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Prevalence of Metallo-Beta-Lactamase Producers among Non-Fermenting Gram Negative Bacilli

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Abstract:
Background- *Resistance towards Carbapenems and Cephalosporins are increasing among various Non-fermenting gram negative bacilli, which are emerging as potential nosocomial pathogens. This study was undertaken to estimate the prevalence of Metallo-Beta-Lactamase producers among various NFGNB, by phenotypic methods.*
Methodology - *This is a prospective, descriptive study done in Mahatma Gandhi Medical College, Puducherry. It involves 170 Imipenem and/or Ceftazidime resistant or intermediately sensitive Non fermenting Gram negative bacilli, isolated from various non duplicating clinical samples of patients. Those isolates were subjected to IPM/CAZ EDTA Double Disc Synergy Test and IPM/CAZ EDTA Combined Disc and Modified Hodge test to detect the prevalence of MBL production. Final results were obtained by using simple percentage and ratio calculations.*
Results - *Overall prevalence of MBL production among 170 samples was 44.1%. The commonest isolate producing MBL was found to be P.aeruginosa (53.4%). But higher level of resistance was observed in Acinetobacter baumannii (68.4%). Prevalence of MBL producing isolates were seen more commonly in inpatients. More strains were resistant to Ceftazidime than to Imipenem.*
Conclusion*- Prevalence of MBL producing NFGNB is on the rise and so early detection of such isolates should be done for effective hospital infection control. The important limitation of this study is that phenotypic methods were not used to confirm the prevalence rates.*
Statistical analysis used*- Simple percentage and ratio calculation*
Key-words:*Metallo beta lactamase, Non fermenting gram negative bacilli, Pseudomonas aeruginosa, Acinetobacter baumannii*

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I. Introduction

Non fermenting gram negative bacilli are aerobic, non-sporing bacteria, which do not require carbohydrates as their sole energy source. They metabolize carbohydrates by ways other than fermentation.[1]*Psuedomonas aeruginosa, Acinetobacter baumanii* and *Stenotrophomonas maltophila* are some important pathogenic non fermenting bacilli.[2] These groups of organisms are usually isolated from intensive care units or from patients acquiring nosocomial infections or even opportunistic infections in immune compromised patients like in case of burns. Non fermenting gram negative bacilli are now considered as important pathogens in hospital acquired infections.[3, 4]

Carbapenems are being widely used against gram negative bacilli which are resistant to cephalosporins for a while now. But many strains of non fermenters are beginning to show resistance towards carbapenems and other beta lactam drugs.[5] Resistance to carpbapenems by these bacteria is by various mechanisms, among which, production of metallo beta lactamases stand as significant one.[6]

Metallo beta lactamases belong to Ambler class B of metallo enzymes. More than 80 different types of MBL have been identified so far.[7]They contain metal ions in their active site and require zinc for their active functioning and are usually inhibited by chelating agents of different metallic cations, like ethylene diamine tetra acetic acid (EDTA).[8]

There are various phenotypic and genotypic methods for evaluation of MBL production, varying in cost, as well as in sensitivity and specificity. But none of those methods are considered as the gold standard.[9]With a significant rise in incidence of MBL producing strains and without a gold standard method for their identification, these strains have become a major threat in institutions and tertiary care hospitals.[10]

Due to absence of a gold standard method, three different phenotypic methods were included in this study to check the prevalence of MBL production among the non fermenters isolated. The aim of this study was to assess the prevalence of MBL producing NFGNB in our institute.

II. Subjects and Methods

This is a prospective, descriptive study involving Imipenem and/or Ceftazidime resistant Non-fermenting Gram negative bacilli which were isolated from various clinical samples of patients (attending the outpatient and admitted in wards) of Mahatma Gandhi medical college and research institute, Puducherry. The institutional medical Ethics committee had approved this study with a waiver of consent. The study period was from February 2013 to July 2014. Sample size was 170. The sampling procedure used in this study was convenient sampling and it contains only one study group. Repeated samples from the same patient and improperly collected and labelled samples were rejected.

Various clinical samples received for aerobic bacterial culture in the Microbiological laboratory of Mahatma Gandhi Medical College & Research Institure, Puducherry were processed routinely and the non-fermenting gram negative bacilli (*Pseudomonas aeruginosa*, *Acinetobacter baumanii* and other NFGNB) were checked for sensitivity pattern to Imipenem and Ceftazidime. The strains which were resistant or intermediately sensitive to one or both of the above mentioned antibiotics were chosen for the study. Those strains were subjected to three different phenotypic tests namely EDTA combined disc test, EDTA double disc synergy test and Modified Hodge test for detection of Metallo beta lactamase production. The Patient and sample details, organism isolated, antibiotic sensitivity pattern and the results of all the specific tests done for identification of metallo beta lactamase were noted and entered in the Microsoft excel sheet. The prevalence of Non-fermenting Gram negative bacilli producing Metallo beta lactamase was finally calculated. The statistical methods used in this study are simple percentage and ratio calculation.

Among the 170 patients, 98 (57.6%) were males and 72 (42.3%) were females. Thirty two (18.8%) patients out of the 170 were out-patients and 138 (81.2%) were admitted in various wards. Samples were received from various departments in the hospital. Maximum samples were from the Department of General Surgery, followed by Obstetrics & Gynaecology. Among the samples received, most common sample was pus, followed by urine. Other samples were sputum, ear swab, endotracheal tube tip, aspirates, tissue, wound swab, central line catheter tip, synovial fluid and groin swab.

Out of 170 isolates, 97 (57%) were *Pseudomonas aeruginosa*, 54 (31.8%) were other non fermenting gram negative bacilli and 19 (11.2%) were *Acinetobacter baumannii.*

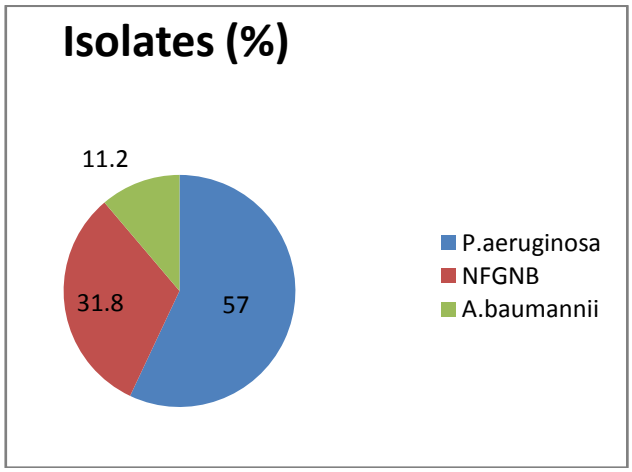


Figure 1: *Various organisms isolated*

Sensitivity patterns to Imipenem and Ceftazidime

Pseudomonas aeruginosa

Antibiotic sensitivity testing for Imipenem by Kirby Bauer disc diffusion method of all 97 test isolates of *Pseudomonas aeruinosa* showed 7 (7.2%) resistant, 11 (11.3%) intermediately sensitive and 79 (81.5%) sensitive results. For Ceftazidime, 51 (52.6%) were resistant, 45 (46.4%) were intermediately sensitive and 1 (1%) was sensitive. Out of 97, 7 (7.2%) isolates were resistant to both Imipenem and Ceftazidime.

Other NFGNB

Antibiotic sensitivity testing for Imipenem by Kirby Bauer disc diffusion method of all 54 test isolates of other NFGNBshowed 10 (18.5%) resistant, 1 (1.9%) intermediately sensitive and 43 (79.6%) sensitive results. For Ceftazidime, 29 (53.7%) were resistant, 25 (46.3%) were intermediately sensitive and none were sensitive. Out of 54 isolates, 10 (18.5%) isolates were resistant to both Imipenem and Ceftazidime.

Acinetobacter baumannii

Antibiotic sensitivity testing for Imipenem by Kirby Bauer disc diffusion method of all 19 test isolates of *Acinetobacter baumanii* showed 7 (36.9%) resistant, 4 (21%) intermediately sensitive and 8 (42.1%) sensitive results. For Ceftazidime, 16 (84.2%) were resistant, 3 (15.8%) were intermediately sensitive and none were sensitive. Out of 19 isolates, 7 (36.9%) were resistant for both Imipenem and Ceftazidime.

III. Results

Prevalence of MBL among various isolates

Pseudomonas aeruginosa:

Results to tests with Imipenem

The 18 *Pseudomonas aeruginosa* isolates which were either resistant or intermediately sensitive to Imipenem were tested for Metallo beta lactamase production by EDTA double disc synergy test, EDTA combined disc test and Modified Hodge test with Imipenem(10µg). The results are as follows.

Table 1: *Results of P.aeruginosa with Imipenem based MBL detection tests*

Tests with Imipenem on *P.aeruginosa* Total isolates - 18	**Positive (%)**
IPM+EDTA DDST	12 (66.6)
IPM+EDTA CDT	12 (66.6)
Modified Hodge test	14 (77.7)

Results to tests with Ceftazidime

The 96 *P.aeruginosa* isolates which showed resistance or intermediate sensitivity to ceftazidime were subjected to EDTA double disc synergy test and EDTA combined disc test with Ceftazidime(30µg).

Table 2: *Results of P.aeruginosa with Ceftazidime based MBL detection tests*

Tests with Ceftazidime on *P.aeruginosa* Total isolates - 96	**Positive (%)**
CAZ+EDTA DDST	39 (40.6)
CAZ+EDTA CDT	39 (40.6)

Results to tests with both antibiotics

Out of the total 97 isolates, 12 (12.3%) isolates of *P.aeruginosa* were positive for MBL production when tested with both Imipenem and Ceftazidime, at least by one method. Out of the 7 isolates which were resistant for both antibiotics, 6 (85.7%) were MBL producers.

Other NFGNB

Results to tests with Imipenem

Out of 54 NFGNB, the 11 isolates which were either resistant or intermediately sensitive to Imipenem were tested for Metallo beta lactamase production by EDTA double disc synergy test, EDTA combined disc test and Modified Hodge test with Imipenem(10µg). The results are as follows.

Table 3: *Results of other NFGNB with Imipenem based MBL detection tests*

Tests with Imipenem on NFGNB Total isolates - 11	**Positive (%)**
IPM+EDTA DDST	11 (100)
IPM+EDTA CDT	11 (100)
Modified Hodge test	11 (100)

Results to tests with Ceftazidime

The 54 other NFGNB isolates which showed resistance or intermediate sensitivity to ceftazidime were subjected to EDTA double disc synergy test and EDTA combined disc test with Ceftazidime(30µg).

Table 4: *Results of other NFGNB with Ceftazidime based MBL detection tests*

Tests with Ceftazidime on other NFGNB Total isolates - 54	**Positive (%)**
CAZ+EDTA DDST	22 (40.7)
CAZ+EDTA CDT	22 (40.7)

Results to tests with both antibiotics

Out of the total 54 isolates, 11 (20.3%) isolates of NFGNB were positive for MBL production when tested with both Imipenem and Ceftazidime, at least by one method. Out of the 10 isolates which were resistant to both antibiotics, 9 (90%) were positive for MBL production.

Acinetobacter baumanii

Results to tests with Imipenem

Out of the 19 *Acinetobacter baumannii* isolates, the 11 isolates which were either resistant or intermediately sensitive to Imipenem were tested for Metallo beta lactamase production by EDTA double disc synergy test, EDTA combined disc test and Modified Hodge test with Imipenem(10µg). The results are as follows.

Table 5: *Results of Acineobacter baumannii with Imipenem based MBL detection tests*

Tests with Imipenem on *A.baumannii* Total isolates – 11	**Positive (%)**
IPM+EDTA DDST	10 (90.9)
IPM+EDTA CDT	10 (90.9)
Modified Hodge test	11 (100)

Results to tests with ceftazidime

The 19 *Acinetobacter baumannii* isolates which showed resistance or intermediate sensitivity to Ceftazidime were subjected to EDTA double disc synergy test and EDTA combined disc test with Ceftazidime(30µg).

Table 6: Results of Acineobacter baumannii with Ceftazidime based MBL detection tests

Tests with Ceftazidime on *A.baumannii* Total isolates – 19	**Positive (%)**
CAZ+EDTA DDST	13 (68.9)
CAZ+EDTA CDT	13 (68.9)

Results to tests with both antibiotics

Out of the total 19 isolates, 10 (52.6%) isolates of *Acinetobacter baumannii* were positive for MBL production when tested with both Imipenem and Ceftazidime, at least by one method. Of the 7 isolates resistant for both Imipenem and Ceftazidime, all 7 (100%) were MBL producers.

Statistical analysis of the results:

Out of the 170 isolates, total of 75 (44.1%) isolates were found to be MBL producers. Among the 75 positive isolates, only 4 were isolated from outpatients. Rest 71 cases were from patient admitted in various wards. Out of all the 75 positive isolates, 45 were from samples collected from males and 30 were isolated from samples collected in females. Out of 75 positive isolates, 44 were isolated from pus samples and 19 from urine samples.

Out of 97 *Pseudomonas aeruginosa* isolates, 40 (41.2%) were MBL producers. Among 54 NFGNB, 22 (40.7%) were found to be positive. In total of 19 *Acinetobacter baumannii* isolates, 13 (68.4%) were found to produce MBL.

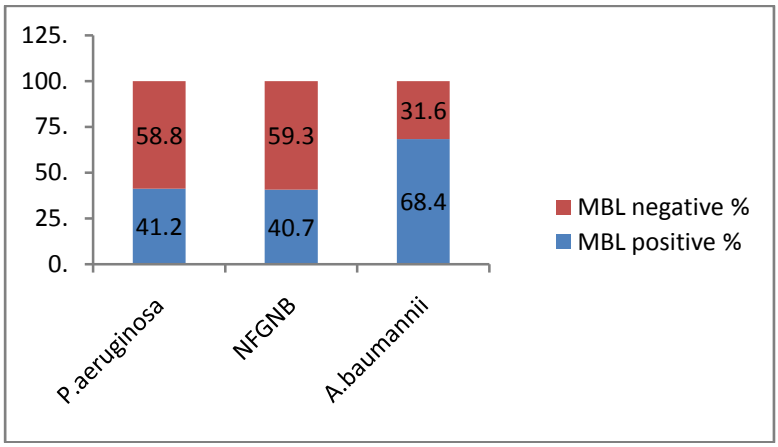


Figure 2: *Prevalence of MBL producers with respect to individual isolate*

Among the 75 positive isolates, 40 (53.4%) were *Pseudomonas aeruginosa,* 22 (29.3%) were other NFGNB and 13 (17.3%) were *Acinetobacter baumannii.*

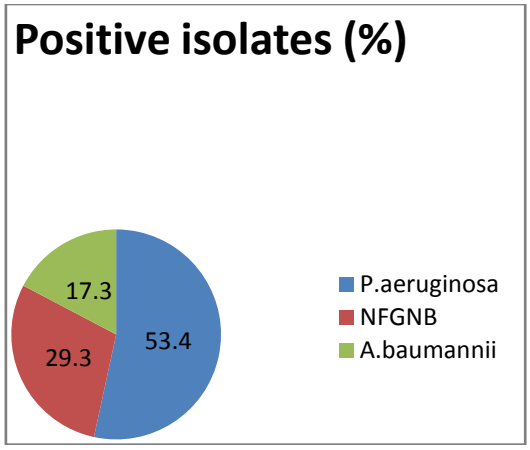
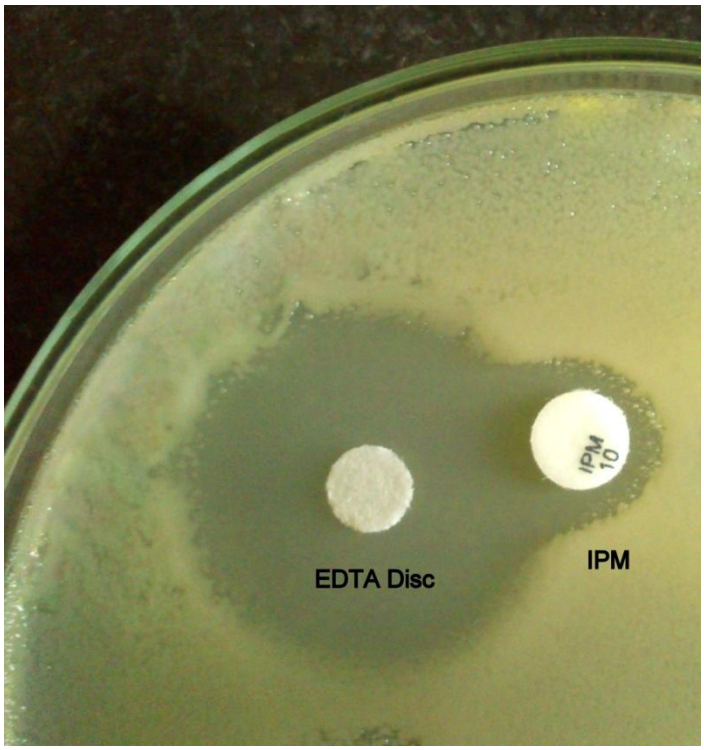
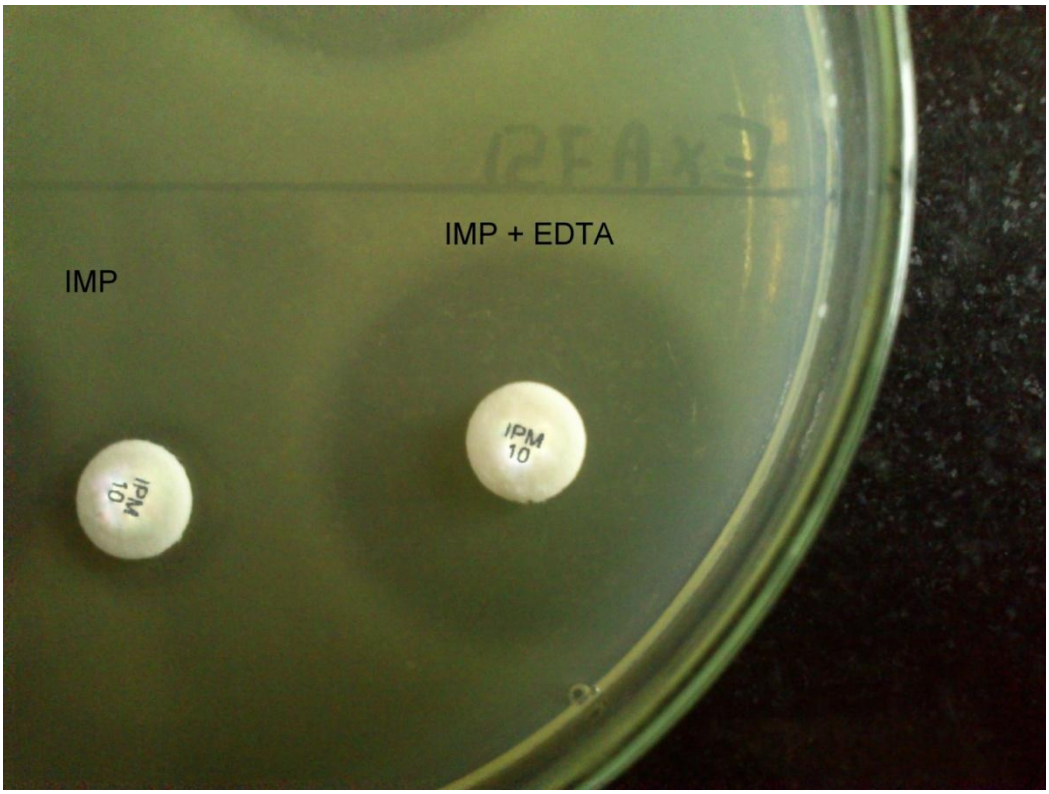
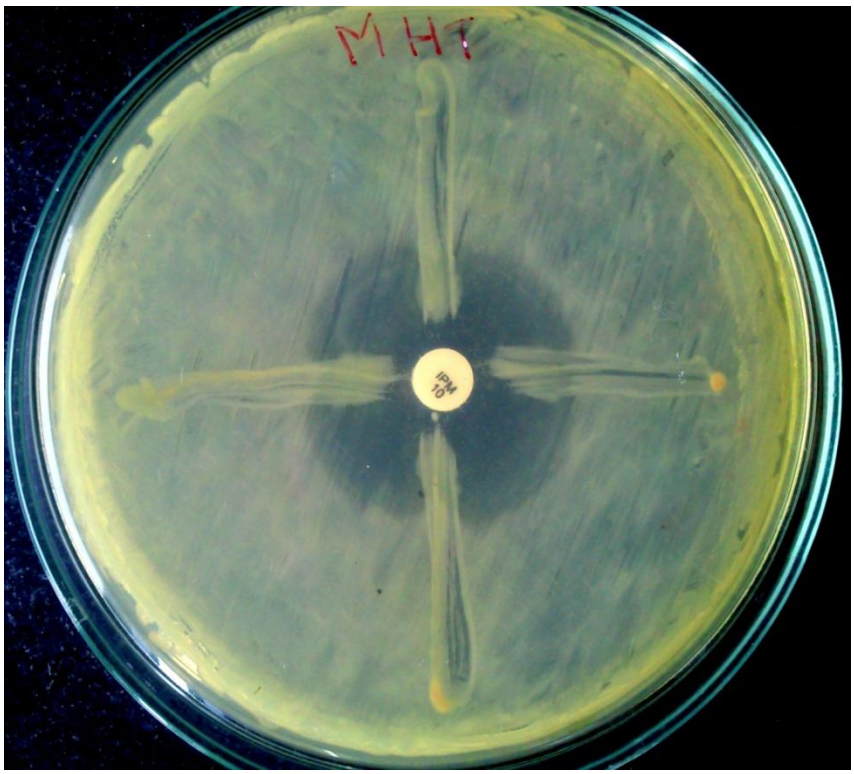
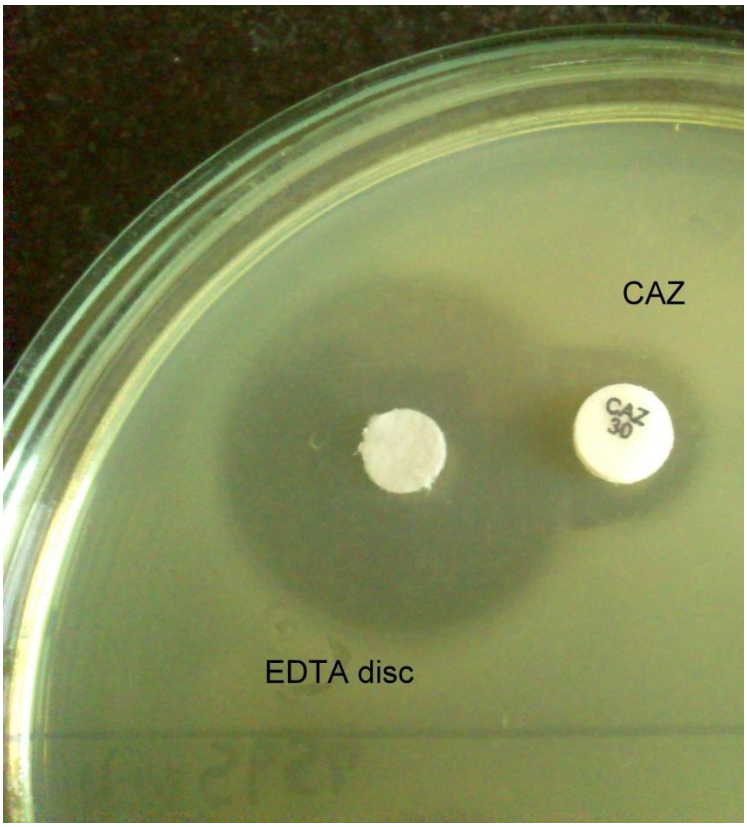


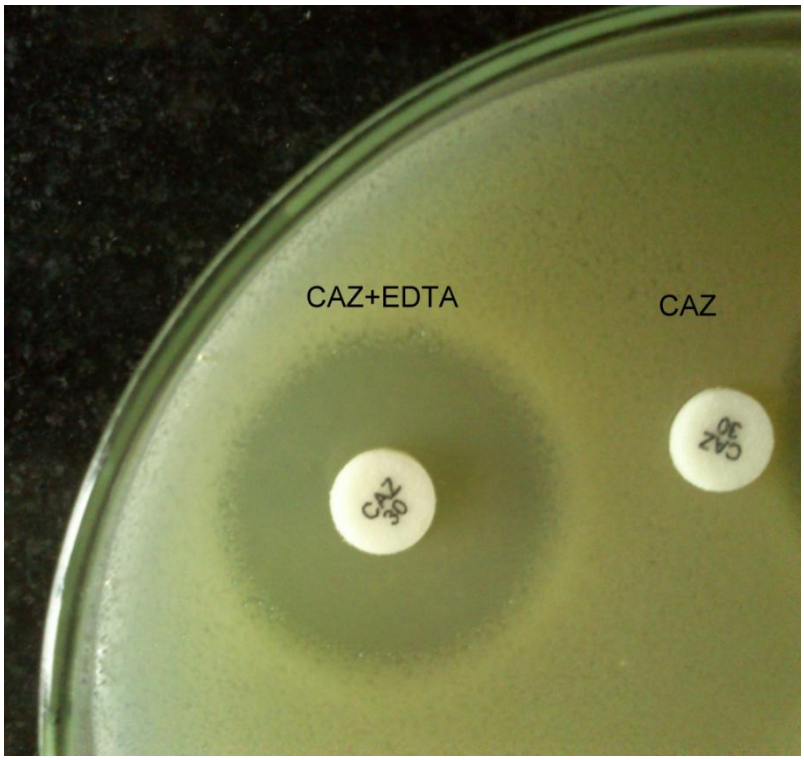
Figure 3*: Percentage of positive isolates*




IMP + EDTA
IMP
IPM 10
IPM 10


MHT
IPM 10


CAZ
CAZ 30
EDTA disc


CAZ+EDTA
CAZ
CAZ 30
CAZ

IV. Discussion

Gender- In our study, males show a higher prevalence rate (60%) of MBL production than females. Similar results have been obtained in study conducted by Senthamarai et al and De et al. This is probably due to their exposure to soil, air and environment for a longer while than females. Other reasons that could be attributed to this finding are their nature of occupation and personal hygiene.[11, 12]

Nature of patients- Surprisingly in our study, 95% of the MBL positive organisms were isolated from patients who were inpatients. This result is in concordance with the studies conducted by Umadevi et al and Gupta et al. The probable reason for this finding could be because NFGNB are emerging as important pathogens, commonly associated with Hospital Acquired Infections in the past few decades.[13, 4]

Intensive Care Units- Out of 13 samples from various ICUs, 11 samples grew MBL producing strains of NFGNB in our study. This result goes hand in hand with studies by Kali et al and Babu et al. Device associated infections like Ventilator Associated Pneumonia, Catheter associated UTI, Central venous catheter associated blood stream infections are more prone to occur in patients who are under intensive care units. This may be the reason responsible for this finding. Longer duration of stay in hospitals can also be an associative factor.[14, 15]

Department- Maximum number of samples received in our study was from the Department of General Surgery. Similar observations were made by Kali et al and Umadevi et al. Patients with wound infections are managed by the surgical departments. Post operative wound infections are also common in such departments. These may be the reasons for the above mentioned finding.[13, 14]

Sample- In our study, the commonest sample received was pus, followed by urine. Amudhan et al and Arunagiri et al claim similar finding. The reason that could be attributed to this finding is that post operative wound infections and catheter associated urinary tract infections are common nosocomial infections and NFGNB are usually nosocomial pathogens.[16, 17]

Isolate- The commonest organism isolated in our study was *Pseudomonas aeruginosa* (57%). *Acinetobacter baumannii* (11.2%) was lesser in number. Similar results were obtained in study conducted by Noyal et al in Puducherry.[18] But studies done by De et al and Gupta et al in Mumbai and Chandigarh respectively, say *Acinetobacter baumannii* was more common.[12, 4] This may because of regional prevalence percentage of various bacteria or it can imply that *Pseudomonas aeruginosa* more commonly associated with HAI than *Acinetobacter baumannii.*

Susceptibility to Imipenem and Ceftazidime- Our study showed more number of isolates resistant to Ceftazidime than to Imipenem. This result is concordant with studies done by Buchunde et al, Behera et al and Agarwal et al.[19, 10, 2] This may imply that Non fermenters exhibit a higher degree of resistance towards Cephalosporins than Carbapenems.

Overall prevalence of MBL producers- The overall prevalence of Metallo beta lactamase producing Non fermenters in our study was found to be 44.1%. This result goes hand in hand with studies by Owlia et al in Iran, Vinitha et al in Nainital and Noyal et al in Puducherry.[20, 21, 18] Some studies like Gupta et al and Safari et al[1, 22] show prevalence as high as 86% and 99% in contrast with studies by Mishra et al and Agarwal et al[23, 2] which show prevalence of only 3% an 8% respectively. This implies that prevalence of MBL production varies from region to region.

Prevalence of MBL producing *P.aeruginosa*

Among Imipenem resistant strains- In our study, Prevalence of MBL producing *P.aeruginosa* strains among Imipenem resistant strains was 78%. This is in concordance with the studies done by Kali et al[14], Pitout et al[24] and Yilmaz et al[25] which showed 73% , 70% and 74% MBL producing Imipenem resistant *P.aeruginosa* strains respectively. But studies done by Manoharan et al[26], Samuelson et al[27] and Franklin et al[2] with similar isolates, gave only 33%, 2% and 21% positivity respectively. This may be due to the reason that the former studies employed only phenotypic methods while the latter ones used both phenotypic and genotypic methods.

Among Ceftazidime resistant strains- The prevalence of MBL producers among Ceftazidime resistant *P.aeruginosa* strains was 41% in our study. A study by Bogiel et al[9] in Poland shows a similar result of 43%. But a similar study, using similar isolates and methods, conducted in our institute by Umadevi et al[13] shows 65% prevalence. This discordance implies the need of genotypic tests, to confirm MBL production.

Among strains resistant to both drugs- The prevalence of MBL producers among the *P.aeruginosa* isolates which were resistant to both Imipenem and Ceftazidime was 86% in our study. This result is in concordance with the study done by Kali et al[14], implying that Multi drug resistant *P.aeruginosa* are more prone to produce MBL.

Prevalence of MBL producing other NFGNB

The prevalence of MBL producers among other NFGNB was found to be 40.7%. This result is in concordance with the study conducted by Vinitha et al[21] which shows 36% MBL producers. But it is in discordance with the study done by Gupta et al[1] which gives a 86% positivity for MBL production.

Prevalence of MBL producing *A.baumannii*

Among Imipenem resistant strains- Out of 11 strains of Imipenem resistant *Acinetobacter baumannii* strains, 10 were found to be MBL producers in our study. This finding is similar to a study conducted by Shazeera et al[28], where in all Impenem resistant *A.baumannii* strains were MBL positive.

Among Ceftazidime resistant strains- The prevalence of MBL producing Ceftazidime resistant strains of *A.baumannii* in our study was 69%. This result goes hand in hand with a study conducted by Amudhan et al[16] in Chennai. They have reported 65% positivity for MBL production by Ceftazidime resistant *A.baumannii.*

Among strains resistant to both drugs- A positivity of 100% was seen for MBL production among *A.baumannii* isolates which were resistant to both Imipenem and Ceftazidime. This finding is concordant with a study conducted by Shazeera et al[28], where all the *A.baumannii* strains which were resistant to Imipenem and Ceftazidime were MBL producers.

Susceptibility pattern among MBL positive isolates

Among Imipenem resistant strains- In our study, most of the Imipenem resistant NFGNB were found to be resistant to Ceftazidime and other Cephalosporins also. But they were sensitive to antibiotics like Piperacillin-Tazobactum, Cefaperazone-Sulbactum, Polymyxin and Colistin. This finding is concordant with various other studies like Chako et al, Carvalo et al, Amudhan et al.[29, 30, 16]

Among Ceftazidime resistant strains- In our study, most of the Imipenem resistant strains were resistant to Cephalosporins too. But the vice versa was not observed. So Imipenem can be used as treatment option for Ceftazidime resistant NFGNB strains. Other than Imipenem, Polymyxin therapy in combination with Aminoglycosides can also be used, as the isolates in our study were sensitive to Piperacillin-Tazobactum and Cefaperazone-Sulbactum. Similar results were observed by Umadevi et al.[13]

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