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PHENOTYPIC CHARACTERIZATION OF CARBAPENEM RESISTANT ACINETOBACTER BAUMANNII CLINICAL ISOLATES IN INTENSIVE CARE UNIT IN A TERTIARY CARE HOSPITAL IN SHILLONG, MEGHALAYA

Neeta Gogoi[1], W.Valarie Lyngdoh[2]

[1]Senior Resident, Department of Microbiology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya, India.
[2]Professor, Department of Microbiology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya, India.

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Corresponding Author:
Dr. W.Valarie Lyngdoh
Professor, Department of Microbiology, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya, India.
Email: drvalarielyngdoh@gmail.com.

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ABSTRACT

Background: Unprecedented levels of antimicrobial resistance in bacterial isolates have prompted great concerns globally and have imposed significant life threatening risks to several different populations, especially those in intensive care units (ICUs). Among Gram-negative bacteria, *Acinetobacter baumannii* is notorious as a frequent opportunistic pathogen associated with critically ill patients The objective of the present study is to determine the prevalence and risk factors of Carbapenem Resistant *Acinetobacter baumannii* (CRAB) infections among patients admitted in ICU in a tertiary care hospital in North East India.

Materials and Methods: A total of 215 *Acinetobacter baumannii* isolates obtained from patients admitted in ICU between 2019-2020 were included in the study, retrospectively. All the isolates were screened for carbapenem resistance by Kirby Bauer Disc Diffusion method and were further subjected for MIC (Minimum Inhibitory Concentration) testing by VITEK 2 automated system. The statistical analysis was done using MedCalc for Windows version 19.1 (Ostend, Belgium). Significance of statistical association had been calculated from standard probability (p- value) using Chi-Square test.

Results: Carbapenem resistance was observed in 149 (69%) out of 215 *Acinetobacter baumannii* isolates. Majority of the resistant isolates had MIC values of ≥16µg/ml and ≤64µg/ml (85.2% for Imipenem and 87.3% for Meropenem). Most common risk factors of infection were mechanical ventilation (56.4%), prolonged ICU stay (44.5%) and multidrug resistance (43.6%). The isolates were highly resistant to Cephalosporins including Ceftazidime (91.9%) and Ceftriaxone (81.2%) whereas they showed maximum sensitivity towards Levofloxacin (54.4%), Aminoglycosides including Gentamicin (53.7%) and Amikacin (53%).

Conclusion: This study highlights an increasing trend of carbapenem resistance amongst *Acinetobacter baumannii* isolates in North East India.

Keywords: *Acinetobacter baumannii*, Intensive Care Unit, Carbapenem resistance.

INTRODUCTION

Resistance to antimicrobial agents is increasing worldwide imposing significant life threatening risks to several different populations, especially those in intensive care units (ICUs). Among the Gram-negative bacteria, *Acinetobacter baumannii* is notorious as a frequent opportunistic pathogen associated with critically ill patient. The genus Acinetobacter is highly diverse, comprises of oxidase-negative and catalase positive, nonpigmented, Gram-negative coccobacilli with DNA G + C content of 39% to 47%.[1] They are non-

motile and non- fermenters, are strictly aerobic and are capable to grow at a wide range of temperatures. Most clinical strains grow optimally at 37°C, while the environmental isolates prefer lower temperatures. *Acinetobacter. baumannii (A.baumannii)* is often transmitted to patients via persistence on environmental surfaces and transient colonization of the hands of health care workers.[2,3] Acinetobacter is intrinsically resistant to desiccation, which contributes to its persistence in environments and transmission in health care settings. Nosocomial spread by aerosolized bacteria from infected or colonized patients has also been reported.[4] Humidifiers and water baths have often been implicated as environmental reservoirs, and a high level of humidity has been postulated to facilitate growth of the bacteria.[2]

Infections caused by Acinetobacter spp. emerged in earnest during the 1960s and 1970s in parallel with increasing utilization of complex intensive care[5,6] and has transformed, over the years, from a pathogen of questionable clinical significance to one of the most virulent, multidrug resistant pathogenic organism in the ICU, with the predominant predispositions to infection being the factors such as colonization pressure, exposure to broad-spectrum antibiotics, and disruption of anatomical barriers (e.g. placement of catheters or endotracheal tubes and traumatic or surgical injury to skin and integument). Clinically, such infections are associated with mechanical ventilation, intravenous and urinary catheterization, surgery, invasive procedures, and prolonged broad spectrum antimicrobials, especially in patients who suffer from burns, have trauma, or are in ICUs.[7,8,9]

A. baumannii is attracting much attention owing to the increase in antimicrobial resistance and occurrence of strains that are resistant to virtually all available drugs.[10] This organism is generally intrinsically resistant to a number of commonly used antibiotics, including aminopenicillins, first- and second- generation cephalosporins and chloramphenicol.[11,12] It also has a remarkable capacity to acquire mechanisms that confer resistance to broad-spectrum β-lactams, aminoglycosides, fluoroquinolones and tetracyclines.[13] Of particular concern is resistance to carbapenems — broad-spectrum β-lactams that were introduced by 1985 and that, for years, have been the most important agents for the treatment of infections caused by MDR *A. baumannii*. Although clinical *A. baumannii* isolates were shown to be invariably susceptible to these drugs in early studies.[11,12] hospital outbreaks caused by carbapenem-resistant strains had already been reported by the early 1990s.[14]

The resistance of *A. baumannii* to carbapenems can be mediated by resistance mechanisms, which include enzymatic inactivation, active efflux of drugs, and modification of target sites. The production of naturally occurring carbapenem-hydrolizing beta-lactamases and oxacillinases encoded by genes of the blaOXA-23, blaOXA-40 and blaOXA-58-like lineage are the commonest enzymatic mode of carbapenem resistance.[15] Potent class B metallo carbapenemases of the VIM, IMP and SIM type have been found *in A. baumannii* which confer high-level resistance to carbapenems.[16,17,18] Resistance to carbapenems may also be explained by other mechanisms, such as porin loss or modification.[19]

Carbapenem resistance in *A. baumannii* is now an emerging issue worldwide. The percentage of carbapenem resistant isolates gradually increased over the years in Europe, North America, and Latin America.[20] A worldwide collection of 5127 Acinetobacter spp. collected between 2005 and 2009 from 140 hospitals in 32 countries in North America (17.1%), Europe (22.9%), Latin America (25.2%) and the Asia-Pacific region (34.8%), showed that the nonsusceptibility percentage had increased from 27.8 and 37.5% in 2005 to 62.4% and 64.4% in 2009 for imipenem and meropenem, respectively. [21] In Philippines 54.1% of 3,575 *A.baumannii* isolates were resistant to carbapenems in 2015, a significant rise compared to 27.2% and 22.1% in 2006 and 2010, respectively. In Thailand 73.7% of the country's *A.baumannii* isolates between January and September 2015 were found to be resistant to meropenem, making a significant increase from 62.5% in 2010.[22] have generally exceeded 40% throughout all of India. In a study from Central India a total of 155 /368 (42.11%) isolates *A. baumannii* were found to have reduced susceptibility to imipenem by disc diffusion method. Among these 155 isolates tested 130 (83.87%) isolates showed MIC values for imipenem and meropenem ranging from16-64 mg/L. [23] Goel et al in 2011 reported a rapid emergence of carbapenem resistance in *Acinetobacter baumannii (*74%) in a tertiary care hospital in Delhi, India.[24] In a study conducted in South India, out of a total of 332 *Acinetobacter baumannii* isolates obtained from CCU, 75% were resistant to carbapenems.[25]

In North-East India there is paucity of data regarding the prevalence of carbapenem resistance in *Acinetobacter baumannii* isolates in ICU settings. Hence this study was planned to detect the prevalence of carbapenem resistance in the *A. baumannii* isolates using screening phenotypic methods and determining the minimum inhibitory concentration (MIC) using the standard VITEK method and also the associated risk factors contributing to such infections.

MATERIAL AND METHODS

Study Design

The study was a cross sectional analytical study carried out in the department of Microbiology in a tertiary care center, Shillong, Meghalaya for a period of one year (2019-2020).

Inclusion Criteria

All *Acinetobacter baumannii* isolates obtained from various clinical specimens from patients admitted in Intensive care unit (ICU) were included in the study.

Exclusion Criteria

Repeat isolates from the same patient from repeat specimen were excluded from the study to avoid duplication of isolate.

Ethical consideration

The study was conducted after obtaining ethical clearance from the Institutional Ethics Committee with reference to NEIGR/IEC/T37/19/37.

Sample Collection

Various clinical specimens like blood, endotracheal secretion, urine, exudates, sputum, cerebrospinal fluid, pleural fluid, etc were obtained from patients admitted in Intensive Care Unit were cultured on appropriate routine bacteriological media and further processed and analysed for the detection of carbapenem resistant *Acinetobacter baumannii.*

Morphological and biochemical identification

Biochemical identification was performed according to the standard laboratory procedures.[26] Various samples obtained from the patients were inoculated and streaked onto the surface of MacConkey agar (Himedia, India) for isolated colonies. Characteristic discrete non lactose fermenting colonies produced after 24 hours of incubation aerobically at 37°C were streaked onto fresh sterilised Nutrient agar (Himedia, India) and identified by conventional biochemical tests such as indole, triple sugar iron (TSI) , citrate and urease and motility tests. The isolates that were non-motile, negative to indole and urease tests giving alkaline/alkaline (K/K) reaction without gas and hydrogen sulphide production on TSI but positive to citrate test were identified *as A. baumannii.*

Phenotypic methods for detecting carbapenem resistance

Screening by disc diffusion method

30µg Carbapenem (Imipenem and Meropenem) discs,[27] were put on the Muller Hinton Agar (MHA) plate for screening carbapenem resistance according to Kirby – Bauer's disc- diffusion method following standard laboratory protocols.[27] A suspension of each isolate in Mueller- Hinton broth, adjusted to the density of a 0.5 McFarland standard, was swabbed in three directions to ensure uniform growth onto Mueller-Hinton agar plates. Once the agar surface was completely dry, Carbapenem discs were applied (25 mm apart) to each plate with sterile forceps, and the plates were incubated at 35◦C for 16 to 20 hours. Zones of inhibition were measured and interpreted as per CLSI 2019 guidelines.[27]

Identification and MIC detection by Automated Bacterial culture system

All the screened isolates were further subjected to VITEK-2 Identification system (VITEK-2, BioMerieux France). Identification and Antimicrobial susceptibility testing (AST) for a panel of antibiotics including carbapenems was performed using Gram negative identification (GN ID) card and AST-N280 card for determination of resistance pattern and Minimum Inhibitory Concentration (MIC) respectively. The standard procedures recommended by the manufacturer were followed for Identification and AST.[28] Interpretation of test was done as per CLSI 2019 guidelines.[27] Carbapenem resistance was defined as MIC values of (Imipenem≥8µg/ml) and (Meropenem≥8 µg/ml).

Quality control

Quality control of the test was done by standard ATCC strain Escherichia coli 25922 and Pseudomonas aeruginosa 27853.[29]

Data analysis

The data on demographic and clinical parameters were tabulated and graphed using Microsoft Excel v2007 for Windows. Significance of statistical association had been calculated from standard probability (p-value) using Chi-Square test. The observation was considered statistically significant if the p-value was less than 0.05. The statistical analysis was done using MedCalc for Windows version 19.1 (Ostend, Belgium).

RESULTS

During the study period (March 2019 to February 2020), a total of 215 non-duplicate, consecutive patient-specific *Acinetobacter baumannii* isolates were obtained from different clinical samples of patients admitted in ICU. All these 215 isolates were subjected to screening for Carbapenem resistance by Kirby Bauer's disc-diffusion method following which they were further subjected for susceptibility testing by VITEK-2 system where only 149 (69%) isolates showed Carbapenem resistance.

Age and Gender distribution

Out of the total 149 carbapenem *resistant A. baumannii* (CRAB) isolates, 66% were obtained from males and 34% from females as shown in figure 1**.** Maximum were observed in the age group of 51 – 60 years (21%) followed by age group of 31-40 years (18%) as shown in figure 2 and the mean age of the patients was 45.38 years.

Clinical spectrum of CRAB isolates:

Maximum number of the resistant isolates were obtained from the patients admitted in ICU due to Central Nervous System (CNS) manifestations (45%) followed by sepsis (13.4%) and respiratory infections (7.4%), renal (6.7%) and Cardiovascular system (CVS) manifestations (5.4%) as shown in figure 3.

Source of resistant isolates

Most of the carbapenem resistant isolates were obtained from Minibal (27.5%) followed by tracheal secretion (19.5%) and blood (18.1%) as shown in figure 4.

Distribution of MIC values of the CRAB isolates by VITEK: The MIC values ranged from ≥8 µg/ml to ≥32 µg/ml. 14.8% (for Imipenem) and 12.8% (for Meropenem) had MIC values of ≥8µg/ml, 57% (for

Imipenem) and 58.4% (for Meropenem) had MIC values of ≥16µg/ml and 28.2% (for Imipenem) and 28.9% (for Meropenem) had MIC values of ≥32µg/ml but ≤ 64 µg/ml as shown in table 1.

Antimicrobial susceptibility profile of CRAB isolates : The CRAB isolates as detected by MIC using VITEK were highly resistant to Cephalosporins including Ceftriaxone (91.9%) and Ceftazidime (81.2%), Fluoroquinolones like Ciprofloxacin (79.9%) and β-lactam inhibitors including Piperacillin-Tazobactam (60.4%) and also Ampicillin-Sulbactam (59.7%). The isolates showed maximum sensitivity towards Levofloxacin (54.4%), Aminoglycosides including Gentamicin (53.7%) and Amikacin (53%) as shown in figure 5.The resistance to Ceftriaxone was found to be statistically significant (p=0.0466) as shown in table 2.

Risk factors associated with CRAB isolates

Risk factors for CRAB in the decreasing order of frequency were as follows: mechanical ventilation (56.4%), prolonged ICU stay (44.5%), multidrug resistance (43.6%), presence of indwelling catheter (16.1%), major surgery (11.4%) and major trauma (10.1%). In our study, 56.4% of the patients harbouring CRAB were on mechanical ventilation in comparison to 25.8% of the patients who had non-CRAB infections. This was found to be statistically significant (**p=0.0219**) as shown in table 3. It was also observed that majority of the study patients (73.8%) harbouring CRAB infections had a duration of ICU stay ranging between 24-31 days (73,8%) followed by 16-23 days (18.1%).

Antibiotic exposure of CRAB isolates: Most of the CRAB isolates had previous administration of Piperacillin and Tazobactam (41.6%), Ceftriaxone (30.2%), Amikacin (13.4%) and Imipenem (6.7%**)** as shown in table 4.

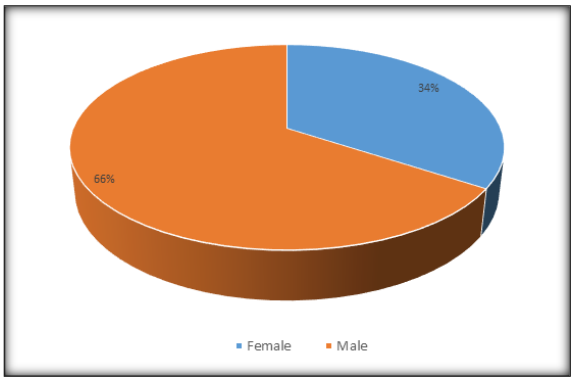

Figure 1: Gender distribution of the CRAB isolates

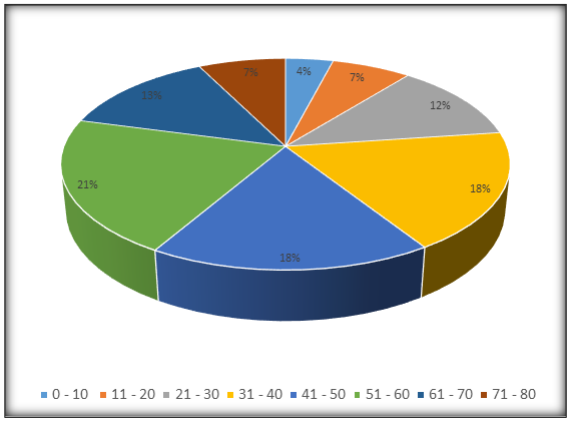

Figure 2: Age distribution of the CRAB isolates

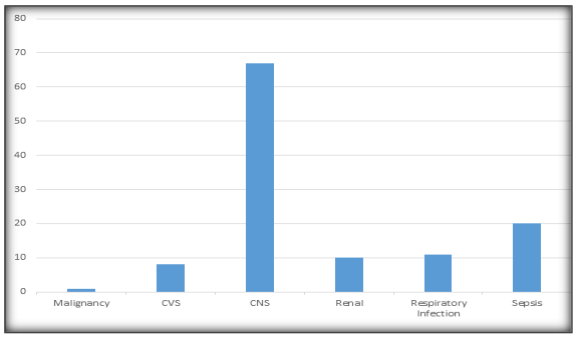

Figure 3: Clinical spectrum of the patients with CRAB infections

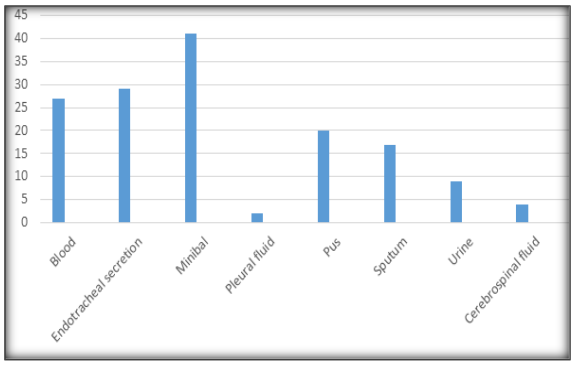

Figure 4: Source of the CRAB isolates

Table 1: MIC values of the CRAB isolates by VITEK

Values(µg/ml)	Imipenem			Meropenem	
	Nos	%		Nos	%
≥8 to ≤16	22	14.8		19	12.8
>16 to ≤32	85	57.0		87	58.4
>32 to ≤64	42	28.2		43	28.9
Total	**149**	**100.0**		**149**	**100.00**

Table 2: Antibiotic susceptibility profile of the CRAB isolates versus Non-CRAB isolates

Antibiotics	SENSITIVE					RESISTANT				
	CRAB		Non-CRAB		p value	CRAB		Non-CRAB		'p' value
	Nos	%	Nos	%		Nos	%	Nos	%	
Gentamicin	77	51.7	27	40.9	0.5129	72	48.3	39	59.1	0.4518
Amikacin	80	53.7	41	62.1	0.1103	69	46.3	25	37.9	0.1699
Ciprofloxacin	30	20.1	16	24.2	0.7499	119	79.9	50	75.8	0.5537
Levofloxacin	81	54.4	33	50.0	0.6708	68	45.6	33	50.0	0.6793
Ceftazidime	12	8.1	6	9.1	0.9442	137	91.9	60	90.9	0.8164
Ampicillin -Sulbactam	60	40.2	33	50.0	0.7730	89	59.7	33	50.0	0.7772
Piperacillin and Tazobactam	59	39.6	24	36.4	0.7873	90	60.4	42	63.6	0.7260
Ceftriaxone	28	18.8	5	7.6	0.5463	**121**	**81.2**	**61**	**92.4**	**0.0466**
Ceftazidime	12	8.1	6	9.1	0.9442	137	91.9	60	90.9	0.8164

Table 3: Risk factors associated with CRAB isolates versus Non-CRAB isolates

Serial Number	Factors	CRAB	%	Non-CRAB	%	'p' value
1	Major Surgery	17	11.4	2	3.0	0.7224
2	Major Trauma	15	10.1	3	4.5	0.7685
3	Length of Stay in ICU					
	0 - 7 days	2	1.3	1	1.5	0.9923
	8 - 15 days	10	6.7	6	9.1	0.8663
	16 - 23 days	27	18.1	11	16.7	0.9160
	24 - 31 days	110	73.8	48	72.7	0.8858
4	**Mechanical Ventilation**	**84**	**56.4**	**17**	**25.8**	**0.0219**
5	Indwelling Catheter	24	16.1	6	9.1	0.6698
6	MDR	65	43.6	23	34.8	0.4649

Table 4: Antibiotic exposure of the CRAB isolates

Antibiotic	Nos	%
Amikacin	20	13.4
Amikacin and Ceftriaxone	1	0.7
Amikacin and Imipenem	1	0.7
Amikacin and Levofloxacin	1	0.7
Ceftriaxone	45	30.2
Ceftriaxone and Metronidazole	1	0.7
Ceftriaxone and Moxifloxacin	1	0.7
Ertapenem	1	0.7
Imipenem	10	6.7
Meropenem	3	2.0
Metronidazole	1	0.7
Moxifloxacin	2	1.3
Piperacillin and Tazobactam	62	41.6

DISCUSSION

The carbapenem class of antibiotics is largely considered as an antibiotic of last-resort when treating *A. baumannii* infections, however, incidences of carbapenem-resistant *A. baumannii* are rising in several parts of the world.[30] These are broad-spectrum β-lactams that , for years, have been the most important agents for the treatment of infections caused by multidrug (MDR) *A. baumannii.* Increasing prevalence of carbapenem resistance worldwide limits treatment options for *A. baumannii* infections. Virulence factors, intrinsic and acquired resistance mechanisms, together with laboratory challenges in the detection and antibiotic susceptibility testing of *A. baumannii* make this a truly problematic resistant isolate. Therapeutic options are exceedingly limited, relying on polymyxins in combinations with other antibiotics, with few, if any, new active agents in the pipeline.[30] This study was an endeavour to characterize and determine the prevalence of carbapenem resistance among the various *A. baumannii* isolates from various clinical samples of patients admitted in Intensive Care Unit in a tertiary care hospital in North-East India.

In this study, 149 (69%) out of 215 CRAB isolates showed resistance to carbapenem by VITEK MIC. This is similar to the study by Bali et al in 2013 where prevalence of carbapenem resistance was 60%.[31] However, it is in contrast to a study by Khajuria et al in 2014 where prevalence of carbapenem (Imipenem) resistance was 42.11%.[15]

Majority of the carbapenem resistant isolates obtained were from males (65.8%). This is not statistically significant as higher number of males were admitted. Maximum number of patients with CRAB infections were of age group 51 to 60 years, which could be attributed to weakened immune system and associated comorbidities with advancing age. Male preponderance and more risk with increasing age were also presented in a study by Huiping Huang et al in 2018.[32]

Maximum (34.2%) CRAB isolates were obtained from patients presenting with CNS manifestations who were shifted to ICU from Neurology department. This may be attributed to the fact that the patients suffering from diseases involving the

Central Nervous System usually require intensive critical care management in majority of the cases thereby increasing the risk of infection. Most (27.5%) of the CRAB isolates were obtained from respiratory (Minibal) samples indicating that the respiratory tract was the commonest site of infection. Similar to our study, a predominance of lung infections (54.7%) was observed in a study by Iara Rossi et al in 2014.[33]

The MIC values by VITEK for the CRAB isolates ranged from ≥8µg/ml to ≤64µg/ml (for both Imipenem and Meropenem). Majority of the study isolates had MIC values of ≥16µg/ml and ≤64µg/ml (85.2% for Imipenem and 87.3% for Meropenem) which is similar to a study by Khajuria et al in 2014 where 86.8% of the CRAB isolates had MIC values ranging from ≥16µg/ml and ≤64µg/ml for both Imipenem and Meropenem.[15]

In our study, the CRAB isolates as detected by MIC using VITEK were highly resistant to Cephalosporins including Ceftazidime (91.9%) and Ceftriaxone (81.2%). High resistant rates were also observed against Fluoroquinolones like Ciprofloxacin (79.9%) and β-lactam inhibitors including Piperacillin and Tazobactam (60.4%) and Ampicillin-sulbactam (59.7%) and this could be due to excessive use of these antibiotics in the hospital. Similar resistance pattern was presented in a study by Goel et al in 2011 where resistant rates for 3rd generation cephalosorins, fluoroquinolones and β-lactam inhibitors were 88% ,86% and 80% respectively.[24] In our study it was also found that the CRAB isolates showed significant resistance to Ceftriaxone (**p=0.0466**) in comparison to the non-CRAB isolates.

The isolates showed maximum sensitivity towards Levofloxacin (54.4%) and also Aminoglycosides including Amikacin (53.7%) and Gentamicin (51.7%) which could be due to controlled use of these drugs in our hospital. Our findings were similar to a study by Nashiket D et al.[34] where sensitivity rate for Amikacin was 30% , however in contrast, higher resistant rates for Levofloxacin (89%) and Aminoglycosides (80%) were reported by Nashiket D et al.[34] and by Goel et al respectively.[24]

The risk factors that predispose individuals to the acquisition of and infection with *A. baumannii* are similar to those that have been identified for other MDR organisms. These include host factors such as major surgery, major trauma, exposure related factors such as length of stay in ICU and factors that are related to medical treatment such as mechanical ventilation, the presence of indwelling devices (intravascular catheters, urinary catheters, drainage tubes). In our study, the risk factors in the patients harbouring carbapenem resistant *A. baumannii* in the decreasing order of frequency were mechanical ventilation (56.4%), prolonged ICU stay (44.5%) multidrug resistance (43.6%), indwelling catheter (16.1%), major surgery (11.4%) and major trauma (10.1%). It was also observed that majority of the study patients (73.8%) harbouring CRAB infections had a longer duration of ICU stay of approximately one month which could be due to prolonged exposure to hospital environment as well as prolonged use of broad spectrum antibiotics. Similar risk factors were also reported in a study by Garcia-Garmendia et al in 2001.[35] Only presence of mechanical ventilation in them was found to be statistically significant (**p=0.0219**) in comparison to those patients having non-CRAB infections. Thus association of mechanical ventilation with CRAB infection due to cross contamination and colonization of respiratory equipment followed by invasion could be of concern. A similar finding of mechanical ventilation as a significant risk factor (p = 0.009) was presented in a study by Vitkauskiene et al in 2012.[36] Our study revealed a multidrug resistance rate of 43.6% amongst the CRAB isolates which is similar to a study by by Huiping Huang et al in 2018 where MDR rate of 39.88% was reported. However a comparatively higher rate of 91% multidrug resistance was reported for CRAB isolates in a study by Rynga et al in 2015.[37]

Majority of them also had a history of previous exposure to antibiotics such as Piperacillin-Tazobactam (41.6%) and Ceftriaxone (30.2%) which could be explained by the fact that use of broad spectrum antibiotics can increase the risk of acquiring drug resistant infections due to *Acinetobacter baumannii.*

CONCLUSION

The present study highlights an increasing prevalence of carbapenem resistance amongst *Acinetobacter baumannii* isolates especially in the intensive care unit.The detection and surveillance of carbapenem resistant *Acinetobacter baumannii* infections are matters of major importance for the selection of appropriate therapeutic schemes and the implementation of infection control measures. Interventions such as hand hygiene, contact precautions, patient and staff cohorting, healthcare personnel education, minimizing device use are essential for curbing this menace.Antibiotic stewardship programmes to reduce the antibiotic resistance besides improving the patient care with reduced treatment failure are of utmost importance. It is essential to conduct a regular survey for bacterial contamination and to increase worker awareness and education about hygiene standards.

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