

Research Article

Phenotypic and Genotypic Characterisation of AmpC-Producing SPICE Organisms From Clinical Isolates in a Tertiary Care Center

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DOI: <https://doi.org/10.24321/0019.5138.202635>

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How to cite this article:

Pyenthamizh, Bhaumik N, Lavanya. Phenotypic and Genotypic Characterisation of AmpC-Producing Spice Organisms From Clinical Isolates in a Tertiary Care Center. J Commun Dis. 2026;58(2):105-111.

Date of Submission: 2025-10-27

Date of Acceptance: 2026-05-27

A B S T R A C T

Background: AmpC β -lactamases are a major resistance mechanism in Gram-negative bacteria, especially SPICE organisms (*Serratia*, *Pseudomonas*, *Indole-positive Proteus*, *Citrobacter*, and *Enterobacter species*). Their inducible nature and resistance to cephalosporins complicate treatment, while detection remains challenging. This study aimed to characterize AmpC producers using phenotypic and genotypic methods.

Methods: A prospective observational study was conducted at Saveetha Medical College from August 2024 to January 2025. Fifty non-duplicate SPICE isolates from pus, urine, blood, and respiratory samples were included. Cefoxitin screening followed by the cefoxitin-cloxacillin double-disc synergy test was used for phenotypic detection. Multiplex PCR targeting six AmpC genes (*blaDHA*, *blaACT*, *blaACC*, *blaCMY*, *blaCIT*, *blaFOX*) was performed.

Results: Of 50 isolates, 11 (22%) were AmpC producers. PCR identified *blaCMY* (45.5%) as the most common gene, followed by *blaDHA* (27.3%) and *blaCIT* (18.2%). Three isolates showed phenotypic positivity but no amplification, suggesting uncommon variants. *Pseudomonas aeruginosa* was the predominant isolate, with pus as the main specimen source (60%).

Conclusion: AmpC producers were detected in 22% of SPICE isolates, with *blaCMY* being most prevalent. Combining phenotypic and genotypic methods enhances detection accuracy and supports appropriate antimicrobial stewardship

Keywords: AmpC β -lactamase, SPICE organisms, cefoxitin-cloxacillin test, multiplex PCR, antimicrobial resistance

Introduction

Antimicrobial resistance (AMR) is a significant global health threat that compromises decades of progress in treating infectious diseases. It occurs when microorganisms develop the ability to resist antimicrobial agents, often through mutations or gene transfer.¹ In 2019, bacterial AMR led to 1.27 million deaths and contributed to approximately 4.95 million deaths worldwide, highlighting its severe impact.^{2,3}

In Gram-negative pathogens, antibiotic resistance may result from several mechanisms, including enzymatic inactivation of antibiotics, structural alterations in porin proteins, overexpression of efflux pumps, and modification of drug targets. Among these, enzymatic inactivation through the production of β -lactamases poses a particularly significant challenge, especially given the central role of β -lactam antibiotics in the treatment of severe infections.⁴ AmpC β -lactamases represent a distinct class of cephalosporinases (Ambler Class C; Bush-Jacoby Group 1) capable of hydrolyzing third-generation cephalosporins (3GCs), cephamycins such as cefoxitin, and monobactams like aztreonam, while being poorly inhibited by traditional β -lactamase inhibitors such as clavulanic acid and sulbactam.⁵

AmpC β -lactamases may be chromosomally encoded or plasmid-mediated. Chromosomal AmpC genes, intrinsic to several Enterobacterales, can be inducible, with expression regulated by cell wall-associated transcription factors that respond to β -lactam exposure. Under selective pressure, this leads to derepressed overproduction of AmpC and the emergence of high-level resistance during therapy. Plasmid-mediated AmpCs, by contrast, are typically constitutively expressed and transmissible between bacterial strains, further exacerbating the spread of resistance.^{6,7}

Of particular clinical concern are the so-called SPICE organisms (*Serratia* spp., *Pseudomonas* spp., *Indole-positive Proteus*, *Citrobacter freundii*, and *Enterobacter aerogenes*). These organisms are frequently implicated in healthcare-associated infections, including bloodstream infections, urinary tract infections, pneumonia, biliary and intra-abdominal infections, surgical site infections, and device-associated infections.⁷ Their clinical relevance lies in their inducible chromosomal AmpC β -lactamase genes, which can be derepressed during exposure to β -lactams, leading to the development of resistance in the course of treatment.⁸ Consequently, third-generation cephalosporins, though sometimes appearing active in vitro, are unreliable in the treatment of SPICE infections. Current international guidelines and expert recommendations advise against their use, favoring instead the use of broader-spectrum antibiotics like carbapenems, piperacillin-tazobactam, or cefepime.^{9,10} Nevertheless, discussions continue regarding the best therapeutic strategies, especially in light of

concerns over antimicrobial stewardship and the increasing rates of carbapenem resistance.

The detection of AmpC β -lactamases remains a diagnostic challenge. While plasmid-mediated AmpCs can be readily identified through molecular methods such as multiplex PCR, chromosomal inducible AmpCs are less straightforward to detect.¹¹ Phenotypic tests for AmpC detection, although described in the literature, vary in sensitivity, specificity, and reproducibility, and there are currently no standardized Clinical and Laboratory Standards Institute (CLSI) guidelines for their implementation.^{12,14} This lack of standardization contributes to underreporting and misclassification, leading to inappropriate therapy and poor clinical outcomes. The increasing prevalence of AmpC-producing SPICE organisms poses a significant threat to infection management, particularly within hospital environments.¹⁵ Their ability to resist widely used β -lactam antibiotics, coupled with the lack of standardized detection protocols, complicates both diagnosis and treatment.¹⁶ This study aims to conduct a thorough phenotypic and genotypic characterization of AmpC-producing SPICE organisms, with the objective of evaluating their resistance mechanisms, enhancing diagnostic accuracy, and informing more rational antimicrobial therapies. We hypothesize that integrating phenotypic screening with molecular confirmation will improve the accuracy of AmpC detection, thereby facilitating early identification and guiding appropriate treatment strategies for infections caused by SPICE organisms.

Materials and Methods

Study setting and design

This prospective observational study was carried out in the Central Laboratory, Department of Microbiology, Saveetha Medical College and Hospital, following approval from the Institutional Ethics Committee (253/07/2024/PG/SRB/SMCH). The study was conducted over a period of six months, from August 2024 to January 2025. A total of fifty clinical isolates, confirmed to be non-duplicate and non-repetitive, were included. These comprised *Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter* species, which were obtained from various clinical specimens under standard laboratory protocols.

Sample Processing

Clinical isolates were obtained from diverse specimens, including respiratory samples, urine, blood, and exudates. The samples were plated onto MacConkey agar supplemented with crystal violet and incubated aerobically at 37 °C for 18–24 hours. Colonies that grew were subjected to Gram staining, along with oxidase and catalase testing, followed by identification through standard biochemical characterization using IMViC tests for confirmation. The confirmed isolates (*Serratia*, *Pseudomonas*, indole-

positive *Proteus*, *Citrobacter*, and *Enterobacter* species) were preserved by inoculation into nutrient agar butts supplemented with glycerol.

AmpC Detection by Phenotypic Methods

All confirmed isolates were screened for AmpC β -lactamase production using Cefoxitin (30 μ g) discs by the disk diffusion method. Isolates showing reduced susceptibility to cefoxitin (zone diameter \leq 18 mm) were considered potential AmpC producers. Confirmatory testing was performed using the cefoxitin-cloxacillin double-disc synergy test (CC-DDS), wherein an increased zone diameter of \geq 5 mm in the presence of cloxacillin indicated AmpC production.

Molecular Characterization

Genomic DNA Isolation

The preserved isolates were revived by subculturing onto MacConkey agar plates and incubated overnight aerobically at 37 °C for 18–24 hours. From the resulting pure cultures, a loopful of bacterial growth was suspended in 200 μ L of

normal saline. Genomic DNA was then extracted using the QIAamp DNA Mini Kit (Qiagen) following the manufacturer's instructions.

PCR products and analysis

Genomic DNA was amplified using Qiagen Multiplex PCR Master Mix (Cat. No. 206143) on a MiniAmp Plus Thermal Cycler (Applied Biosystems). Each 20 μ L reaction contained 10 μ L Master Mix, 2 μ L primer mix, 2 μ L Q-Solution, 4 μ L nuclease-free water, and 2 μ L DNA template. Primer sequences for the targeted *AmpC* genes were adopted from the protocol described by Pérez-Pérez et al.¹¹ PCR was carried out under the cycling conditions outlined in Table 1, targeting six major *AmpC* β -lactamase genes whose primer sequences are mentioned in Table 2. The amplified products were resolved on a 2% agarose gel containing ethidium bromide with appropriate DNA ladders and positive/negative controls, and the gels were documented for analysis.

Table 1. Shows the PCR mix and Cycling Conditions

Master mix preparation (total volume: 20 μ l)	PCR cycling conditions	Amplicon size
Multiplex master mix: 10 μ l	95°C- 15min 94°C- 30s 65°C- 90s 72°C- 90s 72°C- 10min } 30 cycles	<i>bla_{DHA}</i> : 405bp
Primer mix: 2 μ l		<i>bla_{ACT}</i> : 302bp
Q-solution: 2 μ l		<i>bla_{ACC}</i> : 346bp
Nuclease free water: 4 μ l		<i>bla_{CMY-2}</i> : 462bp
DNA template: 2 μ l		<i>bla_{CIT}</i> : 462bp
		<i>bla_{FOX}</i> : 190bp

Table 2. PCR target sequences of AmpC resistance genes

Primer Name	Primer sequence (5' - 3')	Amplicon size
CMY Forward	GCTGCTCAAGGAGCACAGGAT	520 bp
CMY Reverse	CACATTGACATAGGTGTGGTGC	
CIT Forward	TGGCCAGAACTGACAGGCAA	462 bp
CIT Reverse	TTTCTCCTGAACGTGGCTGGC	
DHA Forward	AACTTTCACAGGTGPGCTGGGT	405 bp
DHA Reverse	CCGTACGCATACTGGCTTTGC	
ACC Forward	AACAGCCTCAGCAGCCGTTA	346 bp
ACC Reverse	TTCGCCGAATCATCCCTAGC	

ACT Forward	TCGGTAAAGCCGATGTTGCGG	302 bp
ACT Reverse	CTTCCACTGCGGCTGCCAGTT	
FOX Forward	AACATGGGGTATCAGGGAGATG	190 bp
FOX Reverse	CAAAGCGCGTAACCGATTGG	

Data Analysis

Data were compiled and analyzed using Microsoft Excel 2019 and SPSS software (version 21; IBM Corp., Armonk, NY, USA). Descriptive statistics were applied to summarize the distribution of bacterial isolates by age, gender, and hospital department. The prevalence of *AmpC* β-lactamase genes was reported as frequencies and percentages.

Results

Socio-demographic characteristics of patients

Distribution of Clinical Samples

A total of 2,418 clinical samples were received during the study period, of which 1,884 (77.9%) yielded Gram-negative organisms and 534 (22.1%) yielded Gram-positive microorganisms. From the Gram-negative organisms, 50 non-duplicate isolates belonging to *Serratia*, *Pseudomonas*, indole-positive *Proteus*, *Citrobacter*, and *Enterobacter* species were identified by biochemical characterization and included for further analysis. The distribution of the isolates is tabulated below (Table 3).

Gender-wise Distribution of Isolates

Among the 50 study isolates, 34 (68%) were obtained from male patients and 16 (32%) from female patients (Figure 1).

Department-wise Distribution of Isolates

The study isolates were obtained from different hospital departments. The majority were from General Medicine (46%), followed by General Surgery (28%), Neurology (11%), Intensive Care Unit (7%), Orthopedics (5%), and Nephrology (3%) (Figure 2).

Specimen-wise Distribution of Isolates

Among the collected isolates, the highest proportion was recovered from pus samples (60%), followed by urine (26%), blood (8%), and respiratory specimens (6%) (Figure 3.)

AmpC Detection by Phenotypic Method

Out of the 50 isolates tested, 11 (22%) were identified as *AmpC* β-lactamase producers by phenotypic detection using the ceftoxitin-cloxacillin double-disc synergy testing.

Molecular Detection of AmpC Resistance Genes

Out of the 50 study isolates, 11 isolates that were confirmed to be *AmpC* producers by phenotypic testing were subjected to molecular characterization for *AmpC* resistance genes (*blaDHA*, *blaACT*, *blaACC*, *blaCMY-2*, *blaCIT*, and *blaFOX*). Multiplex PCR revealed that *blaCMY* was the most prevalent gene (45.5%), followed by *blaDHA* (27.3%) and *blaCIT* (18.2%). Notably, three isolates (27.3%) showed no amplification of the targeted genes despite phenotypic evidence of *AmpC* production. The results of multiplex PCR analysis are summarized in Table 4 and Figure 4.

Table 3. Species-wise distribution of SPICE organisms

Organism	Number of isolates
Indole-positive <i>Proteus</i> species	7
<i>Enterobacter</i> species	11
<i>Citrobacter</i> species	3
<i>Pseudomonas</i> species	22
<i>Serratia</i> species	1

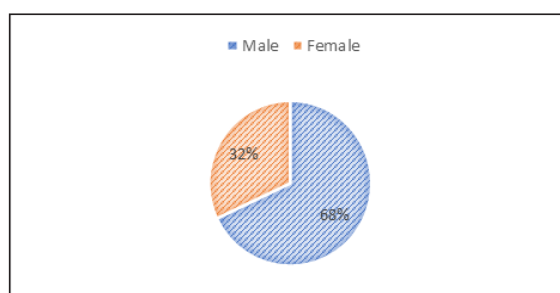


Figure 1. Sex Wise Distribution of Clinical Isolates

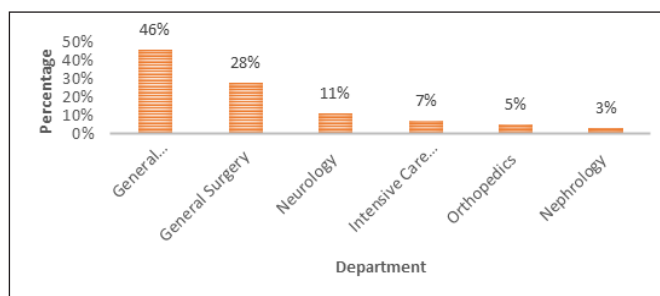


Figure 2. Department Wise Distribution of Clinical Isolates

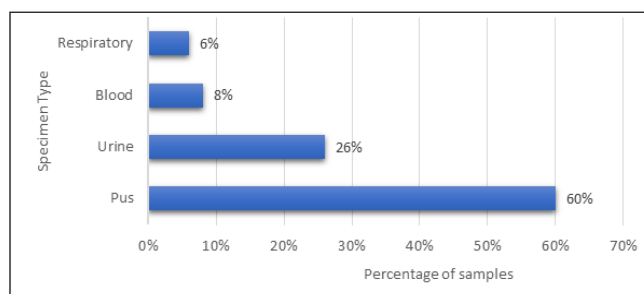


Figure 3. Specimen Wise Distribution of Clinical Isolates

Table 4. Prevalence of AmpC Resistance Genes Among Study Isolates

Isolate ID	Organism	AmpC Multiplex PCR Results
IE2216	<i>Citrobacter koseri</i>	<i>bla</i> CMY
IE2283	<i>Serratia marcescens</i>	<i>bla</i> CIT
IE2637	<i>Proteus vulgaris</i>	<i>bla</i> CMY
IE2642	<i>Enterobacter aerogenes</i>	<i>bla</i> DHA
IE3370	<i>Pseudomonas aeruginosa</i>	<i>bla</i> CMY
IE3376	<i>Enterobacter cloacae</i>	<i>bla</i> CMY
IE3380	<i>Enterobacter cloacae</i>	Negative
IR997	<i>Pseudomonas aeruginosa</i>	Negative
IU5268	<i>Citrobacter koseri</i>	<i>bla</i> CMY, <i>bla</i> DHA
OE405	<i>Proteus mirabilis</i>	<i>bla</i> CIT, <i>bla</i> DHA
OE601	<i>Pseudomonas aeruginosa</i>	Negative

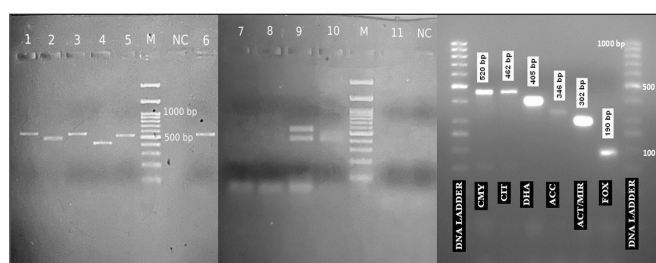


Figure 4. Agarose Gel Electrophoresis of AmpC gene PCR for study isolates

Discussion

AmpC β -lactamases are class C enzymes with a serine-based active site that hydrolyze β -lactam antibiotics, leading to resistance. This resistance can occur through

three mechanisms: inducible chromosomal genes (e.g., *Enterobacter*, *Serratia*, *Citrobacter*, *Pseudomonas*), chromosomal mutations causing constant expression (e.g., *E. coli*, *Shigella*, *Acinetobacter*), or plasmid-mediated

transfer (e.g., *Klebsiella*, *E. coli*, *Salmonella*).^{16,17} Since AmpC production often results in therapeutic failure with broad-spectrum cephalosporins, its detection is critical for ensuring effective antibiotic therapy. Although several phenotypic methods have been proposed for screening and confirmation, a comprehensive diagnostic algorithm that integrates both remains to be established.¹⁸

In our study, SPICE organisms were predominantly observed in male patients (68%), consistent with previous reports.^{19,20} This male predominance may be attributed to gender-related differences in comorbidities, healthcare exposure, and invasive procedures. A retrospective cohort study from two university teaching hospitals in Singapore reported *Enterobacter* spp. (52.5%) as the most frequent SPICE organisms,¹⁹ and similar findings were observed by Moy et al.²¹ In contrast, our study identified *Pseudomonas aeruginosa* as the predominant isolate, likely reflecting differences in local epidemiology and antimicrobial selection pressure.

Most isolates in our study were obtained from pus samples (60%), followed by urine (26%), blood (8%), and respiratory specimens (6%), indicating soft tissue and wound infections as the major source. This differs from the study by Tan et al., where urinary tract infections and vascular catheters were the primary sources of bacteremia.¹⁹ The predominance of AmpC β -lactamase-producing organisms in pus samples is particularly concerning, as these enzymes confer resistance to third-generation cephalosporins and β -lactam/ β -lactamase inhibitor combinations. Such infections pose a significant clinical threat, being frequently associated with multidrug resistance, treatment failure, and prolonged hospital stays.

AmpC β -lactamases are an important mechanism of resistance in Gram-negative bacteria, with global prevalence ranging from 2–46%.¹⁶ In India, reported rates vary between 8% and 47%.²² In the present study, the prevalence of AmpC producers was 22%, which is comparable to earlier reports, such as Shanthi et al. who documented 29.8% AmpC producers.²³ Variability across studies likely reflects differences in bacterial species distribution, patient populations, and diagnostic approaches.

Our molecular characterization revealed blaCMY (45.5%) as the most frequent gene, followed by blaDHA (27.3%) and blaCIT (18.2%). Notably, 27.3% of isolates did not amplify with the targeted primers despite phenotypic positivity, indicating the potential presence of uncommon or novel AmpC variants.

Previous studies have highlighted the heterogeneity of AmpC subtypes worldwide. Owusu et al.²⁴ identified blaFOX-M (64%) as the most common gene, while Mohd Khari FI et al.²⁵ reported predominance of EBC family genes

in *Enterobacter* spp., along with a novel plasmid-mediated blaDHA. Ronnie et al.²² demonstrated blaDHA (22.7%) as the most frequent gene, followed by blaCIT, blaEBC, and blaFOX, and observed frequent co-existence of multiple AmpC genes such as blaFOX + ACC + CIT. Regional differences are also evident, with the CIT family predominating in Southern India, and CMY, DHA, and EBC being more frequent in North Africa and Australia.²⁶

The findings highlight the genetic diversity and regional differences in AmpC β -lactamases. Specifically, the prevalence of the blaCMY gene in this study contributes to the growing global evidence of changing trends in the distribution of AmpC genes. Additionally, the presence of isolates that show phenotypic characteristics of AmpC production without corresponding genotypic confirmation highlights the necessity for broader molecular testing. Accurate identification of these bacteria is crucial, as AmpC producers frequently demonstrate multidrug resistance and can obscure the activity of extended-spectrum beta-lactamases (ESBLs), making therapy and infection management more challenging.

Limitations

This study was limited by its relatively small sample size ($n = 50$) and single-center design, which may restrict the generalizability of the findings. Only a limited panel of AmpC genes was investigated using multiplex PCR without sequencing, leaving the possibility of undetected or novel variants and preventing detailed characterization of gene types.

Conclusion

Accurate detection of AmpC producers remains a major diagnostic challenge due to the absence of standardized phenotypic tests and the genetic diversity of AmpC genes. Integrating phenotypic methods with molecular assays can enhance diagnostic accuracy and facilitate timely initiation of appropriate therapy. Given the therapeutic challenges posed by AmpC producers and their frequent association with multidrug resistance, strengthening surveillance, expanding molecular diagnostic panels, and implementing stringent antimicrobial stewardship strategies are essential to improving patient outcomes and mitigating the spread of resistance.

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