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Research Article

Prevalence of Metallo-Beta-lactamase-producing Gram-negative Bacteria from Clinical Isolates in a Tertiary Care Hospital

Sabina Ansari[1], SyedaNazia Fatima[2], Asra Naweed[3]

[1]Assistant professor, Department of Microbiology, Mallareddy Institute of Medical Sciences, Hyderabad, Telangana, India, 500055.
[2]Assistant Professor, Department of Microbiology, Osmania Medical College, Hyderabad, Telangana, India, 500095.
[3]Associate Professor, Department of Biochemistry, Mallareddy Institute of Medical Sciences, Hyderabad, Telangana, India, 500055.

Corresponding Author:

Sabina Ansari
Assistant professor, Department of Microbiology, Mallareddy Institute of Medical Sciences, Hyderabad, Telangana, India, 500055.

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ABSTRACT

Background: Antibiotic resistance is a big concern due to the rising number of gram-negative bacteria that produce Metallobetalactamases (MBL). Appropriate antibiotic therapy and infection control measures depend on early detection. In order to develop an effective infection control plan and antibiotic policy to stop the spread of these bacteria, this study was conducted to ascertain the prevalence of MBL among the clinical isolates of Gram-negative bacteria in our hospital as well as their pattern of antibiotic sensitivity.
Material and Methods: The study was carried out in a teaching hospital with 1,000 beds over the course of two year. Conventional techniques were used to test isolates included in the study for imipenem resistance.Ipenem (IMP)-ethylenediaminetetraacetic acid combination disc test and E test were used to check for MBL generation in isolates exhibiting imipenem resistance.
Results: 20 (13.3%) isolates of 150 gram-negative bacilli produced MBL, while 29 (19.33%) isolates exhibited imipenem resistance. E. coli, Pseudomonas aeruginosa, and Acinetobacterbaumanni were the next most common isolates, after Klebsiellapneumoniae.The majority of MBL exhibited sensitivity to colistin and tigecycline medications and resistance to cephalosporin-generation medications.
Conclusion: The persistent expansion of MBL is problematic and necessitates the use of vigilant surveillance and prudent antibiotic administration, particularly carbapenem, to stop the emergence of this resistance mechanism.

Keywords*: Gram negative bacteria, Imipenem, Metallo-β-lactamases.*

INTRODUCTION

The most common and clinically significant mechanism of carbapenem resistance is the production of metallobetalactamases (MBL) by Gram negative bacteria, which are increasingly being reported from many parts of the world[1].

Aztreonam cannot be hydrolysed by MBL-producing bacteria, although they can hydrolyse a variety of betalactam antibiotics, such as penicillins, cephalosporins, carbapenems, and cephamycins. Furthermore, commercially available betalactamase inhibitors such clavulanate, tazobactam, and sulbactam typically do not neutralise their catalytic activity[2]. These enzymes fall into group 3 of the Bush classification based on their substrate and inhibitor profiles, and Amber class B beta lactamases based on their homology in amino acid sequences[3,4].

Because MBLs need zinc ions to catalyse the hydrolysis of beta-lactam antibiotics, their catalysis is impeded when metal-chelating compounds such as ethylene diaminetetraacetic acid (EDTA) are present[5]. MBLs are encoded by either heterologous genes obtained through horizontal gene transfer (acquired MBLs) or genes that are a component of the chromosome in some bacterial species (resident MBLs)[6]. The more widely distributed MBLs are New Delhi metallobetalactamase (NDM), imipenemase (IMP), and veronaintegron-encoded metallo-beta-lactamase (VIM). MBLs were prevalent in Acinetobacter and Pseudomonas aeruginosa, but they have more recently become more prevalent in

other Enterobacteriaceaemembers. Additionally, isolates that produce[7] MBL are linked to increased morbidity and mortality[8].

Although polymerase chain reaction (PCR) is accurate and dependable, its accessibility is frequently restricted, and as of right now, no standard approach for MBL detection has been established. Numerous non-molecular methods have been investigated, many of which capitalise on the fact that MBLs need zinc or another heavy metal to function and that chelating substances like EDTA, dipicolinic acid, and thiol compounds impede their activity[9]. The E test, double disc synergy method, and combination disc method are phenotypic approaches for MBL detection. Although the MBL-E test is costly, it is thought to be the phenotypic standard method for MBL detection. Both the combined disc test and double disc synergy are inexpensive and easy to do, but the combined disc test is quantitative and has fewer opportunities for subjective mistake than the double disc test[10].

In addition to being a therapeutic issue, the presence of an MBL-positive isolate in a hospital setting raises significant concerns for infection control management. Early identification is crucial for the implementation of appropriate antibiotic therapy and infection control measures due to the global increase in the prevalence and types of MBLs. In order to develop an effective infection control strategy and antibiotic policy to stop the spread of these bacteria, the current study was conducted to ascertain the prevalence of metallo-beta-lactamase among the clinical isolates of Gram-negative bacteria in our hospital as well as their pattern of antibiotic sensitivity.

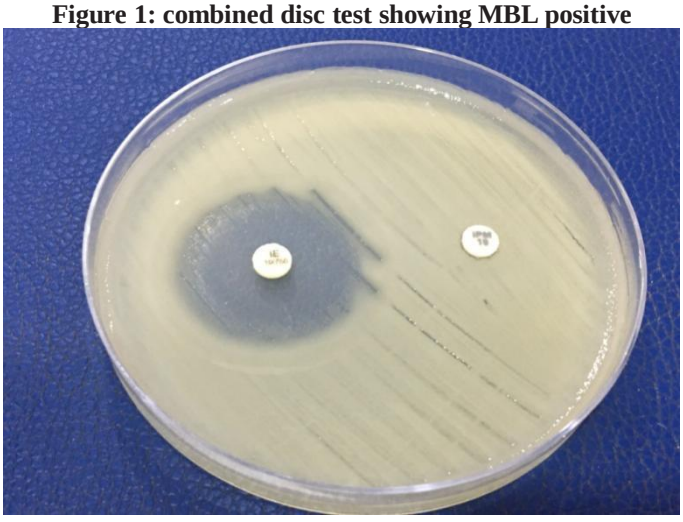
MATERIAL AND METHODS

Blood, urine, pus, sputum, endotracheal (ET) tube aspirates, and wound swabs are examples of routine clinical specimens that were received by the Microbiology department of Deccan College of Medical Sciences, Owaisi Hospital, Hyderabad, Telangana, for a two-year period from January 2019 to December 2020, following ethics committee approval. Standard microbiological procedures were used to treat all the samples[11, 12] and conventional methods were used to identify the isolates to the species level. In accordance with CLSI recommendations, isolates obtained during this time were tested for antibiotic susceptibility using the Kirby Bauer disc diffusion technique[13].

Clinical isolates were screened using a disc containing 10 µg of imipenem. Imipenem screen positive isolates were those with decreased susceptibility to imipenem (zone diameter < 21mm). Two distinct phenotypic techniques, including CDT and E-test, were used to confirm the formation of MBL in imipenem screen-positive isolates.

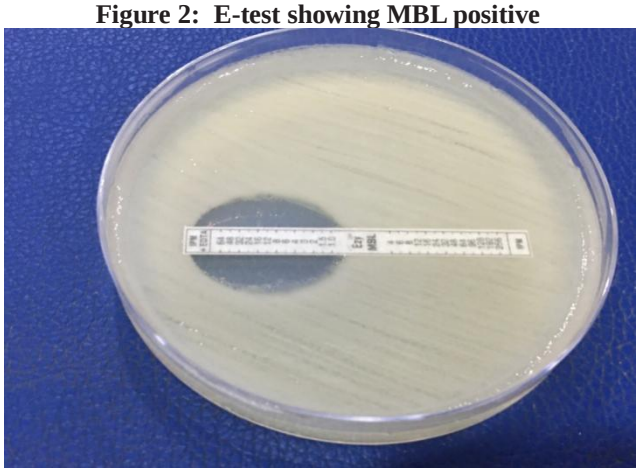
1. IMIPENEM (IMP)-EDTA combination disc test: Muller Hinton agar (MHA) was injected with a lawn culture of the test organism that matched 0.5 McFarland turbidity. On the agar plate, two 10 µg imipenem discs were positioned 30 mm from one another. One imipenem disc was then given 10 µL of a 0.5 M ethylenediaminetetraacetic acid (EDTA) solution. After 16–18 hours of incubation at 37°C, the inhibition zones of the imipenem and imipenem EDTA discs were compared. MBL was defined as a zone size increase of at least 7 mm surrounding the imipenem-EDTA disc as compared to the imipenem disc alone.

Figure 1: combined disc test showing MBL positive



2. E-test: Using a sterile swab stick, a 0.5 McFarland bacterial suspension was applied to MH agar medium. The plates were then incubated at 35 degrees Celsius in air for 16 to 24 hours after an E-test strip with a double-sided seven dilution range of imipenem (4–256 µg/mL) and seven dilution range of imipenem (1–64 µg/mL) with a fixed concentration of EDTA was placed on the surface of the medium.The ratio of imipenem's MIC values to imipenem-EDTA was computed following incubation. The culture is considered MBL positive if the ratio of the imipenem/imipenem+EDTA MIC values is greater than 8 or if the imipenem+EDTA-coated side exhibits a zone while the imipenem-coated side does not.

Figure 2: E-test showing MBL positive



RESULTS

In this investigation, 150 Gram-negative bacterial isolates were collected from 150 inpatients at the Owaisi group of hospitals using a variety of clinical samples, including urine, pus, sputum, blood, and tracheal aspirate. The generation of MBL and the pattern of antibiotic sensitivity in these isolates were investigated. Based on their decreased susceptibility to imipenem by disc diffusion test, 29 isolates (19.33%) out of 150 isolates were first screened for carbapenemase production. Of the 150 isolates, 25% were in the 61–70 age range, and 17% were in the 41–50 age range [Table 1]. Among them, 33.3% were female and 66.6% were male.

Urine had the highest isolation frequency (40%) followed by pus (20%) and blood (20%). Klebsiellapneumoniae was the most prevalent of these isolates (16.4%), followed by Acinetobacterbaumanni (7.69%), Escherichia coli (12.76%), and Pseudomonas aeruginosa (11.4%) [Table 1].

These many isolated Gram-negative bacteria have been found to have a diverse pattern of antibiotic susceptibility [Table 2]. Of these, isolates of Klebsiellapneumoniae exhibited 66.6% susceptibility to piperacillin/tazobactam, 100% susceptibility to colistin, and 77.7% susceptibility to tigecycline. Amikacin and Ciprofloxacin showed just 22.2% and 33.3% susceptibility, respectively. All of the isolates of Klebsiellapneumoniae (100%) shown resistance to ceftriaxone, ceftazidime, and cefepime.

Escherichia coli exhibited 66.6% susceptibility to Tigecycline, 100% susceptibility to Colistin, 66.6% susceptibility to Piperacillin/Tazobactam, and 33.3% susceptibility to Aztreonam and Amikacin. 25% in levofloxacin and ciprofloxacin. Additionally, Gentamycin showed just 16.6% susceptibility.

It was found that Pseudomonas aeruginosa was 50% susceptible to Aztreonam, 75% susceptible to Piperacillin/Tazobactam, and 100% susceptible to Colistin. There was a 25% susceptibility to levofloxacin, ciprofloxacin, and amikacin.

The sensitivity of Acinetobacterbaumanni to tigecycline and colistin was 100%.

Table 1: Organism resistant to Imipenem and producing MBL

Organism	*Klebsiellapneumoniae*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Acinetobacterbaumanni*	Total
Total no. of isolates tested	55	47	35	13	150
Total no. of imipenem resistant isolates	14	9	5	1	29
No. of isolates positive for MBL	9	6	4	1	20
% of total isolates producing MBL	16.4%	12.76%	11.4%	7.69%	13.3%

Table 2: Antimicrobial sensitivity pattern of MBL positive isolates

	Klebsiellapneumoniae N=9 (%)	*Escherichia coli* N=6 (%)	*Pseudomonas aeruginosa* N=4 (%)	*Acinetobacterbaumanni* N=1 (%)
Amikacin	2 (22.2)	2 (33.3)	1(25)	0
Gentamycin	2 (22.2)	1(16.6)	0	0
Cefipime	0	0	0	0
Ceftazidime	0	0	0	0
Ceftriaxone	0	0	-	0
Tigecycline	7 (77.7)	4(66.6)	-	1(100)
Piperacillintazobactam	6 (66.6)	4 (66.7)	3 (75)	0
Aztreonam	3 (33.3)	2(33.3)	2 (50)	-
Ciprofloxacin	3 (33.3)	2 (25)	1 (25)	0
Levofloxacin	3 (33.3)	2 (25)	1 (25)	0
Imipenem	0	0	0	0
Colistin	9 (100)	6 (100)	4 (100)	1 (100)

DISCUSSION

All imipenem-resistant isolates from routine cultures were used in this investigation to determine the formation of MBL using two phenotypic techniques: the combined disc test and the E-test method.

Males (66.6%) were more likely than females (33.3%) to isolate Gram-negative bacteria in the current study, and isolation rates were higher in the age group of 61–70 years (25%) than in females.

Out of 150 gram-negative bacterial isolates in the current study, 19.3% (29/150) were found to be imipenem resistant. These results are comparable to those reported by Kaur J et al[14]. Kumar S et al[15]. andDatta P from North India (7.9%)[16]. According to certain research, the prevalence is extremely high (78.25% by Chakraborty D et al[17]. 62% by PanduranjanS et al[18]. and 43.4% by Diwakar J et al[19]. The incidence of microbes resistant to antibiotics varies widely, according to the results from this research.

According to several research conducted worldwide, the prevalence of carbapenem resistance is 15.2% in Nigeria (Oduyebo OO) and 12.12% in Ethiopia (Legese MH). Okoche D. observed a slightly elevated frequency of 28.6% in Uganda[20].

20/150 (13.33%) of the 29 imipenem-resistant isolates in the current investigation were reported to produce MBL (Table 3). Comparable research by Chaudhary AK et al[21]. found that the prevalence of MBL was 13.6%, while PriyankaMeel's study found that the prevalence was 10%.[22] Of the 20 isolates that produce MBL, 9 (45%) are Klebsiellapneumoniae, followed by 6 (30%) Escherichia coli, 4 (20%) Pseudomonas aeruginosa, and 1 (5) Acinetobacter.

Table 3: prevalence of MBL producing organisms (%)

	Klebsiellapneumoniae	*Escherichia coli*	*Pseudomonas aeruginosa*	*Acinetobacterbaumanni*	Total
Isolates	55	47	35	13	150
MBL	9	6	4	1	20
%	16.4%	12.76	11.4%	7.69%	13.3%

Out of the 55 isolates of Klebsiellapneumoniae, 16.4% produced MBL, which was comparable to the 18.55% reported by Agarwalet al[23]. Klebsiellapneumoniae was the most common MBL producer in our investigation.

The current study's 6 (12.76%) prevalence of MBL-producing E. coli was comparable to a finding by Rao J M et al[24]. that indicated a 10% prevalence. Enwuru N V[25] reported a low prevalence of 5.7%.
The current study's prevalence of MBL-producing Pseudomonas was 4 (11.4%), which was comparable to findings from studies by Deeba Bashir et al[26]. Muneesh Kumar et al[27]. and others that showed 11.66% and 11.11%, respectively. Pratigya P et al[28]. found a 14% frequency in another study (Table 4).

The current study's MBL-producing Acinetobacter prevalence was 1 (7.69%), which is comparable to the 7.14% prevalence reported by P. Pandya[29]. Low prevalence was reported by Mishra K et al who reported 4.8%[30].

Table 4: Occurrence of MBL isolates in other studies

Study	Total isolates	Percentage of MBL			
		Klebsiellapneumoniae	*Escherichia coli*	*Pseudomonas aeruginosa*	*Acinetobacter baumanni*
P Pandya et al [29]	450	7.3%	2.87%	10%	7.14%
Rao J M et al [24]	100	33.3%	10%	30%	16%
Muneesh Kumar et al [27]	176	19.4%	33.3%	11.11%	16.67%
our study	150	16.4%	12.76%	11.4%	7.69%

The majority of imipenem-resistant isolates in the current investigation were found in urine (34.4%), followed by pus (21%), blood (21%), sputum, tracheal aspirates (14%), and sputum (10%). This result is consistent with NagarajS et al[31]. who found that urine made up the majority (42%), followed by respiratory secretions (16%) and wound discharge (18%).Urine accounted for eight (40%) of the MBL-producing specimens in this study, followed by pus four (20%), blood four (20%), sputum four (10%), and tracheal aspirate one (10%). The majority of the MBL-producing bacteria were found in 52.27% urine, 12.5% tracheal aspirates, 9% sputum, 8% wound swabs, 5.7% blood, and 2.3% pleural fluid, according to similar findings reported by Chakraborty D et al. 17. The majority of MBL isolates, however, were found in swab 17 (42.5%), urine 14 (35%), pus 9 (22.5%), and blood 5 (12.5%) in a research by Jain p et al[32]. The large number of MBL producers found in urine and pus in this investigation suggests that patients may have picked up these organisms from the hospital setting. This suggests that the transmission may have been person-to-person, so it is essential that visitors and medical staff wash their hands properly while caring for patients.

Males made up 60% and females 40% of the MBL producers in this study, with the majority being between the ages of 61 and 70. These findings were consistent with those of Chakraborty D et al.17, who demonstrated that the majority of MBL producers were between the ages of 61 and 80, with men making up 66.8% and women 33.2% of the total. MBL-positive organisms' affinity for the elderly may be caused by a general debilitating condition, cellular damage and diseases linked with senility or both. When it comes to sex distribution, the results show that men are far more likely to get infected with MBL germs. This could be because males have aggressive characteristics that make infection by these organisms easier, or females have protective factors.

The antibiotic sensitivity pattern of MBL-producing Klebsiellapneumoniae in the current investigation was 22.2% sensitive to amikacin and 22.2% susceptible to gentamycin, which is consistent with a study by Bora et al[33]. that revealed sensitivity of 20.51% and 15.38%, respectively[34].Klebsiella pneumoniae and Escherichia coli isolates showed no susceptibility to ceftazidime, ceftriaxone, or cefepime, which is consistent with the research done by Bora et al[33].In line with the findings by Bora et al.[33] the current investigation demonstrated 100% sensitivity to colistin against Klebsiellapneumoniae and Escherichia coli.

PriyankaMeel et al.22 found 99% sensitivity in another investigation.The ciprofloxacin and levofloxacin sensitivity of 33.3% of Klebsiellapneumoniae isolates was different from that of 10.25% and 24.39%, respectively, reported by Bora et al.[33]Klebsiella pneumoniae isolates were responsive to tigecycline in 77.7% of cases, compared to 100% in a research by Bora et al.[33]Klebsiellapneumoniae and Escherichia coli demonstrated 33.3% sensitivity to Aztreonam, compared to 12.5% sensitivity reported in a study by PriyankaMeel et al.[22]

Klebsiellapneumoniae and Escherichia coli had 66.6% susceptibility to piperacillintazobactam, compared to 14.8% in a research by P Pandyaet al[29]. Escherichia coli was 33.3% sensitive to amikacin and 16.6% sensitive to gentamycin, which is consistent with a research by Bora et al.[33] that found 20.95% sensitivity to amikacin and 17.07% sensitivity to gentamycin.In contrast to a research by Bora et al.[33] that claimed 100% sensitivity to tigecycline, Escherichia coli demonstrated 66.6% sensitivity to the antibiotic.

Escherichia coli shown a 25% sensitivity to ciprofloxacin and levofloxacin. In contrast, a research by Bora et al.[33] reveals 28.2% sensitivity to levofloxacin and 7.31% sensitivity to ciprofloxacin.

The antibiotic sensitivity pattern of MBL-producing pseudomonas in the current investigation was most responsive to the combination of piperacillin and tazobactam (75%). This supports the findings of studies by Maria et al.[34] and Chaudhary AK et al. 21 that found 76.2% and 78%, respectively. Another study by Mishra SK et al.[30] and Ami Varaiya et al.[35] demonstrates sensitivity of 84% and 92.64%, respectively.Pseudomonasaeruginosa's sensitivity pattern for Amikacin 25% in the current investigation was comparable to that of a study by Nandy S et al.[36], which found 23.53% sensitivity.It was found that pseudomonas aeruginosa was 25% sensitive to ciprofloxacin.In contrast, a research by Anita-E-chand et al.[37] indicates a ciprofloxacin sensitivity of 33.3%.Similar to a research study by Mehta et al.[38].25% of pseudomonas isolates were susceptible to levofloxacin,[39] which is consistent with a study by Nandy S et al.[40] that found 23.53% sensitivity.

In contrast to the study by Nandy S et al.[40], which found 23.53% sensitivity, isolates of pseudomonas showed no sensitivity to cefepime, ceftazidime, or imipenem. According to the study by SmitaSoodet al.[39], all isolates of pseudomonas aeruginosa were susceptible to colistin.

Acinetobacterbaumanni demonstrated 100% sensitivity to tigecycline in the current investigation. However, a research by Pratigya P et al.28 reveals that 85.7% of people are sensitive to tigecycline.

Acinetobacterbaumanni shown 100% sensitivity to colistin, which is consistent with the findings of the Mishra SK et al.[30] investigation.

Twenty of the 29 imipenem-resistant isolates in the current investigation were found to create MBL using the Kirby Bauer disc diffusion method, while nine isolates tested negative for MBL production using both the CD and MBL E tests.[41] Other than MBL production, the cause of these isolates' carbapenem resistance on the Kirby Bauer disc diffusion method may be reduced production of porins, efflux pumps, or Amp C.

It was discovered that the E test and the combined disc were equally sensitive for detecting MBL.However, a straightforward technique like the combined imipenem/imipenem+EDTA method can be employed given the E-test's financial limitations.

The creation of phenotypic tests intended to identify metallo-beta-lactamases will be an essential first step in the large-scale surveillance of these newly developing resistant bacteria. The development of a solid antimicrobial policy in a hospital requires critical reflection and good infection control procedures while prescribing beta lactam medications. Piperacillin, tazobactam, and colistin should be preserved as backup medications and should only be administered to patients with infections brought on by organisms that are resistant to several treatments, particularly strains that produce MBLs.

According to the available data, MBLs are a diverse set of enzymes, which could make it challenging to create compounds that are effective against every MBL. MBLs could present a therapeutic difficulty. The genes of mobile MBLs have the ability to propagate horizontally among Enterobacteriaceae nosocomial strains. It's possible that Pseudomonas aeruginosa and other gram-negative nonfermenters have significantly raised awareness of these enzymes, making them one of the main risks for drug resistance in the 21st century.

The automated systems are unable to distinguish between the different betalactamases, but the phenotypic approaches can since they are simpler to use. Therefore, in situations when molecular approaches are not available, phenotypic methods should be used on a regular basis. The lifespan of carbapenems, which are antibiotics used as a last option, can be prolonged by strict infection control procedures, prudent antibiotic administration, and early detection of MBL transmission.

early detection of an MBL-producing organism outbreak, identification of the type of MBL implicated, and identification of potential mechanisms for resistance dissemination. Regular MBL detection will guarantee the best possible patient care and the prompt implementation of suitable infection control measures.

CONCLUSION

At Owaisi Hospitals, the prevalence of Gram-negative bacteria that produce MBL is 13.3% (20/150). Twenty of the 29 resistant isolates tested positive for MBL on both the CD and E tests. This demonstrates that MBL synthesis is a key mechanism in carbapenem resistance.

In order to stop the emergence of this resistance mechanism, active surveillance and prudent administration of antibiotics, particularly carbapenem, are necessary due to the problematic ongoing spread of MBL. The adoption of a straightforward, trustworthy laboratory technique to identify the generation of MBLs is helpful, especially when carbapenems are recommended or indicated as a treatment regimen. The E-test appears to be the most effective quantitative technique for identifying MBLs.

However, because the E test is costly, a straightforward phenotypic approach such as the Combined Disc test is a recognised substitute. CD is simple, cost-effective, and is equally effective at detecting MBLs.

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