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SURVEILLANCE OF MULTI DRUG RESISTANT GRAM NEGATIVE AEROBIC BACILLI IN A TERTIARY CARE HOSPITAL

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Abstract

Background: Antimicrobial resistance is a major public health problem. Bacterial pathogens are increasingly exhibiting resistance to the commonly used antibiotics. During the last two decades ESBL producing Gram negative bacilli have emerged as a major problem in many settings. Timely and accurate reporting of microbiology susceptibility test results allows selection of more appropriate and focused therapy .

Methods: A prospective cross sectional study was carried out which included all the gram negative bacilli isolated from various clinical specimen received in microbiology department. Growth was identified by conventional method. Total 290 Gram negative aerobic isolates were identified. The antimicrobial susceptibility testing of all the Gram negative isolates was done using disc diffusion method. All the gram Negative bacilli were screened for ESBL production and metallo Beta lactamase production by disc placement method .

Results: Out of the 290 strains isolated ,maximum isolates were of Klebsiella (40.34%), followed by E.coli (31.72%), 30-40% of isolated strains were multi drug resistant, 229 (78.96%) were ESBL producers. All the strains (100%) of Non fermenters,Acinetobacter and Burkholderia from indoor patients were ESBL producers followed by Klebsiella (96.03%),E.coli (95.58%) and Pseudomonas (86.04%).

Conclusion: This study will help the Infection control committee in formulating antibiotic policy l. The data generated through this surveillance can guide the physician for appropriate therapy. ESBL detection should be routinely undertaken, to avoid misuse of beta-lactam antibiotics.The data of resistance strains within the hospitals should be generated not only at the local level but should be done at national level, so that region specific guidelines and policies on antibiotic prescription and usage may be formulated.

INTRODUCTION

Antimicrobial resistance is an issue of great significance for public health at the global level. Antibiotics which are considered as wonder drugs are often prescribed inappropriately and inadequately. Bacterial pathogens causing acute infections are increasingly exhibiting resistance to the commonly used antibiotics and have become a great threat to public health. The increasing antibiotic resistance problems in hospitals and community is a cause of great concern.[1]

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Compared to infections caused by drug susceptible gram negative bacteria infections caused by Gram negative bacteria are associated with higher morbidity and mortality particularly if inappropriate empiric al antibiotic therapy is prescribed.[2]

Hospital antibiograms can be a useful means for guiding empiric therapy and tracking the emergence of bacterial resistance among nosocomial isolates.[1]

Antimicrobial resistance is a growing threat worldwide. Resistance mechanisms have been found for every class of antibiotic agents. During the last 2 decades, extended-spectrum β-lactamases (ESBLs) found in gram-negative bacilli have emerged as a significant mechanism of resistance to oxyimino-cephalosporin antibiotics. [3]

With the spread of ESBL producing Gram negative bacilli in hospitals all over the world, it is necessary to know the prevalence of ESBL producing Gram negative bacilli in a hospital so as to formulate an antibiotic policy in high risk units where infections due to resistant organisms is higher.[4]

Institution-specific data, such as susceptibility patterns and local antibiotic use need to be studied. Tailoring antimicrobial therapy based upon culture and sensitivity results wherever available will help reduce cost, decrease the incidence of super-infections, and minimize the emergence of resistance & mortality. [5]

First described in 1980's in Europe Extendeded spectrum beta latctam producing Enterobacteriaciae have emerged as serious nosocomial pathogens.[6]

Clinical laboratories play a vital role in providing accurate information and guidance in the treatment of microbial infection.[7] Antimicrobial resistance among enteric gram negative bacteria is fast becoming a global public health concern with rapid increase in multi drug resistant organisms.[8,1]

The prevention of nosocomial infections and their transmission requires reliable microbiological diagnosis, rational antibiotic prescribing and effective infection control. The most important determinants in treating patients with infections in the ICU is prompt initiation of effective empiric therapy .[9]

All over world epidemics due to resistant Gram negative bacilli are increasing rapidly.World Health Day 2011 theme was "Antimicrobial Resistance;no action today,no cure tomorrow". [10]

MDR: Multi drug resistance among gram negative bacteria was defined as resistance to three or more of the following antibiotics Ceftazidime, Ciprofloxacin, Meropenem, Gentamicin, Ampicillin/sulbatam, or Piperacillin/tazobacam. These antimicrobials were chosen because they are commonly prescribed by physicians.[11]

Considering all these facts this study was planned to carry out the surveillance of antibiotic resistance in a tertiary care hospital .

AIMS & OBJECTIVES

1. To isolate gram negative bacilli from various clinical specimen.
2. To carry out antibiotic sensitivity of all isolates.
3. To know the frequency of multidrug resistant Gram Negative Bacilli.

MATERIAL & METHODS

Study design : Prospective cross sectional study
Sample size : All the gram negative bacilli isolated from various clinical specimen received in microbiology department of a tertiary care hospital for a duration of 3 months.

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All the samples received in Microbiology Lab were inoculated on Blood Agar and MacConkey Agar. These plates were incubated aerobically at 37^0c for 24 hrs . Growth was identified by conventional method.[12] Total 290 Gram negative aerobic isolates were identified from various clinical specimen (IPD &OPD).

The antimicrobial susceptibility testing of all the Gram negative isolates was done using disc diffusion method.[13] Test organisms were suspended in normal saline to 0.5 McFarland standard and then inoculated on Muller Hinton agar plates followed by overnight incubation at 37^0c for 18-24 hrs. For urinary isolates the antibiotic sensitivity was tested against Amoxycillin+Clavulanic acid,Norfloxacin, Ciprofloxacin, Nitrofurantoin,Cotrimoxazole,Ceftriaxone and Ceftazidime disk.For isolates which were obtained from other samples the antibiotic disks used were Gentamicin, Amoxycillin+Clavulanic acid, Ciprofloxacin, Cefuroxime, Ceftriaxone &Ceftazidime disk.

For Pseudomonas and acinetobacter species Imipenem, Ciprofloxacin, Gentamicin, piperacillin, Ceftriaxone & Ceftazidime disk were used.

ATCC E.coli 25922and ATCC Psedomonas aeruginosa 27853 were used as control strains for quality control of disk diffusion test. Interpretation was done using guidelines laid down in the CLSI manual, which provides break points corresponding to zone of inhibition diameter.[13]

All the gram Negative bacilli were screened for ESBL production and metallo Beta lactamase production by disc placement method described by Camella Rodrigues.The lawn culture of test organism was made on Muller –Hinton Agar as done for disk diffusion antimicrobial susceptibility test in the centre of the plate, Imipenem (10ug)disk was applied. At the distance of 20 mm, the disc of cefotaxime (30ug)was placed .

From this disk, in a circular manner, clockwise, the disk of Cefoxitin (30ug), ceftriaxone(30ug),ceftazidime930ug),ceftazidime+clavulanic acid(30+10ug) and Aztreonam (30ug) were placed such that any two adjacent discs were 20 mm apart from centre to centre. On overnight aerobic incubation at 37^0 c the diameter of zones of inhibition were measured and interpreted as follows [14] :

ESBL

1)Zone diameter for aztronam $\leq$27mm,cefotaxime$\leq$27mm, ceftazidime $\leq$22mm,

ceftriaxone $\leq$25mm.

2) Susceptible to cefoxitin

3) Increase in zone size with addition of inhibitor (ceftazidime+cavulanic acid) by

5mm or more.

Metallo Beta lactamases were identified as Strains showing resistance to Imipenem.

OBSERVATIONS & RESULTS

Total 290 strains were isolated from various clinical specimen during a period of three months. The distribution of specimen was as follows .

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Table I Distribution of specimen n=290

Sample	IPD	OPD	TOTAL
Urine	85	17	102
Pus	55	13	68
Sputum	33	8	41
Pleural fluid	33	00	33
ET Secretions	28	00	28
Blood	12	00	12
Ascitic Fluid	6	00	6
Total	252	38	290

As seen from Table I Out of the 290 strains isolated maximum isolates (102) were from Urine samples followed by pus and Sputum.

Table II Frequency of Gram Negative Bacilli among clinical specimen n=290

Organism	Specimen							
	Urine	Pus	Sputum	Pleural fluid	E.T. Secretions	Blood	Ascitic Fluid	Total (%)
Klebsiella	26	15	28	29	19	00	00	117(40.34%)
E.coli	56	20	00	00	00	10	06	92(31.72)
Pseudomonas	16	32	05	00	05	00	00	58(20%)
Non fermentor	02	01	04	02	02	02	00	13(4.48%)
Acinetobacter	00	00	02	02	02	00	00	06(2.06)
Burkholderia	00	00	02	00	00	00	00	02(0.68%)
Proteus	02	00	00	00	00	00	00	02(0.68%)

Table II shows the distribution of Gram negative bacilli among the clinical specimen. Out of 290 organisms maximum isolates were of Klebsiella (40.34%), followed by E.coli (31.72%), Pseudomoas (20%). Whereas few strains of Non fermenters (4.48%), Acinetobacter(2.06%),Burkholderia(o.68%) and Proteus (0.68%) were isolated in this study.

Table III Distribution of organisms in Indoor patients n=252

Organism	In patient
Klebsiella	102(40.47%)
E.coli	81(32.14%)
Pseudomonas	48(19.04%)
NonFermenter	13(5.15%)
Acinetobacter	06(2.38%)
Burkholderia	02(0.79%)
Proteus	00(00%)
Total	252

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As seen from Table III out of the 252 strains isolated from Indoor patients maximum strains were of Klebsiella(40.47%) and E. Coli (32.14%).

Table IV Distribution of organisms in Outdoor patients n=38

Organism	Out Patient
Klebsiella	15(39.47%)
E.coli	11(28.94%)
Pseudomonas	10(26.31%)
NonFermenter	00(00%)
Acinetobacter	00(00%)
Burkholderia	00(00%)
Proteus	02(100%)
Total	38(13.10%)

From Table IV it is evident that both the proteus strains isolated during this study were from outdoor patients.

Table V Antibiotic resistance pattern of Gram Negative bacilli isolated from Urine n=102

Antibiotic	No.Sensitive(%)	No.Resistant (%)
Amoxycillin+Clavulanic acid	28 (27.45 %)	74 (72.54%)
Norfloxacin	69(67.64%)	33 (32.35%)
Ciprofloxacin	78(76.47%)	24 (23.52%)
Nitrofurantoin	89 (87.25%)	13 (12.74%)
Cotrimoxazole	72 (70.58%)	30 (29.41%)
Ceftriaxone	68 (66.66%)	34(33.33%)
Ceftazidime	72 (70.58%)	30 (29.41%)

Table V shows the antibiotic sensitivity pattern of Gram negative bacilli from Urine samples. Out of 102 strains 72.54% were resistant to Amoxycillin +clavulanic acid.Almost 30% strains are resistant to Norfloxacin,cotrimoxazole,ceftriaxone and ceftazidime. Wereas only 12.74% strains were resistant to Nitrofurantoin.

TableVI Antibiotic Resistance pattern of Gram Negative bacilli isolated from specimen other than urine n=124

Antibiotic	No.Sensitive (%)	No.Resistant (%)
Amoxycillin+Clavulanic acid	33(26.61%)	91 (73.38%)
Gentamicin	97 (78.22%)	27 (21.77%)
Ciprofloxacin	85 (68.54%)	39 (31.45%)
Cefuroxime	69 (55.64%)	55 (44.35%)
Ceftriaxone	71 (57.25%)	53 (42.74%)
Ceftazidime	68 (54.83%)	56 (45.16%)

Out of 124 strains from samples other than urine ,73.38% strains were resistant to Amoxy+Clavulanic acid,about 40%strains were resistant to Cefuroxime and 3rd generation cephalosporins,while resistance to ciprofloxacin was noted in 31.45% and to Gentamicin in 21.77%.

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Table VII Antibiotic resistance pattern of Pseudomonas & Acinetobacter isolated . n=64

Antibiotic	No.Sensitive(%)	No.Resistant(%)
Imipenem	60 (93.75%)	04 (6.25%)
Ciprofloxacin	38 (59.37%)	26 (40.62%)
Gentamicin	50 (78.12%)	14 (21.87%)
Piperacillin	31 (48.43%)	33 (51.56%)
Ceftriaxone	41 (64.06%)	23 (35.93%)
Ceftazidime	52 (81.25%)	12 (18.75%)

Table VII shows that in this study the Pseudomonas and Acinetobacter species were resistant to Imipenem in only 6.25% strains, followed by Ceftazidime (18.75%),Gentamicin(21.87%),Ceftriaxone(35.93%),Ciprofloxacin(40.62%)and Piperacillin(51.56%).

From the Tables V,VI,VII it is evedent that almost 30-40% strains are multi drug resistant.

Table VIII ESBL producing Gram Negative Bacilli

Organism	Number isolated	Number of ESBL Producers (%)
Klebsiella	117	101(86.32%)
E.coli	92	68(73.91%)
Pseudomonas	58	43(74.13%)
NonFermenter	13	09(69.23%
Acinetobacter	06	06(100%)
Burkholderia	02	02(100%)
Proteus	02	00(00%)
Total	290	229(78.96%)

All the gram negative isolates in this study were tested for ESBL production. Table VIII shows that out of 290 Gram negative bacilli isolated 229 (78.96%) were ESBL producers. All the strains of Acinetobacter and Burkholderia were ESBL producer whereas no strain of proteus showed ESBL production. Maximum ESBL production was observed in Klebsiella (86.32%), followed by Pseudomonas (74.13%), E.coli (73.91%) and Nonfermenters (69.23%).

Table IX Distribution of ESBL producing isolates from Indoor &Outdoor patients n=229

Organism	In patient	Out Patient	Total
Klebsiella	97(96.03%)	04(3.96%)	101
E.coli	65(95.58%)	03(4.41%)	68
Pseudomonas	37(86.04%)	06(13.95%)	43
NonFermenter	09(100%)	00(00%)	09
Acinetobacter	06(100%)	00(00%)	06
Burkholderia	02(100%)	00(00%)	02
Proteus	00	00	00
Total	216(94.32%)	13(5.67%)	229

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From Table IX it is evident that out of 229 ESBL producing Gram negative bacilli 216(94.32%) strains were isolated from indoor patients and only 13(5.67%) from outdoor patients. All the strains (100%) of Non fermenters,Acinetobacter and Burkholderia from indoor patients were ESBL producers followed by Klebsiella (96.03%),E.coli (95.58%) and Pseudomonas (86.04%).

DISCUSSION

Cephalosporins are widely used as drug of choice for Gram negative infections. Their inappropriate use leads to development of drug resistance. The hospital strains are becoming multi drug resistant in many health care setups. Most of the Gram negative isolates from critical areas are ESBL producers .

This study was planned to know the frequency of multidrug resistant Gram negative bacilli. Total 290 strains of Gram negative bacilli were isolated from various clinical specimen. Maximum isolates (102) were from Urine samples followed by 68 from pus samples, 41 from Sputum. 33 Gram negative strains were isolated from pleural fluid and 28 from ET Secretions. Whereas only 12 strains were isolated from blood culture and 6 from ascitic fluid.

In a study carried out by Kalidas Rit et al in 2013 highest number of non fermenters were from Pus specimen. Clinical conditions associated with non fermenting Gram negative bacilli were Surgical site infections, Ventilator associated pneumonia, urinary tract infection and septicaemia. Pseudomonas and acinetobacter were more commonly isolated from SSI and UTI.[15]

In the present study it was observed that maximum isolates were of Klebsiella (40.34%),followed by E.coli (31.72%),Pseudomonas (20%). Whereas few strains of Non fermenters(4.48%),Acinetobacter(2.06%),Burkholderia(o.68%) and Proteus (0.68%) were isolated in this study.

In a study conducted by Stephen E Mshana et al in Tanzania in 2009 E.coli was the commonest organism isolated from urine specimen and Acinetobacter from infected wounds.[9] In another study also E. Coli was isolated from maximum samples followed by Klebsiella.[7]

Deep Gagneja et al reported that from Lower respiratory tract infections (LRTI) commonest organism was Pseudomonas (30-50%) followed by Klebsiella but from 2005-2006 onwards ,the rate of isolation of Acinetobacter species increased from 11.8%(2004-2005) to 25% (2008-2009).[16]
Jethawani in 2014 reported that most common isolates in their study were Acinetobacter spp. (31.25%) followed by Klebsiella spp.(21.87%), E-coli (21.87%) and Pseudomonas Spp. (17.7%).[17]
From our study it is evident that most of the Gram negative bacilli isolated were resistant to Amoxy+clavulanic acid, Gentamicin and 3rd generation cephalosporins (more than 30 %) indicating multi drug resistance.

RUBEENA HAFEEZ ET AL 2009 reported 100% susceptibility to Imipenem for all the isolates and to Amikacin (85%).[7] Whereas in another study most of the Gram negative bacilli were resistant to Ampicillin and 43.5 % of isolates were resistant to 3rd Generation cephalosporins.[9]

In a study conducted by Jethwani for aminoglycosides, strains were equally sensitive to amikacin, gentamicin and tobramycin (47%). Among fluoroquinolones, strains were equally sensitive to ciprofloxacin, levofloxacin and gatifloxacin (24%). All the strains of E.coli were sensitive to carbapenems, colistin, polymyxin B and sensitivity to 3rd generation cephalosporins-cefotaxime, ceftriaxone and ceftazidime was 22%. All Strains of Klebsiella were resistant to 3rd generation cephalosporins. Sensitivity to piperacillin-tazobactam was 33%.[17]

Satyajeet K.Pawar et al reported 19.1% sensitivity to Aminoglycosides and 62.2% of total isolates were multidrug resistant. Less susceptibility to cephalosporins might be due to ESBL producing strains while over use of quinolones and penicillin group may be responsible for resistance against these group.[10]

In a study from Chandigarh in 2003 a total of 42% strains of Pseudomonas aeruginosa were found to be resistant to Imipenem.[18]

Study by Van Eldere showed that amikacin among aminoglycosides and ciprofloxacin among fluoroquinolones were the potent antibiotics against Pseudomonas spp.[19] Similarly in Banglore,Pseudomonas showed 60-70% resistance to Amikacin, ceftazidime and ciprofloxacin. [20]

Erdem et al reported 59% P. aeruginosa isolates resistant to ceftazidime, 32% to imipenem, and 62% to ciprofloxacin. [21,19] while in another study Pseudomonas isolates were highly susceptible to colistin, Imipenem, Amikacin and Cefaperazone/sulbactum combination.[15]

Pathmanathan et al in 2009 showed 77.3% and 79.4% of Pseudomonas isolates were susceptible to meropenem and imipenem respectively.[22]

In 2014 Jethwani reported that 5 (24%) isolates were resistant to carbapenems . Antipseudomonal agents- piperacillin, ceftazidime and piperacillin-tazobactam had 29%, 41% and 35% sensitivity respectively. [17]

In our study the Pseudomonas and Acinetobacter species were resistant to Imipenem in only 6.25% strains, followed by Ceftazidime (18.75%), Gentamicin (21.87%) , Ceftriaxone (35.93%), Ciprofloxacin(40.62%)and Piperacillin(51.56%).

The antibiotic susceptibility pattern may change with time and may vary from hospital to hospital. Beta lactamase enzymes produced by Gram negative organisms confer resistance to broad spectrum beta lactam antibiotics.

Studies on ESBL production among enterobacteriaceae isolated from clinical specimen showed a variable incidence ranging from 1% to 74%.[23,24]

In our study out of 290 Gram negative bacilli isolated 229(78.96%) were ESBL producers. All the strains of Acinetobacter and Bueholderia were ESBL producers whereas no strain of proteus showed ESBL production. Maximum ESBL production was observed in Klebsiella (86.32%),followed by Pseudomonas (74.13%),E.coli (73.91%)and Nonfermenters (69.23%).

In India prevalence of ESBL production varies from 10%-84% [25]. In a study done by Nathisuwan S in 2001 ESBL were more prevalent in Klebsiella followed by E.coli.[26] A study from North India on Uropathogens showed that 26.6 % of the isolates were ESBL producers whereas a study from Nagpur showed that 48.3% of cefotaxime resistant Gram negative bacilli were ESBL producers. [27]

Babypadmini S carried out the study in tertiary care hospital in 2004 and observed that 41% E.coli and 40% Klebsiella showed ESBL production.[28]

In a similar study by Mathur et al 62% of the E.coli and 73% of the Klebsiella isolates were reported to be ESBL producers.[29] Predominant prevalence of ESBL among E.coli isolates was also reported by Ananthakrishnan et al.[25] and Kumar et al.[30]

In a study done by RUBEENA HAFEEZ ET AL prevalence of ESBL production in Gram Negative isolate was found to be 35.5% in which prevalence of 44.8% and 38.6% was found for E.coli and Klebsiella respectively.[7]

ESBL production was 81% in E.coli and 74% in Klebsiella in a study done by UMADEVI S.[31]

In Indian hospitals ESBL producing Klebsiella species were predominant organisms responsible for high morbidity.[5] Recent studies on ESBL production among the members of Enterobacteriaceae which were isolated from clinical specimens showed an increase in the occurrence of ESBL producers. [32]

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In one study Gram negative isolates showing resistance to 3rd generation cephalosporins were tested for ESBL production and ESBL prevalence was found to be 98.51% .[33]

50% E- coli and 38% of Klebsiella pneumonia strains were ESBL producers in a study done by Jethwani.[17]

The occurance of Multi drug resistant organisms not only limits the therapeutic options but also poses a challenge for Microbiology labs to identify them.

In our study resistance to Imipenem was noted in only 6.25% strains of Psedomonas. Gladstone P while evaluating respiratory isolates also found lower resistance of 12.2 % to carbapenems in non fermenters.[34]

High prevalence of resistance to Imipenem in E.coli,Klebsiella, Pseudomonas, Acinetobacter in wards and ICU as 2&13%, 31&51%, 39&59%, 57&80% respectively by Chand Wattal et al in 2010.[5]

The clinical microbiology laboratory is a key component in the function of antimicrobial stewardship programme. Timely and accurate reporting of microbial susceptibility test results allows selection of more appropriate and focused therapy and may help reduce broad spectrum antimicrobial use.

CONCLUSION

The data generated through surveillance of antibiotic resistance in Gram Negative bacilli, can provide an in depth knowledge regarding impending treatment failures and guides the physician for appropriate therapy.

ESBL detection and its drug susceptibility pattern should be routinely undertaken, to avoid overuse or misuse of beta-lactam antibiotics in clinical practice.

In this study it was observed that about 30-40% strains were multi drug resistant and ESBL production was seen in 78.96% gram negative bacilli. This study will help the Infection control committee in formulating antibiotic policy for our hospital.

This data will help the infection control committee in formulating the antibiotic policy for our hospital which is a backbone of Antibiotic stewardship programme.

Antibiotic susceptibility data generated by the microbiology laboratories should be shared with the clinicians. The data of resistance strains within the hospitals should be generated not only at the local level but should be done at national level, so that region specific guidelines and policies on antibiotic prescription and usage may be formulated.

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