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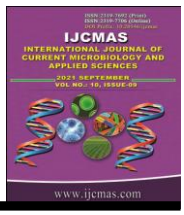

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Metallo - β - Lactamase Producers among Carbapenem Resistant Gram-Negative Isolates from Clinical Samples in a Tertiary Care Hospital

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A B S T R A C T

Gram – Negative Bacilli (GNB) are important cause of UTI, Blood stream infections, hospital acquired pneumonias. With the Carbapenems becoming the drug of choice in treating Multidrug resistant Organisms (MDRO) due to their safety and efficacy, there is rise in Carbapenem Resistant organisms which is becoming a threat to health care setup. Early diagnosis of Metallo – β – lactamase (MBL) producers by routine laboratory methods makes it the need of the hour to prevent spread of resistant strains. To detect MBL producers among Carbapenem resistant GNB. GNB were isolated from 2576 various clinical samples received by Department of Microbiology between December 2020 to March 2021. MBL production among Carbapenem resistant GNB was tested by Combined Disc Diffusion Assay using Imipenem disc and Imipenem + EDTA disc. Results: 899 GNB were isolated among 2576 samples with *E. coli* (35.05%) followed by *Klebsiella* species (28.58%) and *Pseudomonas aeruginosa* (14.90%). 180 isolates (20.02%) were Carbapenem Resistant GNB of which 55 isolates (30.55%) were MBL producers with *Klebsiella* species (29.01%) being highest MBL producer followed by *Pseudomonas aeruginosa* (27.27%). Rapid dissemination of MBL producers is worrisome making routine detection of MBL strains important. Regular surveillance, strict adherence to infection control measures and implementation of proper antibiotic policy is crucial to minimize the increasing Carbapenem resistance.

Introduction

Gram-negative bacilli are responsible for causing various infectious diseases such as urinary tract infections (UTIs), pneumonia, septicemia, soft tissue infection, opportunistic infections, and nosocomial infections. [1,2] Carbapenems are broad spectrum antibiotics used for treatment of nosocomial infections caused by gram negative bacilli. Carbapenem

resistant gram-negative bacilli are an emerging threat to the patient as well as health care system as they are associated with infections leading to high morbidity, mortality prolonging hospital stay and cost with limited options like aminoglycosides, colistin, tigecycline and Fosfomycin. Mainly multidrug resistant gram-negative bacilli comprise of Escherichia coli, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* accounting for 11.5 – 13.5% of the Carbapenem resistant infections in the ICU.[3,4,5,6,] Resistance to carbapenems can be due to lack of porin permeability, increase in expression of active efflux pumps, production of metalloenzymes, target site or outer membrane modifications.[7] When such organisms produce Carbapenemases, the outcome for the patient is usually clinical failure, high ICU mortality.[5]

β – lactams were wonder drugs till β lactamases (ESBL and MBL) producing strains started emerging. Metallo – beta – lactamases (MBLs) are Carbapenem hydrolyzing enzymes inhibited by metal chelating agents like EDTA.[1,6,7]MBL strains are more likely to cause invasive disease and higher hospital case fatality rate compared to other Carbapenem resistant strains.[8,9,10] These organisms carry multidrug resistance genes and only viable treatment options are potentially toxic drugs and are only reserve antibiotics in hospitals. Extensive dissemination of MBL strains among Gram Negative bacilli are responsible for chronicity and relapse of infection leading to high morbidity and mortality, posing a serious health risk to the patients.[1,11,12]Increased mortality rates can be attributed to inadequate empirical therapy and indiscriminate use of antibiotics.[13]

Though various recent advances in diagnosis of resistant patterns with molecular detection techniques, conventional methods are economical, reliable for screening and affordable to the patient.[1]. Hence this study was aimed at detecting Carbapenem resistance among gram negative isolates from clinical samples of ICU patients and detect MBL producers among them.

The main objectives of this study includes to isolate gram-negative bacilli from clinical samples. To detect the antibiotic sensitivity pattern of isolated gram-negative bacilli. And also to detect MBL production (Carbapenem Resistance) among the isolated gram-negative bacilli.

Materials and Methods

Ethical Consideration

Institutional Ethical Clearance was obtained prior to the study.

Place of study

Department of Microbiology, Narayana Medical College & Hospital, Nellore

Source of Clinical Samples

All Clinical samples received by Microbiology laboratory for culture and sensitivity testing

Study Design

Prospective study over a period of 4 months (December 2020 – March 2021)

Inclusion Criteria

Gram negative bacilli isolated from clinical samples.

Exclusion Criteria

Isolates other than gram negative bacilli

Isolation of gram-negative bacilli from clinical samples

Various clinical samples received by the Microbiology laboratory for culture and sensitivity testing were inoculated on Nutrient agar, Blood agar and Mac Conkey agar. The culture plates were incubated at 37°C for 24–48 hours.

Once the growth was obtained, Gram negative bacilli were isolated based on morphology and gram stain

Detection of the antibiotic sensitivity pattern of gram-negative bacilli

Identification and Antibiotic susceptibility tests were performed by VITEK2 based on Clinical and Laboratory Standards Institute (CLSI) guidelines.

Isolates flagged for Carbapenem resistance were taken for further testing

Detection of MBL production

The imipenem resistant strains were tested for MBL production by a combined disc diffusion assay using Imipenem disc and Imipenem + EDTA disc

The zone diameter difference of >5 mm around the imipenem-EDTA disc in comparison to the zone size of the imipenem disc, were confirmed as MBL producer.

Results and Discussion

Out of 2576 clinical samples (Urine, Blood, Pus, Swab, Sputum, ET aspirations, ET tube, Tracheal Section, CSF, Body fluids [pleural fluid, pericardial fluid, bile fluid, synovial fluid, drain fluid]) received by the Department of Microbiology, 899 were culture positive for Gram Negative Bacilli.

In the present study out of 2576 clinical samples, 899 isolates were culture positive for Gram negative bacilli with E. coli being the most prevalent pathogen with occurrence of 35.05% identical to the findings by Dumaru *et al.,* (38%)[1] and Fatima *et al.,* (38%).[14] Higher isolation rates (54%) were reported by Maraki *et al.,*[15]

Several studies have reported E. coli to be the most commonly isolated Gram-Negative Bacilli causing UTI, Septicemia and other infections.[14,16] Klebsiella (28.58%) followed by *Pseudomonas aeruginosa* (14.90%) were isolated in our study similar to findings reported by Sofia Maraki *et al.,* (16.5%)[15] and Yung – Chih Wang *et al.,* (22.22%).[17] M. A. Garbati *et al.,* reported Klebsiella pneumonia to be the most predominant GNB isolated (52.8%) followed by E. coli (22.98%) and Enterobacter (20.6%).[18]

In our study, all the strains were resistant to Ampicillin (100%) followed by higher resistance to Cefixime (65.6%), Cephotaxime (65%) with least resistance being towards Colistin (19.4%). Similar high resistance to 3rd generation cephalosporins and least resistance to colistin (0%) have been reported by Dumaru *et al.,*[1] The reason oh high resistance finding could be widespread use of 3rd generation cephalosporins. These findings are in concordance with findings reported by Kaur *et al.,* (Ceftazidime -56.67%, Cefoperazone – 61.67%)[19] and Bijayni Behera *et al.,* (Ceftazidime 70%).[20] 100% resistance to cephalosporins was reported by Ding *et al.,* which is alarmingly high.[21]In our study the multidrug resistant strains shared significant sensitivity towards colistin making this as reserve drug for treatment of serious infections. Studies by Bandana Baniya *et al.,*[3] and Koomanachai P *et al.,*[22] also show promising sensitivity to polymyxin B and colistin.

In the present study we report 180 isolates among 899 Gram Negative Bacilli (GNB) (20.02%) as Carbapenem resistant GNB with highest resistance reported by Citrobacter species (55.8%). *E. coli, Klebsiella* species and *Pseudomonas aeruginosa* Carbapenem resistance was found as 20%, 18.2% and 22.75% respectively. Similar Carbapenem resistance rates were reported by Maraki *et al.,* (6.4%)[15], Mc Conville TH *et al.,* (11%).[23] The majority of carbapenem resistance was reported by *Klebsiella pneumoniae* (92%).

M. A. Garbati *et al.,*[18] reported 33.33% of carbapenem resistant organisms stressing on the emerging carbapenem resistance among the Enterobacteriaceae as a major global public health problem with increase in healthcare casts, treatment failures with added mortality. Highest Carbapenem resistance was reported by *K. pneumoniae* (51.7%), followed by *E. coli* (24.1%) and *Enterobacter* (20.7%).

Carbapenems have remained as last resort antibiotic due to raising ESBL or plasmid mediated AmpC producing organisms.

These pathogens are reported to be resistant to other classes of antibiotics like quinolones and aminoglycosides. With the increasing prevalence of Carbapenem resistance over the past few years, therapeutic options have become limited with colistin and tigecycline to spare as lifesaving antibiotics.[18] Prevalence of Carbapenem resistant Enterobacteriaceae was reported as 24.7%, 29.8% and 37.5% by Al – Dhaheri *et al.,*[24], Khorasani *et al.,*[25] and Xu *et al.,*[26] respectively. Xu *et al.,*[26] have reported Klebsiella species accounting for maximum CRE (39.3%) followed by E. coli (22.0%). In contrast to our study lowest rate of carbapenem resistance was found in Citrobacter (20%).

Among the mechanisms of Carbapenem resistance in Enterobacteriaceae, the acquisition of specific genes encoding Carbapenemases play a major role which are mostly plasmid mediated and associated with mobile genetic structures like transposons or integrons. This increases the rate of dissemination and spread of Carbapenemases genes. [26, 27]

Among the 180 carbapenem resistant strains in our study, 55 were MBL producers (30.55%). We have reported *Klebsiella* species to be the highest MBL producers (29.01%) followed by *Pseudomonas aeruginosa* (27.27%).

Though Dumaru *et al.,*[1] have reported lower MBL producer rates (16.24%), they have reported Klebsiella species as highest MBL producer (26.53%) followed by Pseudomonas (26.31%) similar to our findings. Similar rates have been reported by Kaur *et al.,* (34.8%)[16], Anuradha *et al.,* (28.57%)[28] and Baniya *et al.,* (22%).[3] Similar higher rates of MBL producers were reported by Charan Kaur *et al.,* (30%)[19] and Mishra SN *et al.,* (58.28%)[13] in concordance with our findings. Lower rates were reported by Yassin NA *et al.,* (12.7%). [29]

Table.1 Gram Negative Isolates among Clinical Samples

	N	%
Total samples	2576	100%
GNB	899	34.89%

Table.2 Organism wise Distribution of Gram-Negative Bacilli

GNB	N	%
Escherichia coli	315	35.03
***Klebsiella* species**	257	28.58
Pseudomonas aeruginosa	134	14.90
Acinetobacter baumanii	48	5.33
***Citrobacter* species**	46	5.11
Serratia	41	4.56
Enterobacter	26	2.89
Proteus	16	1.77
Salmonella typhi	6	0.66
***Aeromonas* species**	6	0.66
***Providencia* species**	1	0.11
Chryseobacterium gleum	1	0.11
Total	899	100

Table.3 Resistance Pattern of Gram-Negative Bacilli– Organism wise (%)

	***E.coli* (315)**	***Klebsiella* (257)**	***Pseudomonas* (134)**	***Acineto-bacter* (48)**	***Citro-bacter* (46)**	***Serratia* (41)**	***Entero-bacter* (26)**	***Proteus* (16)**	***S. typhi* (6)**	***Aeromonas* (6)**
Amp	100	100	NA	100	100	100	100	100	100	NA
CFX	49.2	66.9	NA	83.8	100	36.6	54.5	75	50	NA
CTX	68.3	84.2	NA	72.7	68.4	31.7	63.6	66.7	50	NA
CFX	67.9	94.7	NA	73	94.7	34.1	63.6	66.7	33.33	NA
CPM	62.5	66.7	41.4	70.3	63.2	34.1	63.6	66.7	66.66	33.3
COT	65.1	56.1	61.6	72.7	47.4	14.6	72.7	75	0	33.3
CIP	73.3	45.6	40.4	62.2	47.4	17.1	68.2	100	16.66	66.7
GEN	32.4	31.07	30.3	62.2	68.4	26.8	40.9	50	100	16.7
AMK	23.2	35	27.3	59.5	52.6	24.4	45.5	33.33	100	16.7
TIGE	13.3	47.6	NA	37.8	52.6	22.9	45.5	75	0	NA
Amox/ Clav	57.8	60.7	NA	75.7	94.7	63.4	72.7	66.7	0	NA
Cef/Sulb	52.7	45.2	50.5	70.3	89.7	19.5	77.3	66.7	0	33.3
PIT	38.4	57.1	23.2	67.6	63.2	26.8	50	33.33	0	16.7
IMP	39	33.9	27.3	56.8	57.9	24.4	31.8	33.33	0	16.7
MRPM	23.2	42.9	18.2	65.2	64.47	29.3	31.8	66.7	0	16.7
Colistin	9.8	10.5	25.3	29.7	31.6	100	31.8	50	0	50
CZM	NA	NA	69.7	NA	NA	NA	NA	NA	NA	66.7
LEVO	NA	NA	99	NA	NA	NA	NA	NA	NA	0

Amp: Ampicillin; CFX: Cefoxitin, CTX: Cephotaxime; CFX: Cefixime; CPM: Cefepime; COT: Cotrimoxazole; CIP: Ciprofloxacin; GEN: Gentamicin; AMK: Amikacin; TIGE: Tigecycline; Amox/ Clav: Amoxicillin Clavulanic acid; Cef/ Sulb: Cefaperazone / Sulbactam; PIT: Piepracillin/ Tazobactam; IMP: Imipenem; MRPM: Meropenem; CZM: Ceftazidime; LEVO: Levofloxacin

Table.4 Resistance of Gram – Negative Bacilli

Antibiotic	%
Ampicillin	100
Cefoxitin	58.3
Cephotaxime	65
Cefixime	65.6
Cefepime	57.4
Cotrimixazole	58.1
Ciprofloxacin	58
Gentamicin	36.7
Amikacin	31.7
Tigecycline	28.6
Amox/Clav	61.9
Cef / Sulb	54.9
PIT	40.7
Imipenem	38.1
Meropenem	28.5
Colisitin	19.4

Table.5 Carbapenem Resistant Strains Distribution – Organism Wise

Organism	%
***Citrobacter* species**	55.8
***Proteus* species**	50
Pseudomonas aeruginosa	22.75
***Klebsiella* species**	20.8
E. coli	20
***Enterobacter* species**	18.2
***Aeromonas* species**	16.7
Serratia	2.4

Table.6 Carbapenem Resistance Distribution: Sample wise

Clinical Sample	%
Urine	16.4
Tracheal Section	40
Swab	14.7
Pus	25.5
Blood	9.1
Sputum	14.7
ET tube / Aspiration	45
CSF	50
Body fluids	50.77

Table.7 MBL producers

Organism	N	%
***Klebsiella* species**	16	29.01
Pseudomonas aeruginosa	15	27.27
***Acinetobacter* species**	14	25.45
E. coli	9	16.36
Enterobacter	1	1.81
Total	55	100

Such variations in the detection rates of MBLs can be attributed to various factors like geographical distribution, infection control practices, methods used to detect MBLs.[8] Pseudomonas has been reported High MBL producer by Yassin *et al.,* (12.7%)[29], Mishra SN *et al.,* (58.28%)[13], Vinita Choudhary *et al.,* (20%)[8] and Dardi Charan Kaur *et al.,* (30%)[19]. Baniya *et al.,*[3] reported highest MBL production among *Acinetobacter* species (22%).

Such disparity in the detection rates and the predominant MBL producing organism brings out the importance and the need for epidemiological surveillance and early diagnostic method for rapid identification of MBL producers, since dissemination of MBL producers poses a therapeutic challenge to treating clinicians as it can hydrolyze carbapenems which are being given as best therapy for invasive diseases, critically ill patients, nosocomial infections.[29]

Hence such early rapid detection of MBL producers in a routine laboratory can ensure optimal patient care and also timely introduction of appropriate infection control measures to curtail the dissemination of MBL producers further ultimately improving the quality of patient care in health care setup.

Carbapenem Resistance has enormous therapeutic implications as well as important in regards to infection control as such strains are responsible for rapid intra institutional spread. MBL strains develop mutations and participate in horizontal MBL gene transfer with other pathogens making early detection and timely implementation of strict infection control practices. Though PCR is highly accurate and reliable method for MBL detection, it is limited to reference laboratories. Early detection in routine laboratory using conventional methods could help avoid treatment failure.

Monitoring of resistant patterns, drafting antibiotic policy and guidelines should be implemented for ultimate better patient management. Regular antimicrobial susceptibility surveillance is essential. Continuous effort to contain drug resistance and MDR organisms is highly required to preserve the effectiveness of antibiotics and prevent medical progress to go back to pre-antibiotic era. [30]

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