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Published Online: 2026 June 30 **Brief Report**

Persistence of *bla* $_{CTX-M-15}$ Dominance in ESBL-Producing *Escherichia coli* and *Klebsiella pneumoniae* Strains: A Single-Center Study

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Abstract

Context: Infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* limit treatment options and increase reliance on last-line antibiotics. Although *bla* $_{CTX-M-15}$ is the globally dominant ESBL genotype, recent data on its persistence in individual Malaysian hospitals are limited.

Objectives: This study aimed to determine the prevalence and temporal persistence of *bla* $_{CTX-M-15}$ among ESBL-producing *E. coli* (ESBLEC) and *K. pneumoniae* (ESBLKP) isolates from a tertiary care center over a 2-year period.

Evidence Acquisition: ESBLEC and ESBLKP strains were collected from Hospital Canselor Tuanku Muhriz (HCTM) during two sampling periods: June 2022 to January 2023 and December 2023 to March 2024. Antimicrobial susceptibility testing was performed using VITEK 2, and results were retrieved through the WHONET system. ESBL genes were detected by PCR, and *bla* $_{CTX-M-15}$ was subtyped among *bla* $_{CTX-M-1}$-positive strains.

Results: Blood and urine were the predominant sources of ESBL isolates in both sampling periods. *bla* $_{CTX-M-1}$ was the most prevalent ESBL gene in both species. Among *bla* $_{CTX-M-1}$-positive strains, *bla* $_{CTX-M-15}$ persisted at high prevalence in ESBLEC (68.5% and 66.7% in the two sampling periods, respectively) and ESBLKP (92.9% in both sampling periods); however, temporal continuity across the unsampled interval remains unknown. The proportion of ESBLEC strains resistant to ceftazidime (CAZ) and cefepime (FEP) decreased during the 10-month interval from February to November 2023, whereas ESBLKP resistance profiles remained largely stable.

Conclusions: bla$_{CTX-M-15}$ remains dominant in HCTM, underscoring the need for continued molecular surveillance and antimicrobial stewardship.

Keywords: Extended-spectrum Beta-lactamase (ESBL)-producing *Escherichia coli* (ESBLEC), Extended-spectrum Beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* (ESBLKP), Persistence of *bla* $_{CTX-M-1}$, Antimicrobial Resistance (AMR)

1. Background

Extended-spectrum beta-lactamases (ESBLs) are enzymes that confer resistance to penicillins, third-generation cephalosporins, and monobactams, thereby limiting treatment options for infections caused by ESBL-producing *Escherichia coli* (ESBLEC) and *Klebsiella pneumoniae* (ESBLKP) to last-resort antibiotics such as carbapenems (1). Globally, since the early 2000s, *bla* $_{CTX-}$

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$_{M}$ has emerged as the most prevalent ESBL gene family (2). Within this family, *bla* $_{CTX-M-15}$, a member of the *bla* $_{CTX-M-1}$ group, has become dominant worldwide (2). *bla*$_{CTX-M-15}$ was first detected in 1999 in India and then rapidly achieved pandemic spread across both community and healthcare settings internationally (3). This global expansion established *bla* $_{CTX-M-15}$ as the predominant *bla* $_{CTX-M}$ variant in many regions, including Malaysia, where it was first detected locally in 2006 by Sekawi et al. (4). Subsequently, *bla* $_{CTX-M-15}$ was identified in 76.9% of *bla* $_{CTX-M}$-positive ESBLEC isolated from a southern Malaysian tertiary hospital in 2010 (5). Meanwhile, the prevalence of *bla* $_{CTX-M-15}$ in ESBLKP was 91.3% at the University Malaya Medical Centre in the central region from 2010 to 2012 and 40.7% in a tertiary hospital in southern Malaysia in 2014 (6, 7).

A previous study conducted in 2016 at Hospital Canselor Tuanku Muhriz (HCTM) reported a high prevalence of *bla* $_{CTX-M-1}$ genes among ESBL-producing strains (8). A similar trend was observed in other Malaysian clinical settings, where *bla* $_{CTX-M-1}$ was detected in a substantial proportion of ESBL-producing strains, ranging from 37% in ESBLEC to 80% in ESBLKP (9). Given the global dissemination of *bla* $_{CTX-M-15}$, the apparent local persistence of the *bla* $_{CTX-M-1}$ group may be driven largely by this highly successful subvariant, although this has not been routinely examined in previous studies. Therefore, this study evaluated the prevalence of *bla* $_{CTX-M-15}$ among ESBLEC and ESBLKP strains from HCTM across two sampling periods to assess its temporal persistence within a single tertiary care center.

2. Objectives

This study aimed to determine the prevalence of *bla* $_{CTX-M-15}$ in ESBLEC and ESBLKP strains collected during two sampling periods at HCTM.

3. Methods

3.1. Strain Collection

This study was conducted at HCTM during two sampling periods: June 2022 to January 2023 and December 2023 to March 2024. Strains purified from all specimen types, including those from infection, colonization, and infection-control screening, and identified as ESBLEC and ESBLKP by the Department of Diagnostic Laboratory Services (JPMD), HCTM, were included in the study. For patients from whom multiple strains were isolated, only the first strain was included. Strains were stored at -20°C as 20% glycerol stocks until further use for genotyping.

3.2. Antibiotic Susceptibility Testing

Antibiotic susceptibility testing (AST) was performed by JPMD, HCTM, using the VITEK 2 system (bioMérieux, France), and results were interpreted according to the Clinical and Laboratory Standards Institute (32nd edition). The antibiotics tested were ampicillin (AMP), cefuroxime (CFU), cefotaxime (CTX), ceftazidime (CAZ), cefepime (FEP), amoxicillin-clavulanate (AMC), piperacillin-tazobactam (TZP), ciprofloxacin (CIP), imipenem (IMP), meropenem (MEM), and ertapenem (ETP). AST results were obtained from the WHONET system (https://whonet.org/) and analyzed to construct AST profiles for all tested strains. No additional phenotypic confirmatory ESBL testing was performed by JPMD because routine quality checks (QC) for ESBLEC were performed weekly using the VITEK 2 system.

3.3. DNA Extraction, ESBL Genotyping, and *bla* $_{CTX-M-15}$ Genotyping

DNA was extracted from ESBLEC and ESBLKP strains using the boiling method (10). ESBL genotyping (*bla* $_{TEM}$, *bla* $_{CTX-M-1}$, *bla* $_{CTX-M-9}$, *bla* $_{SHV}$, and *bla* $_{OXA-1}$) was performed as described by Ogutu et al. (11). DNA extracted for ESBL genotyping was also used for *bla* $_{CTX-M-15}$ genotyping, as described by Muzaheed et al. (12). The control strain used for *bla* $_{TEM}$, *bla* $_{CTX-M-9}$, *bla* $_{SHV}$, and *bla* $_{OXA-1}$ genotyping was 2022-ESBLEC-HCTM-28, whereas the control strain for *bla* $_{CTX-M-1}$ was 2022-ESBLEC-HCTM-8; all genes were confirmed by Sanger sequencing (unpublished data). A clinical strain of *K. pneumoniae* (2025-ESBLKP-HCTM-19) was used as the control for *bla* $_{CTX-M-15}$ genotyping.

3.4. Statistical Analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 22 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies. The chi-square test or Fisher exact test, as appropriate, was used to compare AST profiles between ESBLEC and ESBLKP strains across the sampling periods and to compare the prevalence of ESBL genes and *bla* $_{CTX-M-15}$. A P value of < 0.05 was considered statistically significant.

4. Results

4.1. ESBLEC and ESBLKP Strain Collection

A total of 54 ESBLEC and 56 ESBLKP strains were collected from JPMD, HCTM, between June 2022 and January 2023 (HCTM 2022 - 2023). Subsequently, 47 ESBLEC and 31 ESBLKP strains were obtained between December 2023 and March 2024 (HCTM 2023 - 2024). Among the HCTM 2022 - 2023 isolates, both ESBLEC and ESBLKP were predominantly recovered from blood (42.6% and 51.7%, respectively) and urine (40.7% and 19.7%, respectively). A similar distribution pattern was observed for the HCTM 2023 - 2024 isolates; both ESBLEC and ESBLKP were most frequently obtained from blood (46.8% and 45.2%, respectively) and urine (29.8% and 32.3%, respectively).

4.2. ESBLEC and ESBLKP Antibiotic Susceptibility Profiles

All ESBLEC strains from both sampling periods exhibited resistance to AMP and at least one third-generation cephalosporin (Figure 1A). In contrast, although ESBLKP strains from HCTM 2022 - 2023 showed resistance to AMP and at least one third-generation cephalosporin, strains from HCTM 2023 - 2024 exhibited resistance to AMP and fourth-generation cephalosporins (Figure 1B). The proportion of ESBLEC strains resistant to CAZ and FEP decreased (Figure 1C) ($P = 0.02$), whereas resistance to AMC and TZP increased, although these differences were not statistically significant. For ESBLKP, the difference in AMC resistance between the two sampling periods (Figure 1D) was negligible ($P = 0.053$) but may warrant further monitoring. Notably, a carbapenem-resistant ESBLEC strain was detected in HCTM 2023 - 2024. For ESBLKP, resistance to most antibiotics remained largely stable, with slight decreases observed for AMC, TZP, and CIP and an upward trend in resistance to carbapenems (IMP, MEM, and ETP). However, this increase should be interpreted with caution because not all HCTM 2022 - 2023 strains were tested against carbapenems (IMP and MEM: 3 strains not tested; ETP: 1 strain not tested), which may have influenced the observed differences.

4.3. ESBL Genotyping

Distinct differences in ESBL gene distribution were observed between the two species and across the two sampling periods (Table 1). Among ESBLEC, *bla* $_{\text{CTX-M-1}}$ was present in all strains collected in HCTM 2022 - 2023 but declined markedly in HCTM 2023 - 2024, coinciding with the emergence of *bla* $_{\text{CTX-M-9}}$ (42.6%) and *bla* $_{\text{OXA-1}}$ (23.9%). Although *bla* $_{\text{TEM}}$ remained common, its prevalence showed a slight decrease over time. This temporal shift was also reflected in the ESBL gene profiles; isolates from HCTM 2022 - 2023 were predominantly characterized by the *bla* $_{\text{TEM}}$ + *bla* $_{\text{CTX-M-1}}$ combination, whereas those from HCTM 2023 - 2024 displayed greater genotypic diversity, including profiles associated with *bla* $_{\text{CTX-M-9}}$ and *bla* $_{\text{OXA-1}}$. In contrast, ESBLKP demonstrated a more conserved ESBL genotype. *bla* $_{\text{CTX-M-1}}$ and *bla* $_{\text{SHV}}$ were consistently dominant across both sampling periods, with *bla* $_{\text{SHV}}$ detected in all strains from HCTM 2023 - 2024. These genes frequently co-occurred, although the prevalence of the triple-gene combination (*bla* $_{\text{TEM}}$ + *bla* $_{\text{SHV}}$ + *bla* $_{\text{CTX-M-1}}$) decreased in the later period.

4.4. *bla* $_{\text{CTX-M-15}}$ Genotyping

All *bla* $_{\text{CTX-M-1}}$-positive strains were further typed for *bla* $_{\text{CTX-M-15}}$. Although the overall distribution of *bla* $_{\text{CTX-M-1}}$-harboring strains differed between the two sampling periods, analyses restricted to these strains showed that *bla* $_{\text{CTX-M-15}}$ remained highly prevalent and stable over time. Among ESBLEC carrying *bla* $_{\text{CTX-M-1}}$, *bla* $_{\text{CTX-M-15}}$ was detected in 68.5% (37/54) of isolates in HCTM 2022 - 2023 and 66.7% (16/24) in HCTM 2023 - 2024, indicating minimal temporal variation. Among ESBLKP with *bla* $_{\text{CTX-M-1}}$, the prevalence of *bla* $_{\text{CTX-M-15}}$ was substantially higher than that in ESBLEC and was identical in both sampling periods at 92.9% (52/56 and 26/28, respectively). A significant difference was observed between ESBLEC and ESBLKP harboring *bla* $_{\text{CTX-M-15}}$ when sampling periods were not considered ($P < 0.001$, 95% CI: 0.063 - 0.425).

5. Discussion

bla $_{\text{CTX-M-15}}$ is carried on highly transmissible plasmids, which have most likely facilitated its global dissemination (13). Accordingly, this gene has contributed to the widespread distribution of ESBL-producing strains. This dissemination has important clinical implications, including reduced therapeutic options for infections caused by ESBL-producing strains and increased selective pressure for antibiotic resistance. In this study, we aimed to determine the prevalence of *bla* $_{\text{CTX-M-15}}$ among ESBLEC and ESBLKP in our center. Across both sampling periods, both species exhibited similar distribution patterns, with blood and urine consistently representing the predominant sources of pathogen isolation. Although ESBL-producing strains may initially exist as gut colonizers,

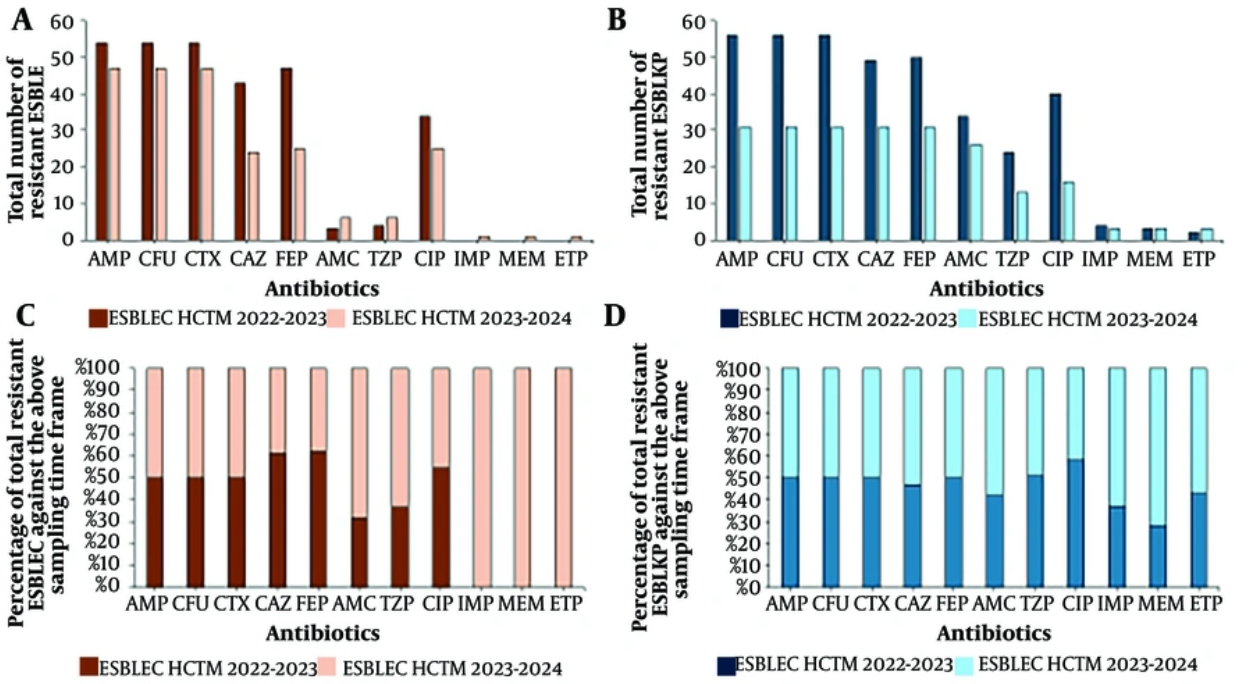

Figure 1. A, ESBLEC strains resistant to tested antibiotics; B, ESBLKP strains resistant to tested antibiotics; C, distribution of total ESBLEC strains according to antibiotic resistance across two sampling periods; D, distribution of total ESBLKP strains according to antibiotic resistance across two sampling periods.

transmission to other body sites can occur, and factors such as prolonged hospitalization, advanced age, prior antibiotic exposure, and immunocompromised status increase the risk of progression to invasive infection (14). Environmental spillover from the initial host and subsequent forward transmission to other patients have also been reported (15).

In our center, ESBLEC strains from HCTM 2023 - 2024 showed a decreasing trend in resistance to CAZ and FEP, whereas a nonsignificant increase was observed for AMC and TZP. In contrast, ESBLKP demonstrated a largely stable resistance profile across both sampling periods. Beta-lactam antibiotics remain central to the treatment of gram-negative infections; however, CAZ and FEP are categorized under the Watch group of antibiotics by the World Health Organization. Recent national reports indicate reduced cephalosporin utilization, particularly ceftriaxone, and a declining trend in CAZ and FEP use in public hospitals. Reduced antibiotic selective pressure may have contributed to the observed decline in resistance to these agents among ESBLEC strains. Another explanation may be the concurrent increase in the prevalence of *bla* $_{\text{CTX-M-9}}$, which codes for a lower level of resistance to CAZ than the *bla* $_{\text{CTX-M-1}}$ group (16).

Across both sampling periods and in both ESBLEC and ESBLKP, *bla* $_{\text{CTX-M-1}}$ was the most prevalent ESBL gene identified. This finding is consistent with a previous study conducted at the same center (8). However, notable shifts in ESBL genotypes were observed over time, particularly among ESBLEC strains. These changes may reflect the influence of antibiotic selective pressure and the hospital environment, which serves as an important reservoir facilitating horizontal gene transfer between strains of the same and different Enterobacterales species. The dissemination of ESBL-producing strains is a multifaceted process involving both the clonal spread of successful lineages between patients and the transfer of resistance determinants via mobile genetic elements across diverse bacterial backgrounds (17). To date, the *bla* $_{\text{CTX-M}}$ family comprises more than 250 genotypes. Among these, *bla* $_{\text{CTX-M-15}}$ has been recognized as one of the most widespread and clinically significant variants (2, 18). The global dissemination of *bla* $_{\text{CTX-M}}$ genotypes reflects their

Table 1. ESBL Genotypes of ESBLEC and ESBLKP Strains [a]

Variables	ESBLEC			ESBLKP		
	HCTM 2022 - 2023 (n = 54)	HCTM 2023 - 2024 (n = 47)	P Value, 95% CI	HCTM 2022 - 2023 (n = 56)	HCTM 2023 - 2024 (n = 31)	P Value, 95% CI
ESBL gene						
bla $_{TEM}$	31 (57.4)	23 (48.9)		43 (76.8)	21 (67.7)	
bla $_{CTX-M-1}$	54 (100)	24 (51.1)	< 0.001, 1.480 - 2.591	56 (100)	28 (90.3)	0.042, 0.987 - 1.242
bla $_{CTX-M-9}$	0 (0)	20 (42.6)	< 0.001, 1.361 - 2.226	0 (0)	0 (0)	
bla $_{SHV}$	0 (0)	2 (4.3)		43 (76.8)	31 (100)	0.004, 0.665 - 0.887
bla $_{OXA-1}$	0 (0)	11 (23.9)	< 0.001, 1.115 - 1.529	0 (0)	3 (9.7)	
ESBL genotype						
bla $_{TEM}$	0 (0)	2 (4.3)		0 (0)	0 (0)	
bla $_{CTX-M-1}$	23 (48.9)	9 (19.1)	0.012, 1.267 - 7.743	0 (0)	0 (0)	
bla $_{CTX-M-9}$	0 (0)	7 (14.9)		0 (0)	0 (0)	
bla $_{SHV}$	0 (0)	0 (0)		0 (0)	0 (0)	
bla $_{OXA-1}$	0 (0)	0 (0)		0 (0)	0 (0)	
bla $_{TEM}$ + *bla* $_{CTX-M-1}$	31 (57.4)	8 (17.0)	0.012, 2.586 - 16.676	0 (0)	0 (0)	
bla $_{TEM}$ + *bla* $_{CTX-M-9}$	0 (0)	9 (19.1)		0 (0)	0 (0)	
bla $_{TEM}$ + *bla* $_{SHV}$	0 (0)	1 (2.1)		0 (0)	3 (9.7)	
bla $_{SHV}$ + *bla* $_{CTX-M-1}$	0 (0)	0 (0)		13 (23.2)	8 (25.8)	
bla $_{CTX-M-1}$ + *bla* $_{OXA-1}$	0 (0)	6 (12.9)		0 (0)	0 (0)	
bla $_{CTX-M-9}$ + *bla* $_{OXA-1}$	0 (0)	3 (6.4)		0 (0)	0 (0)	
bla $_{TEM}$ + *bla* $_{SHV}$ + *bla* $_{CTX-M-1}$	0 (0)	0 (0)		43 (76.8)	17 (54.8)	0.034, 1.063 - 6.979
bla $_{TEM}$ + *bla* $_{CTX-M-1}$ + *bla* $_{OXA-1}$	0 (0)	1 (2.1)		0 (0)	0 (0)	
bla $_{TEM}$ + *bla* $_{CTX-M-9}$ + *bla* $_{SHV}$	0 (0)	1 (2.1)		0 (0)	0 (0)	
bla $_{CTX-M-1}$ + *bla* $_{OXA-1}$ + *bla* $_{SHV}$	0 (0)	0 (0)		0 (0)	2 (6.4)	
bla $_{TEM}$ + *bla* $_{CTX-M-1}$ + *bla* $_{OXA-1}$ + *bla* $_{SHV}$	0 (0)	0 (0)		0 (0)	1 (3.2)	

[a] Values are expressed as No. (%) unless otherwise indicated.

strong association with mobile genetic elements and successful bacterial lineages.

5.1. Study Limitations

This study has several limitations. First, the temporal gap between the sampling periods was relatively short, which may explain why few significant differences were observed. Second, the study focused only on a single subtype of *bla* $_{CTX-M}$; other emerging subtypes were not tested. Third, ethical approval for the study covered only strain collection; demographic and clinical data for the associated patients were not included and therefore were not collected or analyzed, limiting interpretation of disease burden, patient distribution, and specimen distribution in HCTM. Future studies should address these limitations and consider collecting patient data and sequencing *bla* $_{CTX-M}$ genes and plasmids harboring ESBL genes to better characterize circulating ESBL variants. Importantly, implementing routine genomic and plasmid sequencing surveillance would enable more precise tracking of transmission dynamics, clonal spread, and plasmid-mediated dissemination of ESBLs within the hospital setting, thereby strengthening infection control and antimicrobial stewardship efforts.

5.2. Conclusions

In conclusion, *bla* $_{CTX-M-15}$ was highly prevalent among both ESBLEC and ESBLKP in HCTM across two

sampling periods. The continued presence of *bla* $_{\text{CTX-M-15}}$ is a concern; continuous ESBL genotypic surveillance and, where feasible, genomic surveillance of ESBL strains in the hospital will be important.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

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