

Prevalance of Metallo-Beta–Lactamase Producing Gram Negative Bacteria in Patients of Intensive Care Units of Tertiary Care Hospitals and Its Sensitivity to Carbapenem Antibiotics.

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Abstract:

Metallo-beta-lactamases (MBLs) are being reported with increasing frequency and from several countries worldwide and are becoming the prevalent and most clinically significant determinants of carbapenem resistance^(2,13). The New Delhi Metallo-beta-lactamase commonly referred to as Superbug NDM 1⁽⁴⁾, is an enzyme which develops immunity in bacteria to commonly used beta-lactam antibiotics (β lactam)⁽²¹⁾. Carbapenems resistance-conferring gene is spreading in India because of an irrational use of antibiotics^(11, 23, 26). For a long time metallo-beta- lactamases were considered interesting but clinically unimportant^(25,30). In this research project an effort was made to study the prevalence rate of metallo-beta–lactamase producing bacteria following standard methods of isolation and identification techniques for bacterial species from clinical samples in relation to MBL producing bacterial infections. Samples were collected from intensive care unit patients of tertiary care hospitals^(7,20). The clinical outcome and sensitivity to carbapenem antibiotics was studied after antimicrobial treatment. Our finding showed that there is a need for a proper surveillance to detect MBL producing bacterial species and avoid irrational use antibiotics to its prevent spread.

Keyword :

Metallo-beta-lactamas es, carbapenem antibiotics, Imipenem, Meropenem, antibacterial drugs.

Introduction:

The Carbapenems are beta-lactum antibacterial drugs with a broad spectrum of activity⁽¹⁰⁾. Imipenem were often susceptible to degradation by the enzyme dehydropeptidase-1 located in renal tubules^(3, 12). Meropenem, ertapenem, doripenem have increased stability to DHP-1^(22, 27). Carbapenems act by inhibiting bacterial cell wall synthesis by binding to penicillin binding proteins (PBPs) thus inactivating it⁽⁵⁾. The widespread use of carbapenems has resulted in the emergence of a new antibiotic resistance mechanism which is posing threat to medical field^(1, 18, 24). Bacteria acquire resistance to carbapenem by developing structural change in PBPs⁽⁹⁾. Thus acquiring metallo beta lactamases enzyme which degrade carbapenems, or changing their permeability of membrane^(6,8). Treatment would be guided by the antibiotic susceptibility patterns of the bacteria⁽⁴⁾. Gram negative bacteria are the major common isolates in various clinical samples⁽¹⁶⁾ and multidrug resistance bacteria responsible for increasing number of nosocomial infection and community acquired infection^(19, 15). Hence an effort was made to study the prevalance rate and the sensitivity of particular metallo beta lactamase producing gram negative bacteria from ICU patients.

Aim of Investigation:

- In this experiment we studied the prevalence, following standard methods of isolation and identification techniques of these bacteria from clinical materials in relation to MBL producing bacterial infections
- Thus this study was aimed to investigate the impact of this highly virulent group of bacteria in this city.
- This study was aimed to find out the characteristics and nature of MBL producing bacterial infection towards the patients.

Materials and Methods:

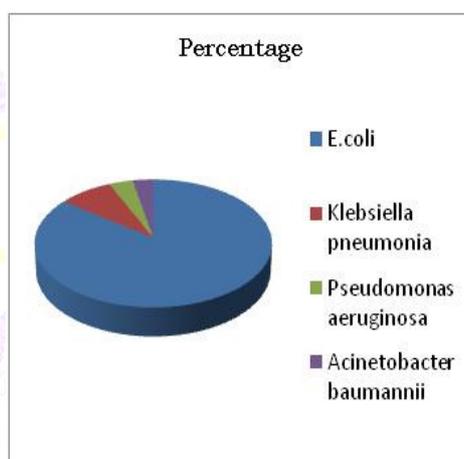


- ◆ **Sample collection:** Urine were collected and examined by routine microscopic examination by wet mount of urine sediments. Out of 350 samples 214 samples show growth of gram negative bacteria which were further identified upto species level by standard CLSI guidelines^(27,29).
- ◆ **Study of MBL production by**
 - Combined disc diffusion method^(14,17)
 - Double disc synergy test
 - Study of biochemical identification parameters of isolated bacteria.
 - General prevalence of MBL positive bacteria in Nagpur city.
 - Antibioqram of MBL producing and non producing bacterial strains were studied⁽²⁸⁾.

Observation and Results:

Table 1: Gram negative bacteria isolated during the study.

Gram negative bacteria	Frequency	
	Number	Percentage
IS-1	72	33.64
IS-2	47	21.96
IS-3	33	15.42
IS-4	29	13.55
IS-5	18	8.41
IS-6	11	5.14
IS-7	2	0.93
IS-8	2	0.93



Antibiotic tested	IS-1 (72)		IS-2 (47)		IS-3 (33)			IS-4 (29)		IS-5 (18)		IS-6 (11)		IS-7 (2)		IS-8 (2)	
	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	
Imipenem	57	15	33	14	26	07	23	06	13	05	04	07	01	01	00	02	
Meropenem	42	30	37	10	28	05	21	08	11	07	03	08	00	02	00	02	
Doripenem	23	49	27	20	21	12	20	09	12	06	03	08	00	02	00	02	
Ertapenem	26	46	23	24	24	09	25	04	16	02	02	09	01	01	01	01	
Ceftazidime	27	45	27	20	25	08	23	06	16	02	05	06	00	02	01	01	
Ceftriaxone	24	48	20	27	21	12	27	02	14	04	09	02	02	00	01	01	
Aztreonam	31	41	31	16	23	10	23	06	11	07	09	02	00	02	02	00	
Cefixime	39	33	34	13	20	13	22	07	14	04	07	04	00	02	01	01	
Tigecycline	22	50	19	28	26	07	25	04	12	06	09	02	01	01	01	01	
Ciprofloxacin	20	52	21	26	23	10	21	08	12	06	08	03	00	02	01	01	
Levofloxacin	18	54	22	25	32	01	20	09	13	05	06	05	01	01	01	01	
Amikacin	18	54	N/A	NA			22	07	17	02	06	05	02	00	NA		
Gentamicin	22	50	21	26	21	12	26	03	12	06	08	03	01	01	02	00	
Cotrimoxazole	26	46	23	24	25	08	28	01	11	07	05	06	01	01	01	01	

Where: IS-1 *E.coli*, IS-2 *Klebsiella pneumoniae*, IS3- *Pseudomonas aeruginosa*, IS4-*Acinetobacter baumannii*, IS5- *Proteus mirabilis*, IS6- *Proteus vulgaris*, IS-7*Providencia rettgeri*, IS-8 *Citrobacter freundii*.



Figure 1: Combined Disc Diffusion test, Cefixime disc (5 mcg).

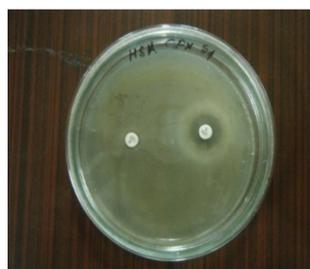


Figure 2: Combined Disc Diffusion test Meropenem disc.



Figure 3: Combined Disc Diffusion test Cefixime disc (5 mcg).



Figure 4: Combined Disc Diffusion test Meropenem disc (10 mcg).

Discussion:

Following bacteria were confirmed up to species level. Out of 214 gram negative bacilli, *E. coli* was most common isolates. (n =72). There is a significant prevalence of MBL producing Gram negative bacteria in patients of intensive care units. Out of total Gram negative strains isolated were, *Escherichia species*, *Pseudomonas species*, *Proteus species*, *Klebsiella species*, *Citrobacter species* respectively. *Escherichia species*, *Proteus species*, *Citrobacter species* were found to be Metallo-beta lactamase producing. In case of MBL positive strains *Escherichia species*, *Proteus species*, *Citrobacter species* were Multi Drug Resistant (MDR), these were resistant to third generation cephalosporins Cefixime and Ceftazidime and Imipenem and Meropenem.

It was found Mortality rate is higher in case of patients infected with Metallo Beta Lactamase producing bacteria as compared to that which were infected with MBL negative bacteria⁽¹⁹⁾. MBL producing bacteria cause more serious type of disease that is non treatable or may lead to death.

Conclusion:

Rapid detection of metallo-lactamase (MBL) producing gram-negative pathogens is critical to prevent their widespread dissemination. Surveillance to monitor the emergence of resistance to these agents as well as implementation of infection control measures should be strengthened. MBL inhibitors are urgently needed. Randomized controlled trials are required in order to evaluate the available therapeutic regimens, including treatment combinations. In a recent comparison of Imipenem and Meropenem, Ceftazidime, for bacteremia involving an MBL-producing *K. pneumoniae*, Imipenem produces the better outcome. Carbapenems resistance-conferring gene is spreading in India because of an irrational use of antibiotics. The emergence of Metallo-beta-lactamases is due to the widespread misuse of antibiotics in the Indian healthcare system, stating that Indian doctors have "not yet taken the issue of antibiotic resistance seriously" and noting little control over the prescription of antibiotics by doctors and even pharmacists.

The *Times of India* states that there is general agreement among experts that India needs both an improved policy to control the use of antibiotics and a central registry of antibiotic-resistant infections.

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