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Original Article

Emergence of OXA-48–Like Genes in Carbapenem-Resistant Klebsiella Pneumoniae at a Tertiary Care Hospital in Pakistan

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ABSTRACT

Objective: To determine the frequency of the Oxacillinase-48-like gene in Carbapenem-resistant Klebsiella pneumoniae isolates using conventional polymerase chain reaction (PCR).

Study Design: Cross-sectional descriptive study.

Place and Duration of the study: Clinical Pathology Laboratory of Army Medical College, Pak Emirates Military Hospital (PEMH), in collaboration with the Department of Molecular Biology, National University of Medical Sciences, Rawalpindi, Pakistan, from Nov 22 to Jun 23.

Methodology: A total of 266 clinical specimens, including blood, respiratory aspirates, pus, body fluids, and tissue, yielding carbapenem-resistant Klebsiella pneumoniae were analyzed. Antimicrobial susceptibility testing was performed using the Kirby-Bauer disc diffusion method on Mueller-Hinton agar. Detection of the oxacillinase-48-like gene was conducted using conventional PCR. The primers used were forward (5′-GCTTGATCGCCCTCGATT-3′) and reverse (5′-GATTTGCTCCGTGGCCGAAA-3′). PCR products were analyzed using agarose gel electrophoresis. A 281 base pair band was considered positive for the OXA-48-like gene.

Results: Out of 266 carbapenem-resistant isolates, 200 tested positive for the oxacillinase-48-like gene, indicating a frequency of 75.18%. The study findings highlight a high prevalence of the OXA-48-like gene among carbapenem-resistant K. pneumoniae, emphasizing the urgent need for robust infection control strategies and strict implementation of antimicrobial stewardship programs.

Conclusion: The frequency of OXA-48-like gene in carbapenem-resistant Klebsiella pneumoniae was 75.1%. Immediate action is required to prevent its spread among high-risk patients, alongside reinforced antimicrobial stewardship efforts.

Keywords: Oxacillinase-48-like gene, Carbapenem-resistant Enterobacterales, Carbapenem-resistant Klebsiella pneumoniae, multi-drug resistance, Intensive Care Unit, Polymerase Chain Reaction, Infection prevention, and control.

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INTRODUCTION

Klebsiella pneumoniae is a Gram-negative bacillus belonging to the family Enterobacterales, a group of facultative anaerobic, glucose-fermenting rods commonly found in the human gut. While several members of this family are opportunistic pathogens, K. pneumoniae is one of the most clinically significant due to its ability to cause a wide range of community-acquired and healthcare-associated infections, including pneumonia, bloodstream infections, sepsis, and urinary tract infections. Its pathogenicity is attributed to virulence factors such as a polysaccharide capsule, lipopolysaccharides, adhesins, and iron acquisition systems.[1,2] These bacteria are widely present in the environment and can persist on medical devices and surfaces, posing a serious threat in healthcare settings, especially to neonates, the elderly, and immunocompromised patients.[3]

In recent years, K. pneumoniae has developed resistance to multiple antibiotic classes, with carbapenem-resistant K. pneumoniae (CRKP) emerging as a major global health concern.[4] Carbapenem resistance is primarily due to the acquisition of Carbapenemase-producing genes such as KPC, NDM, VIM, and OXA-48.[5] Among these, OXA-48-like Carbapenemase are increasingly reported in the Middle East, North Africa, and South Asia, including Pakistan.[6] These enzymes can hydrolyze penicillin and carbapenems but spare extended-spectrum cephalosporins, making phenotypic detection challenging.[7] While phenotypic methods like modified carbapenem inactivation method (mCIM) are used for detection, molecular techniques such as conventional polymerase chain reaction (PCR) provide higher sensitivity and specificity.[8,9] The spread of

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resistance genes via plasmids further facilitates interspecies transmission, accelerating antimicrobial resistance.[10]

Despite the growing prevalence of CRKP in clinical settings across Pakistan, limited data are available on the molecular detection of OXA-48-like genes in these isolates. This study was designed to determine the frequency of the OXA-48-like gene in carbapenem-resistant K. pneumoniae using conventional PCR. Early identification of such resistance mechanisms is crucial for infection control, guiding antimicrobial therapy, and implementing effective antimicrobial stewardship programs.

METHODOLOGY

The study was a cross-sectional descriptive research conducted at Pak Emirates Military Hospital (PEMH), Clinical Pathology Laboratory (CPL), Army Medical College, Rawalpindi, and the National University of Medical Sciences. It was completed over six months, from Nov 22 to Jun 23, and received approval from the ethics review committee and Institutional Review Board on November 18, 2022 (ERC/ID/253). The study used a descriptive cross-sectional design with non-probability convenience sampling. The sample size was calculated using the WHO sample size calculator, with a prevalence of OXA-48 set at 22.2%, based on a local study by Gondal *et al*.[11] The total sample size determined was 266.

Inclusion Criteria: All clinical samples received for culture and sensitivity, including blood, lower respiratory tract specimens, body fluids (peritoneal, pleural, and synovial), urine, and pus, were processed following standard microbiological procedures at CMPH. (Clinical Microbiology Procedures Handbook)

Exclusion Criteria: Duplicate samples from same patients, and Klebsiella pneumoniae isolates that were sensitive to carbapenems were excluded. Samples received for culture and sensitivity other than the respiratory tract, body fluids other than peritoneal, pleural, and synovial, urine, or pus were excluded.

The automated BacT/ALERT BD BioMérieux microbial identification system (USA) was used. Signal-positive blood culture bottles were subcultured on 5% sheep blood agar and MacConkey agar plates. To observe bacterial growth, the plates were incubated for 24 to 48 hours at 35°C±2 at ambient air. Pus was inoculated on blood agar and MacConkey agar for 24 to 48-hour incubation at 35°C±2. Body fluids (peritoneal, pleural, and synovial) were centrifuged and then the sediment was inoculated on culture media accordingly. Samples included bronchoalveolar lavage (BAL) and sputum were inoculated on blood, MacConkey, and chocolate agar. For bronchoalveolar lavage (BAL) and endobronchial washings (EB washings) semi-quantitative culture technique was done to distinguish between colonizers and significant pathogens.

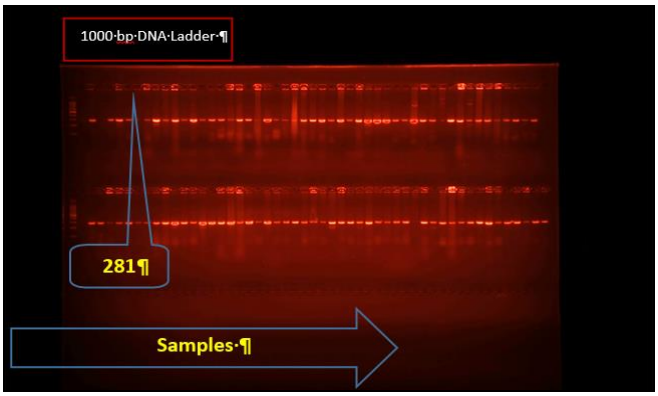

Figure-1: Agarose Gel electrophoresis showing PCR-amplified OXA-48-like gene (281 bp)

After incubation for 18-24 hours, pathogen identification was done by phenotypic characteristics like colony morphology and Gram staining. Blood agar yielded growth of 1-6 mm, large, glistening, mucoid, greyish-white colonies. On MacConkey agar lactose lactose-fermenting colonies were observed. Gram staining yielded Gram-negative rods, which were non-motile. Further identification was done on the basis of biochemical reactions by using Analytical Profile Index for Enterobacterales (API20E), which demonstrated isolates to be citrate positive and indole negative.

For Klebsiella pneumoniae, AST was done according to Clinical and Laboratory Standards Institute (CLSI 2022 M100 32nd Edition) guidelines by using the modified Kirby-Bauer disc diffusion method on Mueller-Hinton Agar (Oxoid, UK). The antibiotic discs used for susceptibility testing were Ampicillin (AMP 10µg), Amoxicillin Clavulanate (AMC 20/10 µg), Ceftazidime (CAZ 30µg), Ceftriaxone (CRO 30µg), Meropenem (MEM 10µg), Imipenem (IMP 10µg), Gentamicin (CN 10µg), Amikacin (AK 30µg), Minocycline (MIN 30µg), Ciprofloxacin (CIP 5µg), Levofloxacin (LEV 5µg) Trimethoprim-sulfamethoxazole (SXT 1.25/23.75µg). For Colistin susceptibility testing was determined by the colistin agar dilution method.

Klebsiella pneumoniae with a zone diameter of ≤19mm for both MEM and IMP were screened for Carbapenemase production. Phenotypic confirmation of Carbapenemase producers was done by the modified carbapenem inactivation method (mCIM) test. According to CLSI 2022 guidelines, the mCIM test was performed with the help of a sterile inoculating loop, 1 µl of test organism was emulsified into a 2 ml tube of tryptic soy broth (TSB), the suspension was vortexed for 10-15 seconds, then 10µg MEM disk was placed into TSB tube and incubated for 4 hours (±15 mins) at 35°C. Escherichia coli ATCC 25922(American Type Culture Collection) known sensitive to carbapenems, with turbidity equivalent to a 0.5 McFarland was prepared.

Muller Hinton Agar (MHA) was inoculated with Escherichia coli ATCC 25922. Then MEM (10 µg) disc was removed from the TSB suspension, placed on inoculated MHA plate, and incubated for 24 hours. Results considered as Carbapenemase positive with a zone diameter of 6-15mm or pinpoint colonies within a 16-18 mm zone and Carbapenemase negative with a zone diameter of ≥19 mm.

Primer Selection: The primers were designed using Primer3plus software. A forward, OXA-48F (5′ -GCTTGATCGCCCTCGATT-3 ′) with 18 base pair and a reverse primer, OXA-48R

(5 ′ -GATTTGCTCCGTGGCCGAAA-3′) with 20 base pair selected.[21] The primers were prepared by e-oligos by Gene Link. Following forward and reverse primers were used for amplification of the target sequence of the OXA-48-like gene in Klebsiella pneumoniae resistant to carbapenems.

PCR protocol: Cycling conditions used were 2 min at 50°C for decontamination before the initial denaturation, Initial denaturation was at 94°C for 10 minutes, denaturation at 94°C for 40 seconds, annealing at 60°C for 40 seconds, extension at 72°C for 1 minute, and final extension at 72°C for 7 minutes made up the thermal cycling process. 35 cycles in all were conducted, with a response time of 2 hours and 10 minutes.

Agarose Gel-Electrophoresis: Gel electrophoresis was used on the amplified products, In 400ml of 1x TBE Buffer (Tris/ Borate/ EDTA), 8 grams of Agarose powder was dissolved (2% gel stained with 0.2-0.5 µl of ethidium bromide (0.5 ug/ml)) 6µl of samples were added into wells, and Gel electrophoresis was run at 120 V for 90 minutes. The gel was then put on a UV illuminator for photo documentation, and the findings were examined. A 1000 bp DNA ladder was used to measure the molecular size of the amplified product (Molecular Biology, Thermo Scientific Company). The OXA-48-like gene was identified with 281bp bands.[12]

Lane 1: 1000 bp DNA ladder. Lane 2: positive control. Lane 3: negative control; Further lanes: test plasmids positive for the OXA-48-like gene.

For qualitative variables, frequency and percentages were calculated, Mean and standard deviation (SD) were used to determine quantitative variables.

RESULTS

In this study, two hundred and sixty-six (n=266) clinical specimens of carbapenem resistant Klebsiella pneumoniae (CRKP) were analyzed. All samples were received from different wards of tertiary care hospital, and the sampling technique was independent of age and gender. Out of 266 carbapenem resistant Klebsiella pneumoniae, OXA-48-like gene was detected in 200 specimens (75.18%), and 66 (24.8%) were negative for OXA-48-like gene. As illustrated by the pie chart in figure2.

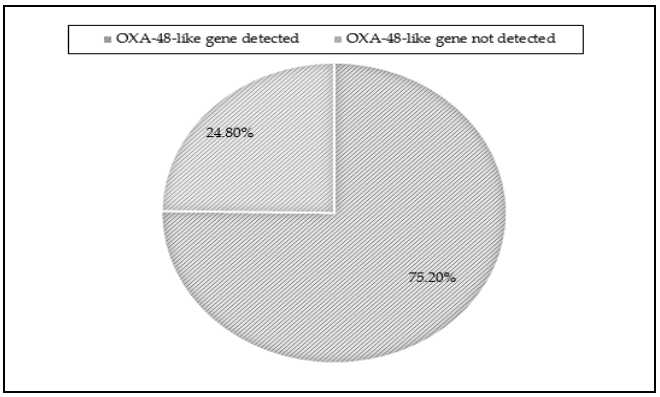

Figure-2: Oxa-48-Like Gene Detected Among Total Sample Size

Patients included in the sample size were ranging in age from newborns to 100-year-old.

Blood culture specimens contained the highest number of carbapenem-resistant Klebsiella pneumoniae harboring the OXA-48-like gene n=86(43%) followed by EB-washings n=54(27%). Remaining OXA-48-like gene were isolated from pus n=26(13%), sputum n=14(7%), urine n=11(5%) body fluids n=9(4.5%), and none was isolated from tissue specimen as shown in Table-I.

All carbapenem-resistant Klebsiella pneumoniae possessing OXA-48-like gene were detected by conventional Polymerase Chain Reaction from

specimen of hospitalized patients with hospital stays of more than 4 days up to 1 month.

Table-I: OXA-48-like Gene Detected Among Different Specimens (n=200)

Specimen	Frequency
Blood	86(43.0%)
Body Fluid	9(4.5%)
EB Washing	54(27.0%)
Pus Swab	26(13.0%)
Sputum	14(7.0%)
Urine	11(5.5%)
Tissue	0

Among 200 detected cases in clinical specimens, 96 were received from intensive care unit (ICU), 29 from neonatal intensive care unit (NICU), 23 from liver transplant unit (LTU), 3 from surgical intensive care unit (SICU), 7 from accident and emergency department(A&E) and 42 from general medical wards, as shown in bar chart in figure 3. Out of 200 detected cases of OXA-48-like gene, 37 patients were on ventilator, and remaining 163 were not on ventilatory support. 162 patients survived among 200 detected cases, and 38 patients expired. Among these 38 expired cases, 26 were from ICU, 9 from NICU, 2 from EMU, and 1 from LTU.

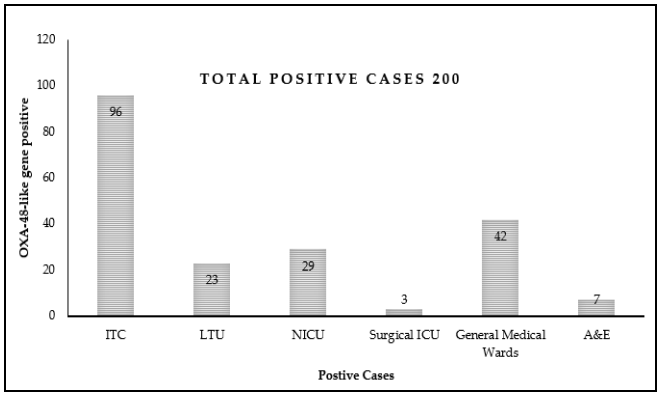

Figure-3:OXA-48-Like Gene Isolated From Different Wards.

and sensitivity of Fosfomycin was applied to urine samples (n=11), which is illustrated in Table-II.

DISCUSSION

Our study identified that the frequency of carriage of OXA-48-like gene in CRKP by using conventional PCR in critically ill patients is high, that is, 75.1%, so urgent actions should be taken to prevent the dissemination of such a pathogen among high-risk patients. The recent literature has also reported that strains of multidrug-resistant organisms (MDROs) and extensively drug-resistant organisms (XDRs) have quadrupled worldwide, posing a significant threat to our public healthcare system. Consequently, as reported by Onorato *et al.,* that clinicians have limited antibiotic options for treatment. Patients in intensive care units and critical care units are more likely to face this concerning situation.[13] Carbapenems are advanced, broad-spectrum β-lactam antibiotics that are effective against many aerobic and anaerobic Gram-positive and Gram-negative organisms, and they are bactericidal, commonly used in ICU and EMU settings. However, in recent years, a study by Rodriguez *et al.,* highlighted that nosocomial organisms have evolved and developed resistance to these drugs.[14] The OXA-48-like gene was discovered from a clinical specimen of carbapenem-resistant Klebsiella pneumoniae and reported in a study by Isler *et al.,* with a skin burn and urinary tract infection at the end of 2001. Since then, it has been identified as a source of nosocomial outbreaks worldwide.[15]

In earlier studies similar to study of Lan *et al.,* it was reported that out of n=117 cases of carbapenem-resistant Klebsiella pneumoniae (CRKP), n=26(22.2%) were positive for OXA-48-like gene; however, n=7(5.9%) of CRKP coharbored both NDM-1 and OXA-48-like gene.[16] PCR findings from our investigation revealed that among 266 isolates of CRKP, OXA-48-like gene was detected in 200 isolates (75.1% percent). This percentage of OXA-48-like gene

Table-II: Antimicrobial Susceptibility Pattern of Detected Cases (n=200)

Antibiogram of detected cases	Minocycline	Cotrimoxazole	Polymyxin B	Gentamicin	Amikacin	Ciprofloxacin	Tigecycline	Fosfomycin
Status (Resistant)	89(44.5%)	190(95.0%)	16(8.0%)	183(91.5%)	179(89.5 %)	187(93.5%)	7(3.5%)	0

***The sensitivity of Minocycline and Polymyxin E was not applied on urine samples (n=11)*
**The sensitivity of Fosfomycin was applied only on Urine samples only(n=11)*

The sensitivity pattern of detected cases was analyzed; the sensitivity of Minocycline and Polymyxin E was not applied to urine samples (n=11), is higher in comparison to a survey conducted in Pakistan, where the percentage was 22.2% and 24%.[16]

In another study conducted by Aslan et al., , out of a total n=132 Klebsiella pneumoniae n=102 were

CRKP and 39.2% were positive for OXA-48-like gene.[17] Al-hazmi *et al.,* conducted a study in Asir southern province of Kingdom of Saudi Arabia, found that increasing age and intensive care unit admission were associated with CRKP isolation. The major type of Carbapenemase was OXA-48-like, with 81.5% (n=44), and it seems to have reached an endemic level.[18] The prevalence of OXA-48-like gene in China was low among carbapenem-resistant Klebsiella pneumoniae, but prevalence of OXA-48-like gene in CRKP increased annually from 13.4% in 2020 to 14.5% in 2021, and 14.6% in 2022. Due to excessive use of carbapenems occurrence of OXA-48-like gene in CRKP has increased.[12]

A study conducted in tertiary care hospitals of Islamabad and Rawalpindi, Pakistan by Imtiaz et al., in 2021 showed carbapenem resistance, in which 200 clinical specimens of Klebsiella pneumoniae isolates were collected from nine different sample sites. The overall resistance level for carbapenems (imipenem and meropenem) was 38%, and the frequency of occurrence for the Carbapenemase-encoding OXA-48-like gene was 24%.[19]

This difference in our analysis is because all the specimens were from critically ill patients admitted to the ICU, A&D, LTU, and NICU, where the use of carbapenem is higher, and bacteria are more resistant in these environments. The frequency of the OXA-48-like gene is also raised due to the consistent lack of an antibiotic stewardship program in Pakistan. Our results are related to studies conducted by Thapa *et al.,* where the percentage of OXA-48-like gene was 72.2% percent, 67.6% percent, and 66.7% percent respectively, in clinical carbapenem-resistant isolates.[20]

In our study, the OXA-48-like gene was detected in 200 of 266 CRKP isolates, representing 75.1%. The most positive cases in our study were detected from blood specimens, n=86 (46%). Therefore, the positive cases in our investigation are consistent with a study conducted by Gurung *et al.,* in which Klebsiella pneumoniae was the etiological agent in 26 cases (72.2%), and the OXA-48-like gene was detected in bloodstream infections.[21]

Isolation of OXA-48-like gene in our scrutiny from clinical specimens goes parallel with a single-center, cross-sectional study conducted by Pourgholi *et al.,* in which 71 CRKP were detected for Carbapenemase, in which the most frequent gene isolated was *OXA-48-like gene* n=48(67.6%) isolates.[22]

Resistant organisms are more frequently isolated because of heavy utilization of antibiotics in healthcare settings in Pakistan, which is as high as 70 percent, according to a study. In health care centers, antibiotics are being prescribed without culture and sensitivity testing of clinical specimens. As a result, clinicians are left with limited options to treat critically ill patients. For the implementation of antibiotic stewardship, awareness should be created.[23]

The rising prevalence of carbapenem-resistant pathogens reflects unchecked carbapenem use and highlights the urgent need for effective antimicrobial stewardship. Tailored antibiotic therapy based on culture, susceptibility testing, and clinical correlation is essential. Additionally, multicenter studies to identify resistance genes beyond OXA-48-like and increased clinician awareness are crucial to limit inappropriate antibiotic use and prevent healthcare-associated outbreaks.

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LIMITATION OF STUDY

The sample size was relatively small, and the study was conducted at a single center, which may limit the generalizability of the findings. Multicenter studies with larger sample sizes are therefore recommended to better represent the epidemiology of carbapenem resistance. Additionally, the analysis was restricted to the detection of OXA-48-like genes; other genetic mechanisms contributing to carbapenem resistance were not investigated. Furthermore, due to budgetary constraints, comprehensive gene sequencing could not be performed, which may have limited the identification of additional resistance determinants.

CONCLUSION

Our study concludes a high frequency of OXA-48-like gene carriage among carbapenem-resistant Klebsiella pneumoniae (CRKP) isolates from critically ill patients. Using conventional PCR, the OXA-48-like gene was detected in 75.1% of the isolates, indicating a substantial burden of this resistance mechanism in the study population.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SN & FH: Data acquisition, data analysis, critical review, approval of the final version to be published.

JU & RI: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

WF & ANU: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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