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"RETROSPECTIVE ANALYSIS OF OUTCOMES IN PATIENTS GROWING GRAM NEGATIVE MULTIDRUG RESISTANT (MDR) ISOLATES FROM A TERTIARY CARE CENTRE"

Anaesthesiology

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ABSTRACT

Introduction- Resistant strains of *Enterobacteriaceae and nonfermenters* have emerged recently due to many variable reasons with the use of carbapenems. Resistance to carbapenems is mostly due to enzymes called carbapenemase. Various studies have been conducted to evaluate the prevalence of carbapenemase producers.

Aims- The present retrospective study was conducted to determine the prevalence, resistance pattern and mortality of carbapenemase producers in our tertiary care centre.

Materials and Methods- Samples were collected from patients admitted to the hospital wards and ICU. Gram negative isolates were screened out from all clinical samples sent to microbiology laboratory. Only Class A carbapenemase, Class B metallo beta-lactamase (MBL) and extended spectrum beta-lactamase (ESBL) isolates were considered for this retrospective analysis.

Results- A total of 1344 organisms were isolated in this study. Of those 1344 strains, 995 strains were gram negative bacteria and 349 strains were gram positive bacteria. The prevalence of *Enterobacteriaceae* and nonfermenting strains producing class A carbapenemase, class B MBL type carbapenemase and ESBL was 34.17% (340/995), 11.35% (113/995) and 7.8 % (78/995) respectively. The 46.63% (464/995) strains were other gram negative bacteria. The observed mortality rates among patients with class A carbapenemase, class B MBL and ESBL were 19.41% (66/340), 31.8% (36/113) and 12.8% (10/78) respectively.

Conclusion- The prevalence of class A carbapenemase and MBL producers is high in our tertiary care setup. Associated mortality, along with duration of ICU stay and number of ventilator days, is also high.

KEYWORDS

Gram negative MDRO, *Enterobacteriaceae,* non-fermenters, class A carbapenemase, class B MBL, ESBL

Introduction:

In 2011, WHO declared, "Combat drug resistance: no action today, no cure tomorrow." In recent years, strains of multidrug resistant organisms have quadrupled worldwide. Presently, antimicrobial resistance (AMR) poses a major threat to patients treatment as it leads to increased morbidity and mortality, increased hospital stay, and severe economic loss to the patient and nation. The clinical isolates such as *Pseudomonas aeruginosa*, *Methicillin Resistant Staphylococcus aureus (MRSA)*, *Enterococci* especially *Vancomycin Resistant Enterococci* (VRE), and members of the family *Enterobacteriaceae*, for example, *Klebsiella pneumoniae*, *E. coli*, and *Proteus sp*., rapidly develop antibiotic resistance and spread in the hospital environment. In the last two decades, there were so much of an increase of infectious diseases that the standard of public health in many parts of the world has become equivalent to pre-antibiotic era.

As per standardized international terminology created by the European Centre for Disease Control (ECDC) and the Centre for Disease Control & Prevention (CDC), Atlanta, the multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) bacteria have been well defined. Multidrug resistant (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively drug resistant (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e.bacterial isolates remain susceptible to only one or two antimicrobial categories). Pandrug resistant (PDR) was defined as non-susceptibility to all agents in all antimicrobial categories.[1]

Carbapenems are widely regarded as the drugs of choice for the treatment of severe infections caused by extended-spectrum betalactamases producing *Enterobacteriaceae*. The emergence of carbapenem-resistant organisms is worrisome since antimicrobial treatment options are very restricted. Resistance of organisms to carbapenem, imparted by the presence of carbapenemase, is an emerging global health problem with high morbidity and mortality. Carbapenemases are a large and diverse family of microbial enzymes that hydrolyze not only carbapenems but also other beta-lactam antibiotics. Detection of carbapenemase-producing organisms in the clinical microbiology laboratory is a matter of major importance for the choice of appropriate therapeutic schemes and the implementation of infection control measures.[2] Inappropriate and indiscriminate use of antibiotics is one of the major causes of virulence and the drug-resistance of *Enterobacteriaceae* and nonfermentors across the world. Classification of beta-lactamases can be defined according to two properties, functional and molecular. The functional classification by Bush et al. proposes to classify the known beta-lactamases into four major functional groups (Groups 1-4) according to the group specific substrate or inhibitor profiles. Group 2 is differentiated into multiple subgroups. The updated system comprises Group 1 (Class C) cephalosporinases; Group 2 (Classes A and D) broad-spectrum, inhibitor resistant, and ESBLs and serine carbapenemases; and Group 3 metallo beta-lactamases (MBLs). In this functional classification scheme, carbapenemases are found primarily in Groups 2 and 3. The second, is a less commonly encountered group of beta-lactamases, or Class B beta-lactamases. These use a divalent transition metal ion, most often zinc, linked to a histidine, or cysteine residue. The divalent transition metal ion reacts with the carbonyl group of the amide bond of most penicillins, cephalosporins, and carbapenems but not monobactams.

Based on molecular studies, carbapenem-hydrolyzing enzymes can be classified into two groups. Serine enzymes possess a serine moiety at the active site. MBLs require divalent cations, usually zinc, as metal cofactors for enzyme activity. The serine carbapenemases belong to Class A or Class D enzymes. They usually result in carbapenem resistance in *Enterobacteriaceae* or *Acinetobacter spp*.[2]

Infections caused by carbepenamases have been associated with increased cost and length of hospital stay as well as frequent treatment failures and death.[3,4]

The frequent isolation and reporting of multidrug resistant (MDR) and extremely drug resistant (XDR) organisms from our laboratory prompted us to undertake a retrospective evaluation to understand the type and number of Carbapenemase producing multidrug resistant organisms growing in our own institute. Ours is a tertiary care center with advanced ICU facilities and advanced laboratory services.

This retrospective evaluation was conducted with the objective –

1. To understand the prevalence of different carbapenemase producing organisms in our institute.
2. To see primary mortality evaluation amongst infected patients and secondary outcome analysis for duration of stay and requirement of mechanical ventilation amongst patients who died.

Subjects and Methods:
After clearance from the Ethics Committee, the retrospective analysis was carried out between Jan 2015 and July 2016. Isolates of gram negative bacteria were screened from all clinical samples which were sent after 48 hours of hospital admission, to the microbiology department during the study period. Only Extended spectrum betalactamases (ESBLs), Class A Carbapenemases (Carbapenem resistant organisms) and Class B Metallobetalactamases (MBL isolates e.g. *Pseudomonas, Acinetobacter* spp.) were considered for this retrospective analysis. Clinical samples were from the ICU and other hospital wards, in the form of blood, urine, respiratory secretions, pleural fluid, bed sore swab etc.

The BacT/Alert 3D60 (automated culture system, Biomerieux) was used for detection of bacterial growth from blood and sterile body fluids. Other samples were processed for culture using manual method. The bacterial isolates were recovered on blood agar and MacConkey agar.

All the isolates were subjected to gram stain. Depending on the gram stain result, further isolate identification and antimicrobial sensitivity testing was carried out using Vitek ID and antimicrobial sensitivity test (AST) cards as per the manufacturer's instructions (Automated ID & AST system Biomerieux). GP ID & AST cards were used for gram-positive bacterial isolates whereas GN ID & AST cards were used for gram-negative isolates.

Antimicrobial sensitivity test: For routine Quality Control of antibiotic susceptibility test, *S. aureus* ATCC 25923, E. coli ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853 were used.

The resistance mechanism and breakpoints were interpreted by Vitek2C software with updated CLSI guidelines(Clinical Laboratory Standards Institute). The Vitek2C interpreted whether the carbapenem resistant isolate was MBL screen positive or OXA positive.

For screening different resistance mechanisms, the following phenotypic methods were used as per CLSI guidelines-

i. ESBL Production- by disk diffusion method
Ceftazidime (30µg) and Ceftazidime-clavulanate (30/10µg) disks
Cefotaxime (30µg) and Cefotaxime-clavulanate (30/10µg) disks

ii. Class A Carbapenemases KPC
Ertapenem nonsusceptibility (Most sensitive indicator of Carbapenemase production) Modified Hodge test using Ertapenem disk (10µg) or Meropenem disk (10µg)

iii. MBL detection in Nonfermentors- Combined IPM-EDTA test
Imipenem(10µg) and Imipenem-EDTA(10µg/750 µg) For confirmation of suspected Carbapenemase resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates ,CarbaNP was used as the standard method described in CLSI guidelines.[5,6,7]

The MDR, XDR, and PDR strains were detected as per criteria described by ECDC and CDC.[8]

The data was captured and subjected to appropriate analysis.

Results:
A total of 1344 non-duplicate bacterial isolates were recovered from a total of 1926 clinical samples tested during the study period between Jan 2015 to July 2016. First it was observed that 995 (74%) bacterial isolates were gram negative bacteria (GNB) and 349 (26%) were gram positive bacteria (GPB).

Amongst gram negative bacteria the predominant pathogens were Class A carbapenemase with n=340 (34.17%). Class B MBL producers represented n=113 of the samples (11.35%). There were no Class C or Class D isolates. Surprisingly the number of ESBL producers was much lower, with n=78 (7.8%). The rest were all isolates of "other gram negative bacteria" n=464 (46.63%).

The species identification suggested that the predominant organism was *Klebsiella* in class A (59%) and class B MBL (37%), as well as in isolates of ESBL's (54%). In class A carbapenemases the second most common species was *E. coli* (28%), where as in Class B MBL producers the second most common species was *Acinetobacter* (26%). Among ESBL producers the second most common organism was again *E. coli* (40%). **(Fig.1)**

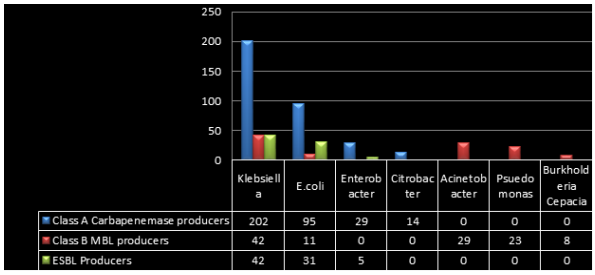

Figure-1 Species wise distribution of class A Carbapenemase, class B MBL and ESBL Producers

A comparison of isolates amongst ICU and general hospital ward patients showed 66% of class A carbapenemases and 75% of MBL growth in the ICU, compared with 34% of Class A carbapenemases and 25% of MBL in general hospital ward patients. ESBL isolates were almost the same in ICU and general hospital ward patients, with 51% and 49% respectively. **(Table-1)**

Table-1 Location wise distribution of class A carbapenemase, class B MBL and ESBL producers

Location wise distribution	Class A carbapenemase (n=340)	Class B MBL (n=113)	ESBL (n=78)
ICU	225 (66%)	85 (75%)	40 (51%)
Wards	115 (34%)	28 (25%)	38 (49%)

When comparing the growth of isolates in different body samples, it was observed that the highest number of class A carbapenemases were isolated from blood, with 45.29%, followed by the respiratory tract, with 22.30 %. Similarly, the largest number of MBL was isolated from blood, with 60%, followed by the respiratory tract, with 18%. The largest number of ESBLs were isolated from blood (35%), followed by pus samples (28%). **(Table-2)**

Table-2 Sample wise distribution of class A carbapenemase, class B MBL and ESBL producers

Sample wise distribution	Class A carbapenemase (n=340)	Class B MBL (n=113)	ESBL (n=78)
Blood	N=154 (45.29%) 94 (ICU), 60 (ward)	N= 68 (60%) 54 (ICU), 14 (ward)	N=27 (35%) 11 (ICU), 16 (ward)
Respiratory Secretions	N= 76 (22.30%) 52 (ICU), 24 (ward)	N= 20 (18%) 13 (ICU), 07 (ward)	N=10 (13%) 08 (ICU), 02 (ward)
Urine	N= 62 (18.23%) 43 (ICU), 19 (ward)	N=9 (8%) 5 (ICU), 4 (ward)	N=19 (24%) 13 (ICU), 6 (ward)
Pus	N=48 (14.11%) 36 (ICU), 12 (ward)	N=16 (14%) 13 (ICU), 3 (ward)	N=22 (28%) 8 (ICU), 14 (ward)

A calculation of the total and percentage mortality from the observed data among patients with Class A carbapenemases, MBL's, and ESBL showed 112 mortalities (21%). Of these, 66 (19.4%) were class A carbapenemase growers, 36 (31.8%) were MBL growers, and 10 (12.8%) were ESBL growers.**(Table 3)**

Table-3 Associated Mortality with class A carbapenemase, class B MBL and ESBL producers

	Class A carbapenemase producers (n=340)	Class B MBL producers (n=113)	ESBL Producers (n=78)
Death	N=66 62 (ICU), 04 (ward)	N=36 35 (ICU), 01 (ward)	N=10 07 (ICU), 03 (ward)
Mortality rate	**19.4% (66/340)**	**31.8%** (36/113)	**12.8%** (10/78)

APACHE II scoring, average length of stay in the ICU and requirement of mechanical ventilation were all also analyzed for those patients who died in our observational study. APACHE II of more than 16 was found

in 57/66 (86.36%) of deaths in Class A carbapenemases growers, 31/36(86.1%) of deaths in MBL growers and 6/10(60%) of deaths in ESBL growers. Average length of stay was 24.5 days, 26.7 days and 21 days amongst Class A carbapenemase growers, MBL growers and ESBL growers respectively. More than one week of ventilatory support was required by 49/66 (74.2%) of Class A carbapenemase growers, 33/36 (91.6%) of MBL growers and 6/10(60%) of ESBL growers.

A comparison of isolated bacteria with associated mortality amongst patients classified above is mentioned in **Table-4**. Associated mortality with *Klebsiella* was highest in class A carbapenemases and the ESBL group whereas mortality associated with *Acinetobacter* was highest in the MBL group.

Table-4 Organisms isolated and associated mortality

Organisms isolated and associated mortality	Class A carbapenemase producers (Deaths n=66)	Class B MBL producers (Deaths n=36)	ESBL Producers (Deaths n=10)
Klebsiella	59 (89.39%)	3 (8.3%)	6 (60%)
Acinetobacter	0	25 (69.4%)	0
E.coli	7 (10.6%)	0	4(40%)
Pseudomonas	0	5(13.8%)	0
Burkholderia cepacia	0	3 (8.3%)	0

Discussion:

We collected our data over a period of 18 months, with a total number of 1344 non-duplicate isolates in our laboratory, of which 995 were found to be gram negative isolates (74%) and 349 were gram positive isolates (26%). Gram-positive isolates were excluded from the study.

The increased prevalence of ESBL was due to an increased use of cephalosporins and inappropriate use of other antibiotics. To manage these ESBLs, carbapenems were used in most cases as an antibiotic. Again, enhanced and indiscriminate use of carbapenems allowed uninhibited growth of drug resistant gram negative *Enterobacteriaceae in the form of* CRE's such as KPC's and MBL species.[9,10,11,12,13,14] Mortality associated with these MDRs is very high with limited treatment options. [15,16] The present scenario warrants identification of these MDRs in the respective laboratories of health care organisations to prevent their widespread growth and outbreak.[9] Recent studies have suggested a continued high prevalence of ESBL's amongst children, with *Klebsiella* being the main ESBL producer. [17,18] Moderate prevalences have been reported from other hospital wards.[19,20] Our study suggests a prevalence of 8%, with the predominant organism being *Klebsiella* (54%). Most isolates were grown from blood, both from ICUs and general hospital wards. The lower prevalence of ESBL in our hospital may be correlated with strict infection prevention practices being followed as a quality control measure in our hospital.

There is a wide range of prevalences of MBL in different ICU setups (2.97%, 33.33%, 12.73% and 10 %). [21, 22,23]The most common MBL producing organisms in these setups are either *Acinetobacter*, *Klebsiella* or *Psuedomonas*.

In our study we observed a prevalence of 11.3%, and most of these MBL producers were from the intensive care unit, with *Klebsiella* representing the most dominant organism producing MBL (37%). Three-quarters of these growths (75%) were from the ICU and one-quarter were from the general hospital ward (25%).

Reported percentages from various studies suggest that the prevalence of class A carbapenemase has increased over time.[24,25] Recent studies also suggest a very high prevalence of class A carbapenemase. [26,27] In our study, we observed that 34% of the gram negative bacteria are class A carbapenemase, and again *Klebsiella* was the predominant species (59%). Similar findings have been reported from other studies conducted in different parts of world. [28,29] Analysis of our ICU and general ward data separately suggested a prevalence of 66% and 34% respectively. Sampling from various sites on patients bodies suggested a higher class A carbapenemase percentage from blood (45.29%) followed by respiratory secretions (22.35%).

Our ICU is a mixed ICU with a good case mix from different specialties, with the exception of cardiac surgery, burns and transplants. Considering the nature of our ICU, with different types of patients, class A carbapenemase seems to be more prevalent. Although the predominant site of growth of class A carbapenemase in our ICU was blood, similar to one another study,[30] high prevalence has also been reported from isolates of tracheal aspirates and sputum,[31,32] as well as from urine samples,[25,28] which suggests that the organism can become dangerously prevalent in different body sites depending on the ICU and patient type.

We separately analysed the length of stay, severity of disease, requirement of mechanical ventilation and mortality with respect to ESBLs, MBLs and class A carbapenemase.

In ESBL positive patients the average length of stay was 21 days in our ICU. 60% of these patients required mechanical ventilation and had an APACHE II score of more than 16. 12.8% of these ESBL producing patients died. Another study shows an average length of stay of 43.9 days, with 71.4% of patients requiring ventilator support and a mortality of 51.7%.[33]

In MBL producing patients the average length of stay was 26.7 days in our ICU, with blood again as the primary site of infection. 86.1% of patients had an APACHE II score of more than 16, 91.6% of patient's required ventilatory support and 31.8% of these patients died.

One study showed an average length of stay to be 23 days. Mortality due to bloodstream infection of MBL producing pseudomonas was found to be 61%.[34]

Another study,[22] reported that more than 95 % of their patients were suffering from sepsis and required ventilatory support. Mortality due to MBL producing *Pseudomonas* was found to be 36% and mortality due to MBL producing *Acinetobacter* was found to be 16.67%.

Among patients with class A carbapenemase, 19.4% died in our observational study, and 86.36% of patients who died had an APACHE II score of more than 16. *Klebsiella* was found to be the predominant organism. Mortality reported from a Brazilian study was 34.6%.[35] In the Brazilian study, the predominant site of infection was the chest and the isolates were predominantly *Klebsiella.* The Indian study[36] reported a mortality rate of 44.8% with combination therapy and 66.6% with colistin monotherapy, and the predominant isolate was also *Klebsiella.* Another study from Korea [27] reported a 28-day mortality rate of 27%. Another study in the USA reported that the most prevalent isolates of CRE were of the *Klebsiella* genus. Another study from Saudi Arabia reported a mortality rate of 31%. The average length of stay in our observational study was 24.5 days. The study from Korea also suggested an average length of stay of 24 days [32] The Brazilian study had an average length of stay of 18 days.[35]

The need for ventilator assistance amongst class A carbapenemase producers who died in our study was 74.2%. In the Korean study, [26] it was 37.8%. The Brazilian study reported that all patients who developed pneumonia eventually required mechanical ventilation (61.4%).

Inference from our study suggests that in recent years the resistance pattern of gram negative bacteria has undergone a very serious developmental change with the formation and growth of Carbapenemase producers. The prevalence of these organisms is increasing rapidly in tertiary care organizations where infections due to serious organisms are treated. Amongst MBL and class A carbapenemase producers *Acinetobacter, Klebsiella* and *Pseudomonas* have maintained their dominance over other organisms of the same enzyme producer. Although they have been found to be most prevalent in the blood and respiratory tract, they are also found in different sites of the body, as referenced from various studies, depending on the ICU and patient type.

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References:

1. Silpi Basak, Priyanka Singh, and Monali Rajurkar (2016). Multidrug Resistant and Extensively Drug Resistant Bacteria: A Study. Journal of Pathogens 2016 : 5.
2. Dahiya S, Singla P, Chaudhary U, Singh B (2015). Carbapenemases: A Review. Int J Adv Health Sci, 2:11-17.
3. Centers for Disease Control and Prevention (CDC) (2009). Guidance for control of

infections with carbapnem resistant or carbapnemase producing Enterobacteriaceae in acute care facilities. Morb Mortal Wkly Rep, 58:256-260.
4. Endimiani A, Hujer AM, Perez F, Bethel CR, Hujer KM, Kroeger J et al. (2009) Characterization of blaKPC-containing Klebsiella pneumoniae isolates detected in different institutions in the eastern USA. J Antimicrob Chemother, 63:427–437
5. Vasoo S, Cuningham SA, Kohner PC et al. (2013) Comparison of a novel, rapid chromogenic biochemical assay, the Carba NP test with the Modified Hodge test for detection of carbapenemase-producing Gram-negative bacilli. J Clin Microbiol, 51:3097-3101.
6. Clinical and Laboratory Standards Institute (CLSI). (2011) Performance Standards for Antimicrobial Susceptibility Testing: Twenty First Informational Supplement. CLSI Document. M100-S21. Wayne, PA, USA: CLSI.
7. Lee K, Chong Y, Shin HB, Kim YA, Yong D, Yum JH. (2001) Modifi ed Hodge and EDTA-disk synergy tests to screen metallo-betalactamase-producing strains of Pseudomonas and Acinetobacter species. Clin Microbiol Infect, 7:88-91
8. A.P. Magiorakos, A. Srinivasan, R. B. Carey et al. (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clinical Microbiology and Infection, 18: 268–281.
9. Saghir S, Faiz M, Saleem M, Younus A, Aziz H. (2009) Characterization and anti-microbial susceptibility of gram-negative bacteria isolated from bloodstream infections of cancer patients on chemotherapy in Pakistan. Indian J Med Microbiol, 27:341–347
10. Seid J, Asrat D. (2005) Occurrence of extended-spectrum beta-lactamase enzymes in clinical isolates of Klebsiella species from Harar region, eastern Ethiopia. Acta Trop, 95 :143–148.
11. Mohanty S, Gaind R, Ranjan R, Deb M. (2009) Use of the cefepime-clavulanate ESBL Etest for detection of extended-spectrum beta-lactamases in AmpC co-producing bacteria. J Infect Dev Ctries, 4: 24–29.
12. Afunwa RA, Odimegwu DC, Iroha RI, Esimone CO. (2011) Antimicrobial resistance status and prevalence rates of extended spectrum beta-lactamase (ESBL) producers isolated from a mixed human population. Bosn J Basic Med Sci, 11: 91–96.
13. Levy Hara G, Gould I, Endimiani A, et al. (2013) Detection, treatment, and prevention of carbapenemase-producing Enterobacteriaceae: recommendations from an International Working Group. J Chemother, 25:129–140.
14. Kumar D, Singh AK, Ali MR, Chander Y. (2014) Antimicrobial susceptibility profile of extended spectrum β-lactamase (ESBL) producing Escherichia coli from various clinical samples. Infect Dis (Auckl) , 7: 1–8.
15. Sahin K, Tekin A, Ozdas S, Akin D, Yapislar H, Dilek AR, et al. (2015) Evaluation of carbapenem resistance using phenotypic and genotypic techniques in Enterobacteriaceae isolates. Ann Clin Microbiol Antimicrob, 14:44.
16. Djahmi N, Dunyach-Remy C, Pantel A, Dekhil M, Sotto A, Lavigne JP. (2014) Epidemiology of carbapenemase-producing Enterobacteriaceae and Acinetobacter baumannii in Mediterranean countries. Biomed Res Int, 305784.
17. Legese MH, Weldearegay GM, Asrat D. (2017) Extended-spectrum beta-lactamase- and carbapenemase-producing Enterobacteriaceae among Ethiopian children. Infection and Drug Resistance, 10: 27-34.
18. Modi DJ, Patel BV, Patel MH, Bhatt SS, Sood NK, Vegad MM. (2012) A Study of Extended Spectrum β-Lactamase (ESBL) and AmpC β -Lactamase Producing Klebsiella Pneumoniae in Neonatal Intensive Care Unit at Tertiary Care Hospital, Ahmedabad. Natl J Community Med, 3:523-8.
19. Peshattiwar PD, Peerapur BV. (2011) ESBL and MBL Mediated Resistance in Pseudomonas aeruginosa: An Emerging Threat to Clinical Therapeutics. J Clino and Diagno Res , 5(8) : 1552-4 .
20. Varaiya AY, Dogra JD, Kulkarni MH, Bhalekar PN. (2008) Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in diabetic foot infections. Indian J Pathol Microbiol ,51:370-2
21. Deshmukh DG, Damle AS, Bajaj JK, Bhakre JB, Patwardhan NS. (2011) Metallo-β-lactamase-producing Clinical Isolates from Patients of a Tertiary Care Hospital. J of Lab Phys , 3(2) :93
22. De AS, Kumar SH, Baveja SM. (2010) Prevalence of metallo-β-lactamase producing Pseudomonas aeruginosa and Acinetobacter species in intensive care areas in a tertiary care hospital. Indian Journal of Critical Care Medicine : Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine, 14(4): 217-219.
23. Babu KVY, Visweswaraiah DS, Kumar A. (2014) The influence of Imipenem resistant metallo-beta-lactamase positive and negative Pseudomonas aeruginosa nosocomial infections on mortality and morbidity. Journal of Natural Science, Biology, and Medicine, 5(2): 345-351.
24. Datta P, Gupta V, Garg S, Chander J. (2012) Phenotypic method for differentiation of carbapenemases in Enterobacteriaceae: Study from north India. Indian J Pathol Microbiol , 55:357-60
25. Shivesh P. (2006) Carbapenem sensitivity profile amongst bacterial isolates from clinical specimens in Kanpur city. Indian J Crit Care Med, 10 :250-53.
26. Bijayini B, Anupam D, Purva M, Arti K. (2008) High prevalence of carbapenem resistant Pseudomonas aeruginosa at a tertiary care centre of north India. Are we under-reporting? Indian J Med Res, 128: 324-25.
27. Mulla S, Charan J, Panvala T. (2011) Antibiotic sensitivity of Enterobacteriaceae at a tertiary care center in India. Chron Young Sci, 2:214-18.
28. Glasner C, Albiger B, Buist G, Tambić Andrasević A, Canton R, Carmeli Y, et al. (2013) Carbapenemase-producing Enterobacteriaceae in Europe: a survey among national experts from 39 countries. Euro Surveill, 18: 28.
29. Ramana KV, Rao R, Sharada ChV, Kareem M, Reddy LR, Mani M. (2013) Modified Hodge test: a useful and the low-cost phenotypic method for detection of carbapenemase producers in Enterobacteriaceae members. J Nat Sci Biol Med, 42:346–348.
30. Baran I, Aksu N. (2016) Phenotypic and genotypic characteristics of carbapenem-resistant Enterobacteriaceae in a tertiary-level reference hospital in Turkey. Annals of Clinical Microbiology and Antimicrobials, 15:20.
31. Malekolkottab M, Shojaei L, Khalili H, Doomanlou M. (2017) Clinical Response and Outcome in Patients with Multidrug Resistant Gram-negative Infections. Journal of Research in Pharmacy Practice, 6:44-51.
32. Lee H-J, Choi J-K, Cho S-Y, et al. (2016) Carbapenem-resistant Enterobacteriaceae: Prevalence and Risk Factors in a Single Community-Based Hospital in Korea. Infection & Chemotherapy, 48:166-173.
33. Felipe Francisco Tuon, Leila Carolina Bianchet, Sergio Ricardo Penteado-Filho. (2010) Epidemiology of extended spectrum β-lactamase producing Enterobacter bacteremia in a brazilian hospital, , Rev. Soc. Bras. Med. Trop, 43
34. Matthias Willmann, Ines Kuebart, Marschal, et al, (2013) Effect of metallo-β-lactamase production and multidrug resistance on clinical outcomes in patients with Pseudomonas aeruginosa bloodstream infection: a retrospective cohort study BMC Infectious Diseases. 13:515
35. De Maio Carrilho CMD, de Oliveira LM, Gaudereto J, et al. (2016) A prospective study of treatment of carbapenem-resistant Enterobacteriaceae infections and risk factors associated with outcome. BMC Infectious Diseases, 16: 629.
36. Porwal R, Gopalakrishnan R, Rajesh NJ, Ramasubramanian V. (2014) Carbapenem resistant Gram-negative bacteremia in an Indian intensive care unit: A review of the clinical profile and treatment outcome of 50 patients. Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine, 18 :750-753.