Original Research Paper

VOLUME - 6 | ISSUE - 2 |April - 2022 | ISSN (O) : 2663-2888 | ISSN (P) : 2663-287X

CORRELATION OF DRUG RESISTANCE PATTERN WITH LIPASE PRODUCTION IN CLINICAL ISOLATES OF KLEBSIELLA PNEUMONIAE

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ABSTRACT **Aim:** The aim of our study is to correlate drug resistance pattern with Lipase production. **Materials and Methods:** Total of 150 clinical isolates of Klebsiella pneumoniae from various clinical samples have been collected during July 2020 – December 2020. Lipase test have been detected by standard technique. And antibiotic susceptibility test has been performed by using Kirby-Bauer disk diffusion method as per CLSI guidelines [8]. ESBL test was detected by combined disc diffusion method and Carbapenemase production was detected by using E-test strip method as per CLSI guidelines. **Results and Discussion:** In 150 consecutive non-duplicate isolates, 74 isolates from Exudate, 7 isolates from Blood and 69 isolates from urine. From those 85(56.6%) isolates produced Lipase production. The number of isolates in ESBL producer were 43(57.3%). In our study, 20(32.25%) isolates produce Carbapenemase production. **Lipase Production:** Phospholipases are a diverse group of lipolytic enzymes utilized by a variety of bacterial pathogens. During the infection process to support the establishment of a replicative niche. It has been shown that hydrolysis of host membranes through the action of the bacterial phospholipases is correlated with extensive host cell destruction. [5].

KEYWORDS

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Introduction

Klebsiella pneumoniae is a member of the Klebsiella genus of Enterobacteriaceae and belongs to the normal flora of the human mouth and intestine. K. pneumoniae subspecies pneumoniae is the most pathogenic to all. It is responsible for severe lobar pneumonia, urinary tract infections, meningitis (neonates), septicemia and pyogenic infections such as abscesses and wound infections [1].

Overuse and misuse of antibiotics leads to antibiotic resistance which has become a significant public health concern. Klebsiella pneumoniae is the most common pathogenic bacteria underlying nosocomial infections due to the expression of virulence factors and occurrence of antibiotic resistance. The emergence of antimicrobial resistance is a rapidly increasing challenge in today's healthcare institutions worldwide. Pathogenic bacteria, for example, Klebsiella pneumoniae are quickly developing multidrug resistant (MDR) strains and commonly pose a serious threat to the patients because of an increased fatality rate due to the reduced effectiveness of therapy options.

Infections with carbapenemase producing strains cause prolonged hospitalization, high mortality and morbidity. Furthermore, Carbapenemase are usually associated with many other resistance determinants, giving rise to multidrug resistance. So, if such strains are detected, infection control measures should be taken to prevent the horizontal spread of resistance genes [3-5].

Phospholipases are a diverse group of lipolytic enzymes utilized by a variety of bacterial pathogens. During the infection process to support the establishment of a replicative niche. It has been shown that hydrolysis of host membranes through the action of the bacterial phospholipases is correlated with extensive host cell destruction.

Pathogenic and commensal microbes regularly interface with their host to promote survival. They do so through the production of myriad surface and secreted factors that facilitates nutrient acquisition, adherence, and evasion of host antimicrobial defenses. Secreted lipases constitute a class of bacterial enzyme that plays a significant role in both microbial infection and commensalism. In lipid-rich environments, many microbes' express Lipase to break down host-derived lipids into free fatty acids for nutrient acquisition, which promotes bacterial colonization and can lead to disease [6].

Materials and Methods:

The proposed study has been carried out in the tertiary care hospital, Pondicherry, India. A total of 150 consecutive, nonduplicate isolates of K. pneumoniae were collected from various clinical specimens such as urine, pus, Sputum, ET aspirate, broncho alveolar lavage, wound swab, tissue, vaginal swab and blood.

Antibiotic Susceptibility Testing:

Antibacterial susceptibility of all the isolates of K. pneumoniae has been determined by the standard Kirby-Bauer disc diffusion method as per the CLSI guidelines [8].

Confirmation of extended-spectrum beta-lactamase detection by combined disc diffusion method:

ESBL detection was done by phenotypic test using combined disc recommended by CLSI [8]. And the antibiotic discs used were cefotaxime and cefotaxime combination with clavulanic acid.

Confirmation of Carbapenemase Production:

The confirmation of Carbapenemase production by using E-test method strip method as per CLSI guidelines. And the strip used were ertapenem/ertapenem with boronic acid (Hi-Media).

Lipase Test:

The isolates were spot inoculated on tween 80 agar. After a week of incubation at 37°C, Lipase producing isolates form an opaque precipitation zone [7].

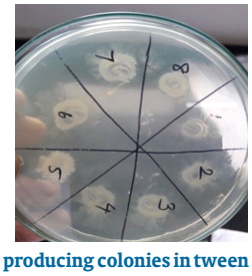

Figure – 1: Lipase producing colonies in tween 80 agar

Results:

In our study 150 nonconsecutive, nonduplicate Klebsiella pneumoniae

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isolates were tested for Lipase production and antibiotic resistance pattern with ESBL& Carbapenemase production. Out of 150 isolates, 74 from Exudate, 7 from Blood and 69 from urine. From those 85(56.6%) isolates produced Lipase enzyme. The number of ESBL producer were 43(57.3%) and carbapenemase producer were 20(32.25%).

Table - 1: Total K. pneumoniae Isolates from clinical samples

Type of Sample	No. of Isolates
Pus	35
Wound swab	7
Sputum	11
ET Aspirate	10
Broncho alveolar lavage	2
Blood	7
Urine	69
Tissue	4
Vaginal Swab	3
Pleural fluid	1
Ear swab	1
Total	150

Table - 1 represents the types of samples and number of isolates in each of the types. For the total number K. pneumoniae isolates 150, it is found that urine sample is the highest and is followed by the pus sample and then other samples.

Antibiotic Resistance Pattern of all Isolates:

Table- 2: Antibiotic Resistance Pattern (N=150)'

Antibiotic Discs	Resistant n (%)
Cotrimoxazole	42(28%)
Ceftriaxone/ cefotaxime	75(50%)
Ciprofloxacin/ norfloxacin	62(41.3%)
Gentamicin	44(29.3%)
Amikacin	36(24%)
Imipenem	37(25%)
Meropenem	25(16.6%)
Piperacillin+Tazobactam	9(11.1%)
Cefperazone+Sulbactam	21(14%)
Nitrofurantoin	26(37.68%)
Nalidixic acid	25(36.2%)

Table- 2 indicates the third-generation antibiotic resistance pattern of K. pneumoniae from all K. pneumoniae isolates. Further in Table 2, it is found that fluoroquinolones drugs (ciprofloxacin/norfloxacin – 50%) is more resistant than aminoglycosides drugs (gentamicin, amikacin – 44%) and other drugs.

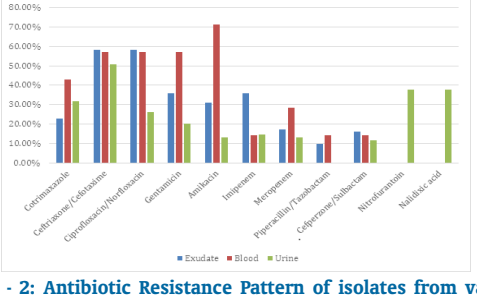

Figure - 2: Antibiotic Resistance Pattern of isolates from various samples

In Figure - 2, Antibiotic Resistance Pattern of isolates chart indicates that the resistance pattern of K. pneumoniae isolates from various clinical samples.

Table - 3: Antibiotics Resistance Pattern of inpatient and outpatient

Antibiotics	Inpatient n=90	Outpatient n=60	P-Value
	Resistant	Resistant	
Cotrimoxazole *	30(33.3%)	12(20%)	0.002
Ceftriaxone/cefotaxime *	57(63.3%)	18(30%)	.00001
Ciprofloxacin/Norfloxacin *	45(50%)	17(28.3%)	.000244
Gentamicin	26(28.8%)	18(30%)	.0997
Amikacin*	28(31.1%)	8(13.3%)	.00047
Imipenem*	26(28.8%)	10(16.6%)	.00374
Meropenem*	18(20%)	7(11.6%)	.01197
Piperacillin+Tazobactam	9(10%)	-	0
Cefperazone+Sulbactam*	17(18.8%)	4(6.66%)	.001933
Nitrofurantoin*	22(24.4%)	4(6.66%)	.0002
Nalidixic acid*	18(20%)	7(11.6%)	.01197

In table, Table - 3, it is found that the inpatient groups for each antibiotic drugs are more resistant to the antibiotics than the patient groups.

Table - 4: - Confirmatory of ESBL production in K. pneumoniae Isolates

Total Isolates	Number of third Generation Cephalosporin Resistant isolates	ESBL Positive
150	75	43

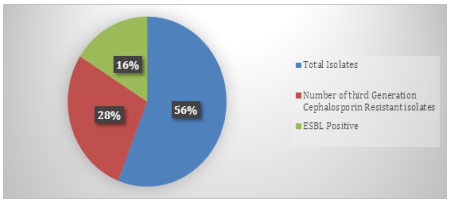

Figure - 3: Confirmatory of ESBL production in K. pneumoniae Isolates pie chart

Figure - 3 shows the pie chart representation of the data from the table: Table -4.

Table -5: Confirmatory of MBL production in K. pneumoniae Isolates

Total Isolates	Carbapenem Resistant	MBL Confirmative
150	37	20

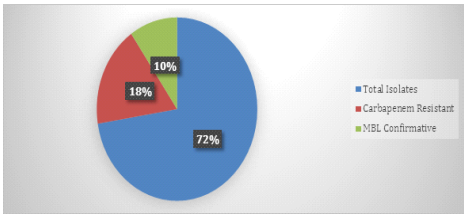

Figure - 4: Confirmatory of MBL Production in K. pneumoniae Isolates

In the Figure - 4, Confirmatory of MBL production in K. pneumoniae Isolates pie chart shows the pie chart representation of the data from Table -5

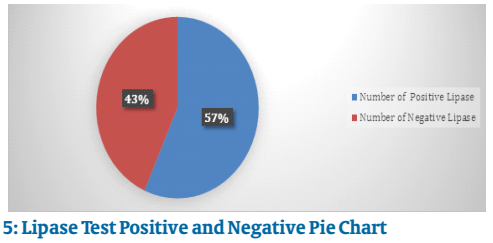

Figure - 5: Lipase Test Positive and Negative Pie Chart

Figure - 5 indicates percentage of positive and negative in Lipase Tests.

Table - 6: Lipase Test Positive and Negative results

Lipase Test N=150	Inpatient N=90	Outpatient N=60
Lipase positive (85)	64(75.29%)	21(24.7.5%)
Lipase Negative (65)	26(40%)	39(60%)

Table - 6 indicates the number of inpatient and outpatient drug resistant pattern.

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Table - 7: Antibiotic Drug Resistance for Lipase Test and P-value

Antibiotics	Lipase test positive resistant N=85	Lipase test negative resistant N=65	P-Value
Cotrimoxazole	23(27.05%)	19(29.23%)	0.237
Ceftriaxone/cefotaxime	35(41.17%)	40(61.53%)	0.694
Ciprofloxacin/Norfloxacin	24(28.23%)	38(58.46%)	0.962
Gentamicin	27(31.76%)	17(26.15%)	0.0580
Amikacin	20(23.5%)	16(24.61%)	0.2202
Imipenem	18(21.17%)	19(29.23%)	0.522
Meropenem	15(17.64%)	10(15.3%)	0.132
Piperacillin+Tazobactam	6(7.05%)	3(4.61%)	0.111
Cefperazone+Sulbactam	10(11.76%)	11(16.92%)	0.530
Nitrofurantoin*	20(23.52%)	6(9.23%)	0.0027
Nalidixic acid	15(17.64%)	10(15.38%)	0.6288

Table-7 indicates that the antibiotic resistant pattern of both Lipase positive and Lipase negative. Further it is concluded that Lipase positive has more drug resistance pattern when compared to with Lipase negative pattern.

Table 8: Correlation between ESBL producer and Carbapenemase Producer with Lipase Production

Lipase Test	ESBL producer N=43	Carbapenemase producer N = 20
Lipase Positive	30 (69.7%)	13(65%)
Lipase Negative	13(30.23%)	7(35%)

Table - 8, it has been shown that number of positive and negative Lipase tests ESBL producers when N=43 and number of positive and negative Lipase tests Carbapenem producers when N=20.

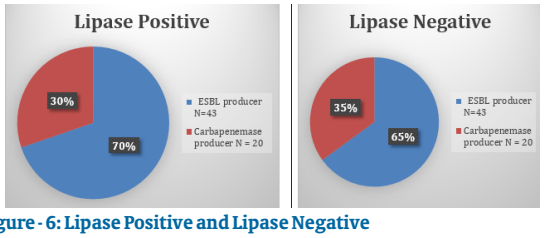

Figure - 6: Lipase Positive and Lipase Negative

Figure - 6 shows the pie chart representation of the number of positive and negative Lipase test in ESBL and Carbapenem producers when N=43 and N-20 respectively.

Table 8: Lipase Test Percentage

Previous Studies	% Of Lipase Test Positive
Gharrah MM et al. [13]	6% & 10%
Alam NG et al. [17]	76.9%
Greice H.S. Peil et al. [18]	61.90%
Emmanuel M.B.et al.[19]	18.8%
Kalaivani.et al. [20]	58.2%

Lastly, in Table - 8, it is shown that how other researchers results for Lipase Test positive have been reported.

Discussions:

Klebsiella pneumoniae are often associated with hospital acquired infections and highly contagious outbreaks with increased mortality rate and longer stay. All of which results in inflated health care costs [26].

In our study, total Klebsiella pneumoniae isolates collected were 150. K. pneumoniae have been collected from the patients in the age group 18 to 65. K. pneumoniae isolates have been mainly isolated from urine followed by pus.

Ashurst and Dawson of USA [27] reported that K. pneumoniae typically colonizes in urinary tract and in invasive infections. From this study [27], K. pneumoniae considered to be the most common cause of hospital acquired infection in the United States.

In another study by Wang et al. from the People Republic of China reported that the respiratory tract was the main infection site of K. pneumoniae.

Seif et al [28] who collected samples from two hospitals in Tehran reported that K. pneumoniae samples had been isolated from urine, surgical wounds, sputum and blood with the percentage of 61.7%,18.1%,11.7% and 8.5% respectively. In this study Seif et al further reported that K. pneumoniae isolates from inpatients and outpatients are respectively 47% and 18% and in blood it is reported to be in 3% and in urine it is reported to be in 40% and 42% respectively. In this study, a total of 58 K. pneumoniae isolates, 22 isolates (37.9%) were from female and 18 (31%) were from male.

In another study [24], 34 (58.6%) isolates from inpatients, which were obtained from intensive care unit 12 (20.7%), pediatrics 7 (12.1%), emergency 7 (12.1%), internal medicine 4 (6.9%), burn 1 (1.7%), surgery 1 (1.7%), ear, nose, and throat 1 (1.7%) and neurology department 1 (1.7%) (23). About 46.5% of the sample was collected from outpatients and 53.5% were from inpatients [24].

Resistance pattern:

K. pneumoniae is known to be resistant to various antibiotics such as ceftriaxone/norfloxacin and gentamicin while piperacillin+ tazobactam is being the least effective to K. pneumoniae while piperacillin+ tazobactam, ceftriaxone + sulbactam, nalidixic acid, and Meropenem have the most favorable profile for treatment.

This report is compared by a study conducted by Madahial that reported that K. pneumoniae isolates were 100% resistant to ampicillin and 100% sensitive to amikacin, ciprofloxacin and amoxicillin–clavulanic acid showed 38.75% and 36.69% resistance, respectively. This finding similar to Cepas et al. who reported 40% of K. pneumoniae strains were resistant to ciprofloxacin and amoxicillin-clavulanic acid.

Antibiotic exposure is the most crucial factor of antimicrobial resistance. The growth of antibiotic resistance is involving many factors such as over use of antibiotics in the hospital community, in animal farm, agriculture, and environment. Freely available to purchase without prescription specially in farm categories antibiotics are used excessively. In the health service setting, intensive and prolonged use of antibiotics are very likely the main underlying factor in the widespread transmission of difficult to cure antibiotic resistant nosocomial infections.

In our study, ESBL detection is found that the third-generation cephalosporin resistant is at 75(50%) and carbapenem resistant strains is at 37 (25%) in the total number of isolates that we collected. After screening ESBL and Carbapenem resistant strains are 43 and 20. In the category of lipase positive it has 30 (69.7%) isolates are ESBL positive and 13 (65%) isolates are carbapenemase positive whereas in lipase negative category it has 13 (30.23%) and 7(35%) isolates respectively produce ESBL and Carbapenemase.

ESBL is now a problem in the hospitalized patients worldwide. First isolated in 1983 in Germany, ESBLs occurrence in K. Pneumoniae spread rapidly to Europe, United states and Asia and are now found all over the world.

From this study it has been reported that high prevalence of ESBL producing isolates showed ESBL production. All 117 multidrug resistant K. pneumoniae isolates were cefotaxime resistant. Out of these isolates, 91 isolates were ESBL positive by ceftazidime clavulanic acid combined disc method and 95 isolates positive in HI chrome ESBL agar.

Faizabad et al [20] in Iran found that 66% of the isolates were carbapenemase producers. Gupta et al [21] in north India studied meropenem resistance was 6.9% whereas Nagaraj et al [22] observed 75% of the K. pneumoniae isolates were carbapenemase resistant in their study in South India. Azeem et al [23] stated that 35.3 % K. pneumoniae isolates in their study were resistant to carbapenemase production in 2016.

Carbapenems exhibit great affinity towards penicillin binding proteins and are not easily hydrolyzed by beta lactamase enzymes. They can easily enter the gram- negative bacterial cell by passing

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through porin channels. ` In our study 85 (56.6%) isolates showed Lipase production and in similar to our study (58%) isolates produce Lipase production was studied by Kalaivani et al [15] in Pondicherry. Gharrah et al [7] encountered 6% and 10 % Lipase production among their ESBL and non- ESBL producers. Alam et al [11] is reported in 76.9% Lipase formation.

Pathogenic and commensal microbes regularly interface with their host to promote survival. They do so through the production of myriad surface and secreted factors that facilitates nutrient acquisition, adherence, and evasion of host antimicrobial defenses.

The major cause of inappropriate antibiotic prescribing is due to a lack of education about infection and antibiotic usage. One of the most relevant steps in antibiotic prescribing is an adjustment antibiotic prescribing is an adjustment of initial antibiotic therapy based on the clinical microbiology result. Therefore, it is essential to perform antibiotic susceptibility testing. Collecting clinical samples before antibiotic administration is also a critical point. Many physicians who prescribe antibiotics do not completely understand if their inappropriate prescriptions can have an impact on bacterial resistance development. Adjusting the initial antimicrobial therapy based on the clinical microbiology result will diminish the selection pressure to the microorganism in hospital – based infections. Thus, it is of paramount importance for each hospital to have an antibiotic guidance or stewardship program for all pharmacists and the physicians based on the most accurate microbiological data. In conjunction with this guidance, a continuous effort in hospital surveillance, infection control, and clinical audits must be conducted to fight against the rapid development of antibiotic – resistant pathogens.

In this study, the antibiotics like nitrofurantoin, nalidixic acid, cotrimoxazole, cefotaxime/ceftriaxone, ciprofloxacin/Norfloxacin, amikacin, imipenem, meropenem, cefperazone and sulbactam are statistically significant in both inpatient and outpatient.

Patients admitted to ICUs are at greatest risk of acquiring nosocomial infections, partly because of their serious underlying disease but also because of exposure to life-saving invasive procedures, prolonged use of in situ invasive devices, therapy with multiple antimicrobials, and extended hospital stays.[4-5] Moreover, antimicrobial resistance in pathogens is more likely encountered in the ICU because of the selection effect of treatment with multiple antimicrobials for a single patient, which may result in amplification of antimicrobial resistance in organisms. The increasing number of ICU beds in hospitals is an important development regarding both antimicrobial resistance and nosocomial infections. The relative magnitude of antimicrobial resistance in ICUs will increase as hospitals devote more beds and resources to those units. In Lipase test, drug resistant pattern, the antibiotic nitrofurantoin only statically significant in Lipase positive and Lipase negative isolates.

Conclusion:

In general, the Lipase enzymatic production in multidrug resistant Klebsiella pneumoniae isolates can cause various life-threatening infections. As we have known that detection of virulence factor might help in management process, as presence of virulence factor increases pathogenic ability leading to therapeutic challenge. Most of the K. pneumoniae isolates showed resistance to a wide range of antibiotics. Most of these were also shown to be Lipase producers of various capacities. Global efforts should be intensified to prevent the spread of multi- drug resistant bacteria and eliminate the hospital born microbes that are causing a dramatic rise in mortality.

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