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Original Research Paper

DRUG RESISTANCE IN ACINETOBACTER SPECIES WITH SPECIAL REFERENCE TO ESBL AND CARBAPENEMASES

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ABSTRACT:

Background: Acinetobacter species are rapidly emerging nosocomial pathogens mainly affecting patients with impaired host defences. Acinetobacter shows different types of drug resistance. Production of beta lactamases is the most common mechanism. Detection of these resistance mechanisms is essential to formulate appropriate therapeutic and control measures. **Aim:** To determine the antibiotic susceptibility pattern of Acinetobacter isolates obtained from clinical samples received in the Department of Microbiology from patients admitted in Government Medical College, Ernakulam and also to identify the mechanism of resistance exhibited by Acinetobacter species in terms of ESBL and Carbapenemases. **Materials and Method**: This descriptive cross-sectional study included 99 Acinetobacter isolates obtained from samples collected from patients admitted in Government medical college Ernakulam. The isolates whose zone diameters of Ceftazidime less than 22mm and that of Cefotaxime less than 27 mm were considered as potential ESBL producers. ESBL confirmation was done using the double disk diffusion method as per the CLSI guidelines. Carbapenem resistant isolates were subjected to Imipenem-EDTA combined disk test for confirmation of one of the Carbapenemase, Metallo betalactamase production. Genotyping for detection of ESBL and MBL genes was also done. The data entered in the excel spread sheet as per the proforma was analysed using Statistical Package for Social Sciences (SPSS) software 16.0. Chi square test was used in the analysis of study variables. The level of statistical significance was taken as p value <0.05. **Result**: In our study, 97% of the Acinetobacter isolates were resistant to Cefotaxime followed by Ceftriaxone(94.9%) and only 41.4% were resistant to Minocycline. Out of the 99 Acinetobacter isolates, 77 (78%) were MDR. 50 (50.5%) isolates were confirmed to be ESBL and 47 (47.5%) isolates were MBL producers. Twenty five (25.2%) isolates had both ESBL and MBL production as the mechanism of resistance. **Conclusion**: In our study, 78% of Acinetobacter isolates showed Multi drug resistance. We could demonstrate statistically significant association of multidrug resistance among the Acinetobacter isolates and age above 60 years, ICU admission, immunocompromised state and present antibiotic usage.

Key words: Acinetobacter isolates; MDR; ESBL; MBL

INTRODUCTION:

Beijerinck in 1911 was credited with isolating a microbe representative of the genera from the soil and naming it Micrococcus calcoaceticus. The genera expanded and underwent numerous defining changes and later on Brisou and Prevot proposed the generic designation of Acinetobacter in 1954(1).The genus Acinetobacter is currently classified in the family Moraxellaceaea and consists of bacteria that are non motile, oxidase negative, gram negative coccobacilli.(2) The pathogenicity of Acinetobacter species relates to its ability to adhere to surfaces utilizing pili, to create biofilm on surfaces and human cells, to survive in iron-limited environments within the host, and to acquire foreign genetic material to enhance survival and develop antibiotic resistance mechanisms.(3) Acinetobacter species are widely distributed in nature, including the hospital environment. The mode of transmission is colonization of hospitalized patients from environmental factors like medical instrumentation. In addition to the inanimate objects, species of Acinetobacter have been reported to colonize the skin in 0.5% to 3% of the general population. They may become established as part of skin and respiratory microbiota of patients hospitalized for prolonged periods.Then the bacteria may be introduced to normally sterile sites and have been isolated from a number of human sources, including blood, sputum, urine, and exudates.(4). Acinetobacter exhibits rapid spread of antibiotic-resistance and continuous acquisition of additional resistance mechanisms(5). The capacity of Acinetobacter species for extensive antimicrobial resistance may be due to the organism's relatively

impermeable outer membrane and their ability to acquire genes encoding resistance determinants.(12). Antimicrobial resistance among Acinetobacter species has increased substantially in the past decade(10)(8)(11). Mechanical ventilation, invasive procedures , central venous catheter ,recent surgery and, exposure to antimicrobial agents, immunosuppressive drugs, Diabetes mellitus, Renal failure and underlying pulmonary disease are risk factors for hospital acquired Acinetobacter infections.(6)(7)(8)(9). Different mechanisms of drug resistance in Acinetobacter species include resistance to Beta lactams, Aminoglycosides, Fluroquinolones and other agents(13). Betalactam resistance in Acinetobacter species include ESBL and Carbapenemase production. Carbapenem resistance in Acinetobacter baumanni is mainly due to class B (metallo beta lactamases) and class D (OXA-type enzymes) of Ambler's classification of Beta lactamases.(13)

AIMS AND OBJECTIVES:

The present study was conducted to determine the antibiotic susceptibility pattern of Acinetobacter isolates obtained from clinical samples received in the Department of Microbiology from patients admitted in Government Medical College, Ernakulam during a period of one year and also to identify the mechanism of resistance exhibited by Acinetobacter species in terms of ESBL and Carbapenemases.

RELEVANCE OF THE STUDY:

Acinetobacter shows different types of drug resistance. Antimicrobial resistance in Acinetobacter is both intrinsic and acquired. Intrinsic resistance is due to naturally occurring plasmid mediated genes such as OXA51. Acquired resistance may be due to either chromosomal or plasmid mediated β lactamases, DNA gyrase mutation or decreased outer membrane permeability through porin loss and aminoglycoside inactivating enzymes. Amongst these, production of beta lactamases is the most common mechanism(14). Multi drug resistance could be due to any one or combination of mechanisms mentioned above. Major risk factors for these resistance patterns include prolonged length of hospital stay, long term antibiotic exposure with high rates of Cephalosporin and Carbapenem usage, instrumentation, and severity of illness(15)(16)(6). Acinetobacter baumannii, has emerged as one of the most troublesome pathogens for health care institutions globally. Its clinical significance has been propelled by its remarkable ability to up regulate or acquire resistance determinants, making it one of the organisms threatening the current antibiotic era(17). The emergence of multidrug resistance (MDR), extensive drug resistance (XDR), and even pan-drug resistance (PDR) is common among Acinetobacter baumannii isolates(18)(19) . As a consequence, MDR, XDR, and PDR now present a significant challenge in the management of bacterial infections. For infections caused by drug-resistant strains, efficacious treatment is limited and therefore Acinetobacter baumannii has become an important cause of nosocomial infections over the past 15 years(20)(21)(22)(23)(24). Recently Carbapenem-Resistant Acinetobacter baumannii (CRAB) was placed on top of the list of priority pathogens for research and development of novel antibiotics(25) The fact that studies on the prevalence and susceptibility pattern of ESBL and Carbapenemase producers among Acinetobacter species are fewer in South India makes this study relevant. Moreover the previous one year record of our lab shows that more than 50% of the Acinetobacter isolates are Carbapenem resistant which makes this study highly relevant. This study enables us to understand the actual drug resistance in Acinetobacter in our institution and to find out the requirement for routine testing for ESBL and Carbapenemase detection. This will also help in developing appropriate therapeutic and control measures. Genotyping methods are vital epidemiological tools for discriminating different bacterial isolates within same species, which in turn provide useful data in tracing source of infection and disease management.(36)

MATERIALS AND METHODS:

Study design : Descriptive cross sectional study

Study setting : Department of Microbiology, Government Medical College, Ernakulam

Study period : 1 year (January 2021 to December 2021)

Sample size was calculated as 99 based on a study done by Banumathy M in 2017 at Coimbatore on 'Multivariate analysis of Acinetobacter species in a tertiary care hospital'

Study population : Acinetobacter isolates obtained from various specimens including blood and other sterile fluids, exudates, sputum, other respiratory samples and urine received in the Microbiology laboratory from patients admitted in Government Medical College, Ernakulam

Inclusion criteria:

All isolates of Acinetobacter obtained from clinical samples received from admitted paediatric and adult patients.

Exclusion Criteria:

Repeat samples from the same patient.

Study procedure: The study was started after obtaining approval from Institutional Research Committee and Institutional Ethics Committee (IEC-40/2020) of Government Medical College Ernakulam. All the clinical samples for bacteriology culture and sensitivity from inpatients received in the

Microbiology laboratory were processed immediately as per the lab guidelines. Direct examination of the samples were done by gram staining. In case of urine, direct wet mount examination was done .The samples were inoculated in respective media and incubated as per standard lab protocol. If growth present, colonies were identified by preliminary tests and biochemical reactions. All gram negative catalase positive, oxidase negative non motile isolates were subjected to a set of biochemical tests. Acinetobacter species are identified as nonfermentative in HughLeifson OF glucose, Indole test negative , Mannitol non fermenting non motile, TSI- alkaline / No change, Simmon's citrate utilized, Christensen's urease not hydrolysed, Nitrate reduction test negative, Lysine not decarboxylated ,Arginine not dihydrolased and Ornithine not decarboxylated. In addition to these routine tests, Hugh Leifson OF Lactose , Hugh Leifson OF xylose and and 10 % Lactose tests were also done for speciation. Antibiotic susceptibility testing:Antibiotic Susceptibilty testing for all Acinetobacter isolates were done on Mueller Hinton agar(Himedia) by Kirby Bauer Disc diffusion method.(26) The following antibiotic discs used were Ceftazidime (30ug), Cefepime (30ug), Ceftriaxone(30ug), Cefotaxime(30ug), Gentamicin (10ug), Amikacin (30ug), Tobramycin (10ug), Ciprofloxacin (5ug), Levofloxacin (5ug), Imipenem (10ug), Meropenem (10ug), Piperacillin-Tazobactam(100/10 ug) and Minocycline(30ug).Zone sizes were measured and results were interpreted as sensitive or resistant as per CLSI guidelines. MDR isolates were noted . Multi Drug Resistance was defined as non-susceptibility (ie, resistant/ intermediate) to atleast one agent in atleast 3 antimicrobial classes of the following **five classes**: i. Cephalosporins (Cefepime, Ceftazidime,Cefotaxime) , ii..Beta lactam/ beta lactamase inhibitors (Piperacillin Tazobactam) , iii.Carbapenems , iv. Fluoroquinolones, v.Aminoglycosides

Detection of resistance mechanism by ESBL It is done by both phenotypic and genotypic methods;

Phenotypic Method:

A. **Screening test**: Isolates with zone size of Ceftazidime less than 22mm and that of Cefotaxime less than 27mm were considered as potential ESBL producers. They were further subjected to the confirmatory test for ESBL production.(26)

B. **Confirmatory test** : (Double disc synergy test): The prepared inoculum of the isolate was lawn cultured onto Mueller Hinton Agar plate; Ceftazidime (30ug) Ceftazidime-clavulanate (30/10ug), Cefotaxime (30ug), Cefotaxime-clavulanate (30/10) disks (each set) were placed at a distance of 30mm (centre to centre) on the plate and incubated. An isolate was confirmed to be an ESBL producer if it showed 5mm or more increase in zone diameter for either antimicrobial agent in combination with Clavulanate versus the zone diameter of the agent tested alone. (26).

Detection of resistance mechanism by MBL:

Phenotypic Method:

A. **Screening test**: Isolates with zone size of Carbapenems less than or equal to 21mm were considered potential Carbapenemase producers. They were subjected to the confirmatory test for MBL detection.(26) b. Confirmatory test: Imipenem-EDTA combined disc test (CDT) The IMP-EDTA combined disc test was performed as described by Yong et al(27) .

B. **Method**: The isolate was lawn cultured on to Mueller Hinton agar plate and two disks of Imipenem (10ug) were placed 20mm apart. After that, 10ul of 0.5M EDTA was added (with sterile precautions) to one of the disks and the plate was incubated. An isolate was confirmed to be a MBL producer if it showed 7mm or more increase in zone diameter for Imipenem disk in combination with EDTA versus Imipenem disk alone.

PCR-based detection of ESBL and carbapenemase genes in the isolates of *Acinetobacter* Species (Genotypic method)

This was done at Central Institute of Fisheries Technology, Wellington Island. DNA extraction was performed from overnight bacterial cultures (grown in brain heart infusion broth) by heat lysis method. All PCRs were carried out by conventional method. Details of the primers and PCR conditions used in this study for the detection of various resistance genes are given in table below:

Primer	Primer sequence (5'-3')	Target gene	PCR conditions	Amplicon size
OXA-23-likeF	GATCGGATTGGAGAACCAGA	$bla_{OXA-23-like}$	Initial denaturation at 94 °C for 5 min; 30 cycles of 94	

OXA-23-likeR OXA-51-likeF OXA-51-likeR	ATTTCTGACCGCATTTCCAT TAATGCTTTGATCGGCCTTG TGGATTGCACTTCATCTTGG	 blaOXA-51-like	°C for 25 s, 52 °C for 40 s and 72 °C for 50 s; and a final elongation at 72 °C for 6 min.	501 bp 353 bp
MultiPER_for MultiPER_rev	GCTCCGATAATGAAAGCGT TTCGGCTTGACTCGGCTGA	PER	Initial denaturation at 94 °C for 10 min; 30 cycles of 94 °C for 40 s, 60 °C for 40 s and 72 °C for 1 min; and a final elongation step at 72 °C for 7 min.	520 bp
NDM-1_a_fw NDM-1_a_rev	CAATATTATGCACCCGGTCG CCTTGCTGTCCTTGATCAGG	bla_{NDM-1}	Initial denaturation at 95 °C for 3 min; 35 cycles of 95 °C for 1 min, 52 °C for 40 S and 72 °C for 1 min; and a final extension at 72 °C for 8 min	632 bp

DATA COLLECTION AND ENTRY:

Clinical details of the patients whose sample yielded Acinetobacter species were collected from case files and entered into the proforma. The same were numerically coded and entered into Microsoft Excel spreadsheet. The identity of the isolates , susceptibility of each antibiotic, the results of screening and confirmatory tests and the mechanism of resistance were also coded and entered into the excel spread sheet.

DATA ANALYSIS:

The data entered in the MS-Excel spreadsheet was analyzed using Statistical Package for Social Sciences (SPSS) software 16.0. Qualitative variables were summarized using frequency or percentage. Chi square test was used in the analysis of study variables. The level of statistical significance was taken as p value < 0.05 in this study.

RESULTS:

A total of 99 Acinetobacter isolates were included in the study.

Maximum isolates were obtained from exudates and respiratory specimen. Both have same distribution(31.3%).Urine being the second highest contribute 25.3%. Of the total 99 isolates 96 (97%) were Acinetobacter baumannii and 3 (3%) were

Acinetobacter lowffii. Majority of the isolates were resistant to Cefotaxime (97%), followed by Ceftriaxone (94.9%), Minocycline being the least resistant(41.4%) among the isolates. 77% of the isolates were resistant to both Imipenem and Meropenem. None of the isolates were Pan sensitive. Among the 99 Acinetobacter isolates, 77 were Multi drug resistant. Among the 77 MDR isolates 58 were PDR.

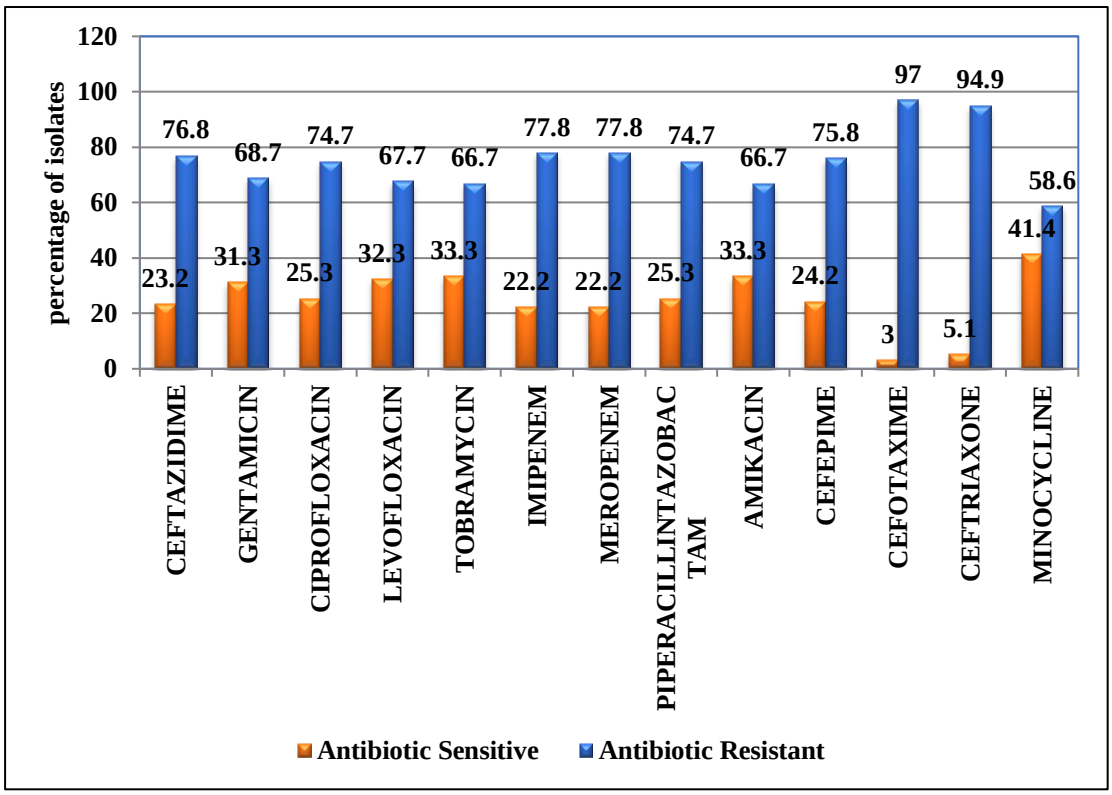


Fig. 1. Antibiotic Sensitivity Pattern

Table .1.Age and MDR strains among the Acinetobacter isolates

Age	Number of patients (n=99)	MDR	Percent
≤ 60	53	35	66.0
Above 60	46	42	91.3
Total	99	77	---
p-value = 0.003			

The association between age and MDR Acinetobacter isolates were tested using chi square test.The p value was found to be 0.003(<0.05).Hence there is a statistically significant association between age above 60 years and MDR isolates in our study.

Table 2. Location wise distribution of MDR Acinetobacter isolates

Location	**Number of patients (n=99)**	**MDR**	**Percent**
Ward	57	40	70.2
ICU	42	37	88.1
Total	99	77	---
p-value = 0.034			

The association between location in hospital and MDR Acinetobacter isolates were tested using Chi square test and the p value was found to be 0.034(<0.05).Hence there is statistically significant association between patients admitted in ICU and multidrug resistance in Acinetobacter in our study.

Table 3. Condition of immunosuppression and MDR Acinetobacter isolates

Immunosuppressive state	Number of patients (n=99)	MDR	Percent
Nil	49	33	67.3
Yes	50	44	88.0
Total	99	77	---
p-value = 0.013			

The association between immunosuppressive state and the risk of getting MDR isolates were tested with Chi square test.The p value was found to be 0.013(<0.05). Hence there is statistical significance between immunosuppressive state and MDR Acinetobacter isolates.

Table 4. Present antibiotic usage and MDR Acinetobacter isolates

Present antibiotic usage	Number of patients (n=99)	MDR	Percent
Not used	16	8	50
used	83	69	83
Total	99	77	---
p-value = 0.004			

The association between present antibiotic usage and MDR Acinetobacter isolates were tested with Chi square test. The p value was found to be 0.004 (<0.05).Hence there is a statistically significant association between present antibiotic usage and MDR isolates.

Mechanism of Resistance in Acinetobacter isolates:

In the screening test ,97(98%) isolates were potential ESBL producers and 77(77.8%)were potential MBL producers . These were subjected to confirmatory test. 50 (50.5%) isolates were confirmed as ESBL producers and 47 (47.5%) isolates were confirmed as MBL producers . 25 (25%) isolates had both ESBL and MBL as the mechanism of resistance

Fig 2. Comparison of ESBL screening, DDST and Genotyping

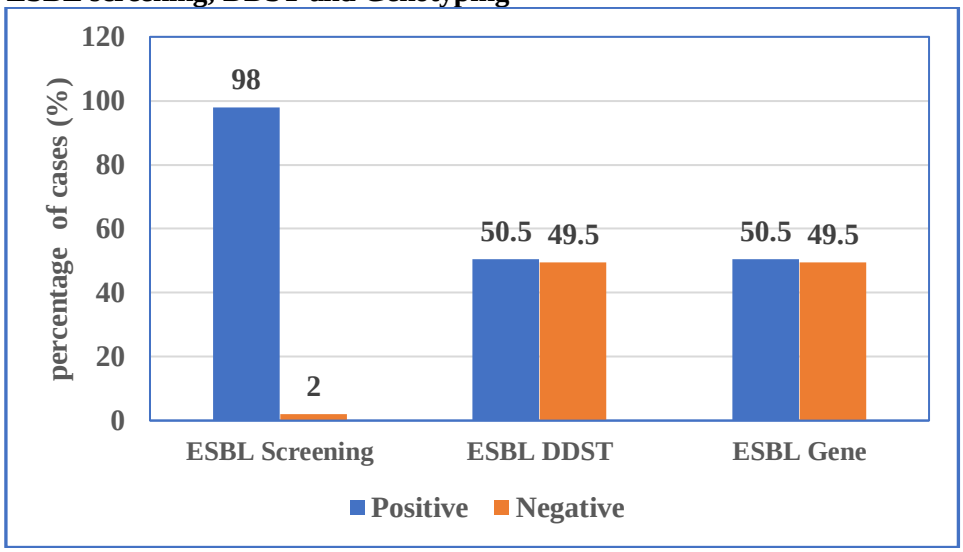
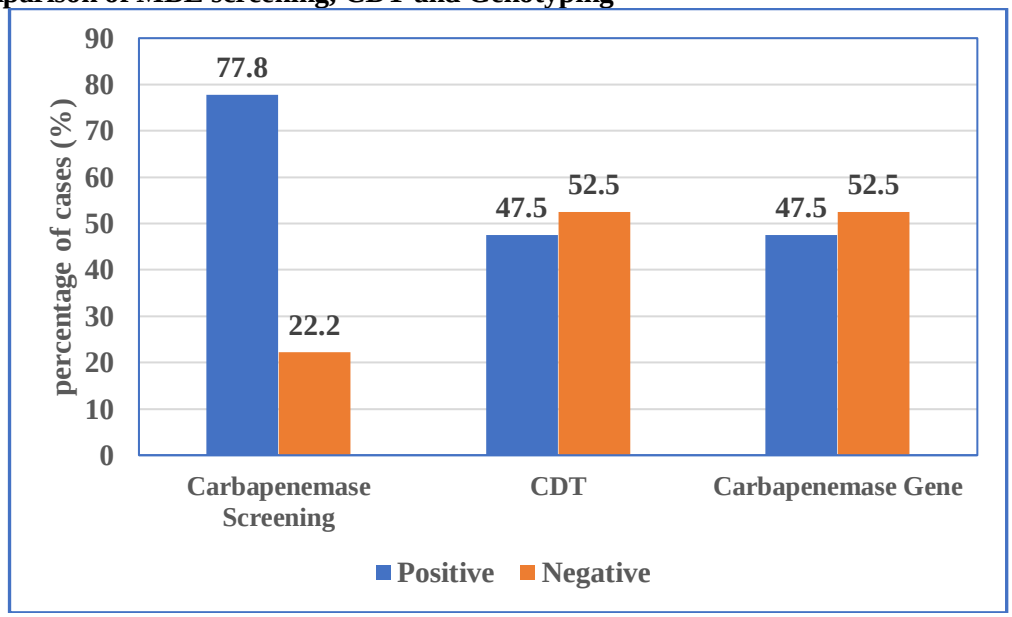


Fig .3 .Comparison of MBL screening, CDT and Genotyping



Genotyping also confirmed the same as all these ESBL positive isolates in Double Disc Synergy test showed genes responsible for ESBL production(PER gene) and MBL positive isolates in Combined disk test showed genes responsible for carbapenemase(OXA-23, OXA-48, NDM-1).

DISCUSSION:

A total of 99 Acinetobacter isolates obtained from samples received from patients admitted in Government medical college Ernakulam were included in the study. The aim of the study was to determine the antibiotic susceptibility pattern of Acinetobacter isolates obtained from clinical samples received in the Department of Microbiology, Government Medical College, Ernakulam during a period of one year. This study also aimed at identifying the mechanism of

resistance exhibited by Acinetobacter species in terms of ESBL and Carbapenemases. In the present study maximum isolates were obtained from exudates and respiratory specimen with same distribution, 31.3% each. Urine being the second highest contribute 25.3%. Our results were comparable with various other studies inside and outside India.(23) (20)(28) In our study, most of the isolates were resistant to Cefotaxime (97%), followed by Ceftriaxone(94.9%). 77% of the isolates were resistant to both Imipenem and Meropenem. Isolates were least resistant to Minocycline, followed by Tobramycin , Amikacin, Levofloxacin, and Gentamicin. Similar findings were seen in studies conducted at South India in 2014, Punjab in 2018 , Nashik in 2018 (29,30 ,11). In our study 77 % of the isolates were MDR. This was in concordance with studies conducted at Trivandrum in2019, South India in 2013, Uttar Pradesh in 2019, Western Nepal in 2020. (23, 31,21,20). In the present study , it is found that there is a statistically significant association between age above 60 years and MDR isolates. Similar finding was seen in a study conducted in USA in 2010.(32) In our study most of the MDR isolates were obtained from sputum followed by exudate. A study conducted in Western Nepal in 2020 also got similar finding.(20) MDR Acinetobacter species were obtained from 88.1% of the patients admitted in ICU , where as only 70.2% of the patients admitted in the wards yielded MDR Acinetobacter species. We got statistically significant association between patients admitted in ICU and MDR Acinetobacter isolates. This is in concordance with the findings of the study in Western Nepal in 2020(20). In our study 85.7% of the patients on invasive devices got MDR Acinetobacter isolates. But we could not prove statistically significant association between Presence of invasive device and MDR Acinetobacter isolates in our study. We could not find studies looking at the association of these two parameters. In this study among 77 MDR Acinetobacter isolates , 44 (57%) were obtained from patients with immunosuppressive state. We got statistically significant association between immunosuppressive state and MDR Acinetobacter isolates. We could not find studies looking at the association of these two parameters. We got a statistically significant association between present antibiotic usage and MDR Acinetobacter isolates in our study. Regarding the category of antibiotic used, in our study 4 patients were on Aminoglycosides and 2 were on fluoroquinolone. MDR Acinetobacter species were isolated from all of them (100%). The study conducted by Sivakami Janahiraman et al in Malaysia in 2015 observed that prior receipt of Carbapenem and Cephalosporin intake is a risk factor for MDR Acinetobacter isolates(15). Since the number of patients on Aminoglycosides and Fluoroquinolones were very few , we were not able to analyse statistical significance for the same. In our study 50 % of the isolates were ESBL producers, 47 % were MBL producers and 25 % showed both the resistance mechanisms (ESBL and MBL) in combination. These results were comparable with findings of studies done in Coimbatore in 2016, Egypt in 2020, Ethiopia in 2017(33)(34)(35). In this study we also observed that phenotypic confirmatory tests were as good as genotypic methods for detection of ESBL and MBL since all the isolates detected by phenotypic methods to produce ESBL and MBL were positive by genotypic methods also. This is in concordance with the findings of the study in Coimbatore by Banumathy M in 2017(33).

CONCLUSION:

A total of 99 Acinetobacter isolates obtained from samples received from patients admitted in Government medical college Ernakulam were included in the study from January 2021 to December 2021. Among the Acinetobacter species isolated from various clinical samples Acinetobacter baumannii was the predominant(97%) . Maximum isolates were obtained from exudates and respiratory specimen. Majority of the isolates in our study were resistant to Cefotaxime followed by Ceftriaxone and least resistant to Minocycline .Out of the 99 Acinetobacter isolates ,77 were MDR. 50 (50.5%) isolates were confirmed as ESBL producers and 47 (47.5%) isolates were confirmed as MBL producers . Twenty five (25%) isolates had both ESBL and MBL as the mechanism of resistance. In our study it was observed that phenotypic confirmatory tests were as good as genotyping for detection of ESBL and MBL . We could prove Statistically significant association of MDR Acinetobacter isolates with age above 60 years, patients admitted in ICU, presence of immunosuppressive state and present antibiotic intake.

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