulate independently of strain lineage via plasmid exchange.

8. CONCLUSION AND RECOMMENDATIONS

The evidence reviewed here, together with the reviewed thesis's findings (80% ESBL

prevalence, CTX-M-15 as the dominant allele, and no imipenem resistance among 50 nosocomial E. coli and K. pneumoniae isolates from Punjab), confirms that ESBL-producing Enterobacteriaceae represent a substantial and ongoing therapeutic challenge in North Indian hospital settings, with CTX-M-15 firmly established as the region's — and much of the world's — dominant ESBL genotype.

Priority measures supported by the literature include: (1) restricting empirical use of ampicillin, first-generation cephalosporins, and nalidixic acid in settings with confirmed high ESBL prevalence; (2) reserving carbapenems for confirmed ESBL infection while monitoring for early signs of carbapenem resistance; (3) evaluating fourth-generation cephalosporins as a carbapenem-sparing option pending susceptibility results; (4) expanding molecular ESBL surveillance (PCR and sequencing) alongside phenotypic testing to track genotype distribution over time; (5) incorporating PFGE or equivalent molecular typing into outbreak investigations, recognising that plasmid-mediated spread can occur independent of clonal relatedness; and (6) strengthening antibiotic stewardship and public education on antibiotic use across Punjab and North India more broadly.

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