PHENOTYPIC EVALUATION OF GROUP-1 B-LACTAMASE IN THE INDIGENOUS GRAM-NEGATIVE PATHOGENS: IMPLICATIONS FOR ANTIBIOTIC RESISTANCE MANAGEMENT

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ABSTRACT: The extensive use of β-lactam antibiotics has led to widespread bacterial resistance, primarily due to β-lactamase enzymes that hydrolyze the β-lactam ring in antibiotics such as penicillin, cephalosporins, carbapenems, and monobactams. These enzymes are classified by the Ambler molecular and Bush-Jacoby functional schemes, with Group 1 β-lactamases capable of hydrolyzing broad-spectrum antibiotics and often resisting the inhibitors such as clavulanic acid and tazobactam. This study aimed to identify β-lactamase and Group 1 β-lactamase production among clinical Gram-negative bacteria. From June 2020 to June 2021, about 235 GNB isolates were collected from various clinical specimens at Diagnostic Laboratories, Hyderabad. After subculturing and confirmatory testing, 220 isolates were included. Of these, 50.5% were from male and 49.5% from female patients, with urine (48.1%) being the most common specimen source. β-lactamase production was detected in 74% (n=163) of isolates using the iodometric strip method. All *S. typhi* isolates were positive, followed by *Acinetobacter* (85.7%), *E. coli* (77.8%), *P. aeruginosa* (70.2%), *K. pneumoniae* (68.1%) and *P. mirabilis* (64.2%). Among β-lactamase producers 33.1% (n=54) strains were identified to produce Group 1 beta-lactamase. Categorically all the *Acinetobacter* strains produced these enzymes, while none of the *S. typhi* did. *K. pneumoniae* showed the highest prevalence (i.e. 36.6%) among remaining species, followed by *P. mirabilis* (33.3%), *E. coli* (30.8%), and *P. aeruginosa* (27.2%). These findings underline the prevalence of β-lactamase-mediated resistance and the significance of Group 1 enzymes in clinical Gram-negative bacterial isolates.

Key words; beta-lactamase, Group 1 beta-lactamases.

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INTRODUCTION

β-lactam antibiotics represent one of the most extensively utilized classes of antimicrobial agents worldwide, encompassing penicillin, cephalosporins, monobactams, and carbapenems (Jacobs, Consol, and Chen 2024). These agents exert potent bactericidal effects by inhibiting bacterial cell wall synthesis (Mora-Ochomogo and Lohans 2021), thereby exhibiting broad-spectrum activity against both Gram-positive and Gram-negative pathogens. Being among the most commonly prescribed antimicrobials worldwide, the beta-lactam antibiotics account up 65% of the global antibiotics market, underscoring their pivotal role in modern clinical therapy (Sargianou *et al*. 2025) (WHO Report on Surveillance of Antibiotic Consumption 2016). However, the widespread and often indiscriminate use of β-lactams has led to the emergence and dissemination of resistance mechanisms (Carmeli Y 2016), most notably through the expression of β-lactamases, which break down the β-lactam ring and neutralize antimicrobial efficacy (Bajaj, Singh, and Virdi 2016) (Bush 2018) (Bush and Bradford 2020). Although β-lactamase inhibitors namely clavulanic acid and tazobactam have been introduced to restore activity (Bebrone 2010) (Papp-Wallace *et al*. 2015), several β-lactamases have evolved to resist even these inhibitor combinations (Sargianou *et al*. 2025). This resistance phenomenon is particularly pronounced among Gram-negative bacteria, where β-lactamase production is frequently inducible in response to antibiotic exposure (Bassetti and Garau 2021). β-lactamases are classified both molecularly (Classes A–D) according to the Ambler system and functionally into three major groups as per the Bush-Jacoby classification (Bush and Jacoby 2010). Group 1 β-lactamases, also known as cephalosporinases, correspond to Ambler Class C enzymes (Tooke *et al*. 2019). These resist inhibitors such as clavulanic acid and tazobactam (Philippon A, *et al*. 2022), and are predominantly chromosomally encoded but may also occur on plasmids, thereby facilitating horizontal gene transfer (Amadi *et al*. 2023). To date, eight major plasmid-mediated *AmpC* β-lactamase families i.e. FOX, ACC, LAT, CMY,MIR, ACT, MOX, and DHA have been described based on amino acid sequence divergence (Merida-Vieyra *et al*. 2020) . Clinically significant Group 1 enzymes include *AmpC*, CMY, ACT, and FOX variants, which display resistance to clavulanic acid and

activity against cephamycins such as cefoxitin (Black, Moland, and Thomson 2005) .

AmpC commonly produced by Escherichia coli, Klebsiella spp., Proteus mirabilis, and Salmonella spp., contributing to multidrug resistance and limiting available therapeutic options (Tooke *et al*. 2019). The plasmid-mediated AmpC enzyme FOX-1, initially identified in *Klebsiella pneumoniae*, exemplifies this resistance mechanism (Leiza *et al*. 1994), while other variants such as MIR-1, CMY-1, CMY-2, MOX-1, and LAT-1 have been increasingly reported in *Klebsiella* and *E. coli* isolates worldwide (Rehana, Pandey, and Singh 2023). Among these, CMY-2 is the most prevalent globally, with reports spanning Asia, Europe, and North America (Koga *et al*. 2019).

The global surge in β-lactam resistance represents a substantial public health threat, particularly in low- and middle-income countries where antimicrobial stewardship remains limited and the irrational use of antibiotics is common (Ndaki *et al*. 2025). In Pakistan, surveillance data on the molecular as well as functional characterization and distribution of Group 1 β-lactamases in clinical Gram-negative pathogens remain scarce. Therefore, this study aims to characterize β-lactamase production, with particular emphasis on Group 1 (*AmpC*-type) enzymes, among clinical Gram-negative isolates from local healthcare settings. By identifying specific enzyme types and determining their prevalence across different bacterial species and clinical specimens, this research seeks to inform rational antibiotic prescribing, strengthen infection control strategies, and contribute to the global effort to mitigate antimicrobial resistance. To the best of our knowledge, this is the first comprehensive profiling of Group 1 β-lactamase enzymes in indigenous Gram-negative clinical isolates from Hyderabad, Pakistan.

METHODOLOGY

Clinical Isolates: The Gram-Negative clinical isolates included in this study were obtained from various Diagnostic and Research Laboratories at Hyderabad. These were specifically isolated from various clinical specimens i.e. blood, pus and urine etc. A total of 220 identified Gram-Negative isolates were collected. These were then sub-cultured on appropriate medium before application of antibiotic sensitivity test and determination of beta-lactamase production at the Institute of Microbiology, (Molecular Microbiology and Genetics Research Laboratory) University of Sindh, Jamshoro.

Iodometric Method for the Detection of β-lactamase: A reagent solution containing 1% starch–iodine and penicillin (10,000 U/mL) was prepared. Whatman No. 2 filter paper was cut into strips and soaked in the solution, excess reagent was drained, and the strips were air-dried at room temperature for approximately 2 hours. The dried strips were stored in a clean, dry, screw-capped container at −20 °C to preserve reactivity until use. For testing, a loopful of freshly isolated bacterial growth was rubbed onto the strip in a circular area of approximately 5 mm in diameter. β-lactamase production was considered positive when the inoculated area became colorless within 5 minutes.

Determination of Group 1 beta-lactamases: For the determination of Group 1 beta-lactamases a set of six different antibiotics belonging to the penicillin, 2nd and 3rd generation cephalosporins and beta-lactamase inhibitors were used; these include Penicillin G, Cefoxitin, Cefuroxime, Ceftazidime, Clavulanate, Tazobactam. Determination of sensitivity and resistance pattern against these was evaluated using Kirbey Bauer disc diffusion test. The sizes of inhibition zones were interpreted as per CLSI guidelines for species. Strains resistant to all of these were interrpreted as Group 1 beta-lactamase producers.

RESULTS

Frequency of GNB in various samples: From June 2020 to June 2021 a total of 235 identified *Gram-Negative Bacteria* (GNB) were received from different Diagnostic and Research Laboratories at Hyderabad. These Clinical GNBs were recovered from blood, pus, Tissue, wound etc. The isolates were obtained irrespective of gender, age or ethnicity of the patient. All the isolates were then sub-cultured on McConkey's and Nutrient agar. Some of the GNB isolates could not survive while a few showed mixed characteristics. Therefore, for their reconfirmation conventionally employed microbiological tests were performed. A total of 220 reconfirmed GNB were eventually included in this study. Out of 220 isolates 111 (50.5%) isolates were from male patients while 109 (49.5%) were from female patients. Categorically a total of 106 (48.1%) GNB were from urine samples, 56 (25.4%) were from blood, 45 (20.4%) from pus, while remaining 13 (5.6%) were from sputum, Tissue fluid and swabs. The absolute counts and relative values for the isolates with respect to the type of specimen and gender of the patient are given in Table 1.

Distribution of Gram-negative isolates in various clinical specimens: From the urine samples the highest percentage GNB were *E. coli* strains (73.5%), while the lowest percentage was of *Acinetobacter* (0.9%). From the Blood samples the highest percentage GNB were *P. aeruginosa* strains (41%), while the lowest percentage was of *P. mirabilis* (3.5%). From the Pus samples the highest percentage of GNB were *P. aeruginosa* strains (33.3%), while the lowest percentage was of *P. mirabilis* (17.8%). From the sputum samples the highest percentage GNB were *E. coli* strains (57%), while the

lowest percentage was of *K. pneumonia* (14.2%). The absolute counts and relative values for the isolates with reference to the type of specimen are given in Table 2.

Comparative analysis of β-lactamase Production between species: A total of 220 bacterial isolates were processed for the determination of Beta-lactamase production using iodometric strip method. 74% (n=163) were found beta-lactamase positive. Of these all of the *S. typhi* were beta-lactamase positive. 85.7% *Acinetobacter* and 77.8% E. coli were beta-lactamase positive. Comparatively the percentage of beta-lactamase positive for *P. mirabilis, P. aeruginosa and K. pneumonia* was 71.4%, 70.2 and 68.1% respectively (Table 3).

Comparative analysis of Group 1 β-lactamase Production between species: Further investigation to identify Group 1 beta-lactamase was conducted using a variety of beta-lactam antibiotics and beta-lactamase inhibitors, employing the Kirby-Bauer disc diffusion method to assess phenotypic expression. The frequencies of Group 1 beta-lactamase producing bacterial species are expressed in table 3. A total of 54 (Overall = 24.5%), (among BLA producers = 33.1%) strains were identified to produce Group 1 beta-lactamase. Interestingly none of the *S. typhi* strains displayed the production of Group 1 beta-lactamase and all of the *Acinetobacter* strains displayed the production of Group 1 beta-lactamase. Comparatively the percentage of Group 1 beta-lactamase production for *K. pneumonia, P. mirabilis, E. coli* and *P. aeruginosa* was 36.6%, 33.3%, 30.8% and 27.2% respectively (Figure 1).

Table 1. The absolute and relative values for various GNB isolates with respect to the type of specimen and gender of the patient/volunteer.

	Specimen	Total	Male	Female
		N (%)	N (%)	N (%)
	Pus	45 (20.4%)	30 (270	15 (13.7)
	Blood	56 (25.4%)	6 (28.8)	24 (22)
	Sputum	7 (3.1%)	3 (21.7)	4 (3.6)
	Fluid	1 (0.4%)	0 (00)	1 (0.9)
	Swab	2 (0.8%)	0 (00)	2 (1.8)
	Urine	106(48.1%)	45 (40.5)	61 (56)
	Tissue	3 (1.2%)	1 (0.9)	2 (1.8)
Total		220	111(50.5)	109(49.5)

Table 2. The absolute and relative values for various GNB isolates with respect to the type of specimen.

	E. coli	*P. aeruginosa*	*K. pneumonia*	*S. typhi*	*Acinetobacter spp.*	*P. mirabilis*	*Total specimens*
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Pus	11 (24.4)	15 (33.3)	11(24.4)	0 (0)	0 (0)	8 (17)	45
Blood	10 (17.8)	23(41)	12 (21.4)	4 (7)	5(8.9)	2(3.5)	56
Sputum	4 (57)	2 (28.5)	1(14.2)	0 (0)	0 (0)	0 (0)	7
Fluid	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1(100)	1
Swab	1 (50)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	2
Urine	78 (73.5)	7 (6.6)	18 (17)	0 (0)	1 (0.9)	2 (1.8)	106
Tissue	0 (0)	0 (0)	1(33.3)	0 (0)	1 (33.3)	1 (33.3)	3
	104 (47.2)	47 (21.3)	44 (20)	4 (1.8)	7 (3.1)	14 (6.2)	220

Table 3. The absolute and relative values for beta-lactamase and Group 1 beta-lactamase positive and negative GNB isolates.

	E. coli	*P. aeruginosa*	*K. pneumonia*	*S. typhi*	*Acinetobacter spp.*	*P. mirabilis*	**Total**
	N [%]	N [%]	N [%]	N [%]	N [%]	N [%]	N [%]
Beta-lactamase-Positive	81 [77.8]	33 [70.2]	30 [68.1]	4 [100]	6 [85.7]	9 [64.2]	163 [75]
Beta-Lactamase-Negative	23 [22.2]	14 [29.8]	14 [31.9]	0 [0]	1 [14.3]	5 [35.8]	55 [25]
Group 1 BLA	25 [30.8]	9 [27.2]	11 [36.6]	0 [0]	6 [100]	3[33.3]	54 [33.1]
Other groups	56 [69.2]	24 [72.8]	19 [63.4]	4 [100]	0[0]	6[66.6]	109[66.9]
Total	**104**	**47**	**44**	**4**	**7**	**14**	**220**

Key : BLA = Beta-lactamase, N = Number.

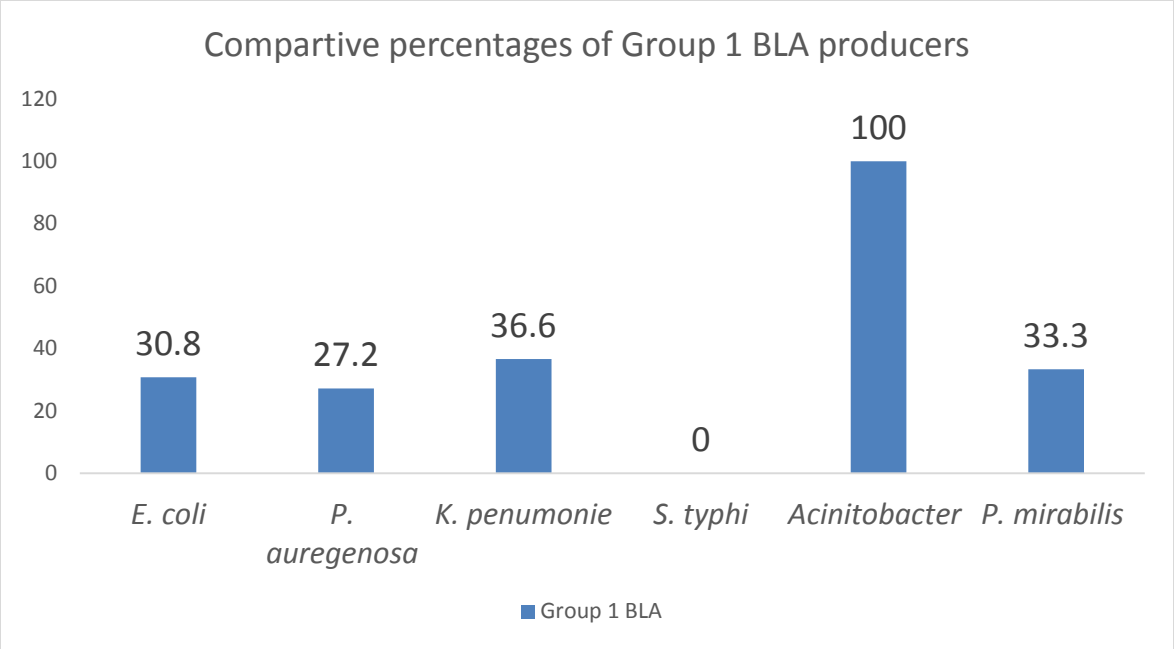

Figure 1 Comparative percentages of group 1 beta-lactamase producing Gram-Negative bacterial species.

DISCUSSION

The growing prevalence of resistance due to the production of β-lactamase among Gram-negative bacteria (GNB) is a one of the major global concerns, threatening the efficacy of one of the most widely used classes of antimicrobial agents, the β-lactams. These antibiotics, including penicillin, cephalosporins, monobactams, and carbapenems, have been indispensable for treating a wide spectrum of bacterial infections. However, their extensive and often inappropriate use has driven the selection of resistant strains capable of producing β-lactamase enzymes that hydrolyze the β-lactam ring, making the drugs ineffective. Among these enzymes, Group 1 β-lactamases (Ambler Class C; *AmpC*-type) play a particularly significant role due to their ability to hydrolyze broad-spectrum cephalosporins and resist inhibitors such as clavulanic acid and tazobactam (Philippon A, *et al*. 2022).

In the present study, β-lactamase production was detected in 74% of all isolates, a figure consistent with previous reports demonstrating high β-lactamase prevalence [i.e. 93.2% (n=262)] among clinical GNB at Peshawar Pakistan (Ambreen Arif *et al*. 2024). The high proportion of enzyme producers among *E. coli* (77.8%), *Acinetobacter spp*. (85.7%), and *K. pneumoniae* (68.1%) highlights the widespread dissemination of resistance determinants in both community and hospital settings. Similar findings have been documented by Jacoby (2009) (Jacoby 2009) and Livermore (2018) (Bush 2018), who emphasized the growing role of *AmpC*-type enzymes in Enterobacterales and non-fermenters (Pérez-Pérez and Hanson 2002).

Group 1 β-lactamase production was detected in 24.5% of all isolates, representing 33.1% of the total β-lactamase-producing strains. Comparable findings have been reported previously; Abrahim F. A. *et al*. (2023) documented Group 1 (*AmpC*) β-lactamase production in 14% of Gram-negative bacteria isolated from cases of chronic suppurative otitis media (Amadi *et al*. 2023). Similarly, studies conducted in Kashmir and Lahore reported frequencies at 30% and 22%, respectively, among Gram-negative clinical isolates (Shagufta *et al*. 2017) (Salamat *et al*. 2016). Notably, all *Acinetobacter* strains expressed Group 1 enzymes, whereas none of the *Salmonella typhi* isolates did. Among Enterobacterales, *K. pneumoniae* and *P. mirabilis* showed the higher frequencies, followed by *E. coli* and *P. aeruginosa*. The high prevalence of Group 1 β-lactamase production in *Acinetobacter* spp. at Hyderabad is striking. Previous reports have documented *AmpC* β-lactamase activity in 41.76%, of *Acinetobacter* isolates at Islamabad and 1.4% at Lahore using phenotypic assays similar to the one employed in this study (Salamat *et al*. 2016) (Shah *et al*. 2013). Pseudomonas aeruginosa exhibited a high level of β-lactamase activity (70.2%), with Group 1 β-lactamase production identified in 27.2% of the isolates. Comparable findings have been reported previously, with a study from Peshawar documenting Group 1 (*AmpC*) β-lactamase production in 28.6% of P. aeruginosa isolates (Ambreen Arif *et al*. 2024). However, a recent study conducted at Karachi reported 55% production in Pseudomonas aeruginosa (Bibi *et al*. 2025). The detection of such resistance in *Pseudomonas* highlights the

challenges in treating infections caused by this pathogen, particularly in intensive care settings where it is a cause of hospital aquired infections. In this study, 36.6% of *K. pneumoniae* isolates exhibited Group 1 β-lactamase production, whereas a higher rate of 46% was reported from Lahore by Sarfaraz and others (Sarfraz and Hasnain 2018). In the present study, 30.8% of Escherichia coli isolates were found to express Group 1 β-lactamase (*AmpC*). In contrast, a lower prevalence of plasmid-mediated *AmpC* β-lactamase production was previously reported from Lahore (19.95%) (Ul *et al*. n.d.), while Jameel *et al*. (2014) reported an even lower rate of 12.6% (Jameel *et al*. 2014).

The regional implications of these findings are substantial. In Pakistan, antimicrobial resistance surveillance remains limited, and empirical therapy often relies heavily on β-lactams without routine susceptibility testing. The detection of high levels of β-lactamase activity particularly Group 1 enzymes suggests that therapeutic options such as cephalosporins may be increasingly ineffective. The presence of plasmid-mediated AmpC genes further indicates the potential for rapid dissemination of resistance among hospital and community isolates.

Overall, this study provides the first comprehensive phenotypic profile of β-lactamase and Group 1 β-lactamase production among clinical GNB isolates Hyderabad. The findings emphasize the urgent need for routine β-lactamase screening, implementation of antimicrobial stewardship programs, and strengthened infection control measures to curb the spread of resistant pathogens. Future work should include molecular characterization of AmpC variants (e.g., CMY, FOX, DHA) using PCR or sequencing approaches to confirm genetic diversity and identify emerging resistance determinants.

Conclusion: The present study demonstrates a high burden of β-lactamase–mediated resistance among clinical Gram-negative bacterial isolates, with nearly three-quarters of the organisms exhibiting β-lactamase activity and a substantial proportion producing Group 1 (AmpC) enzymes. The high prevalence of Group 1 β-lactamase production in Acinetobacter spp. as compared to the prevalence in other cities of Pakistan such as Islamabad (41.76%) and Lahore (1.4%) is noteworthy. Collectively, the results emphasize the urgent need for regular phenotypic screening for β-lactamase production, rational antibiotic use through effective antimicrobial stewardship, and robust infection control practices. Further molecular characterization of AmpC β-lactamases is warranted to better understand their genetic diversity and to inform targeted strategies for the prevention and management of antimicrobial resistance.

Authors' Contribution: *Conceived and designed the experiments:* AA Patoli & BB Patoli, *Performed the experiments:* SN Hashmani and AA Patoli, *Analyzed the data:* AA Patoli, BB Patoli & SN Hashmani, *contributed reagents/ materials/ analysis tools:* BB Patoli, *Wrote the paper:* AA Patoli, BB Patoli & SN Hashmani.

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