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Prevalence of multidrug resistant non-fermenters in a tertiary care centre

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ABSTRACT

Background: Infections due to multidrug resistant organisms especially Gram-negative non-fermenting bacteria such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are increasing, ultimately leading to shortage of clinically effective antibiotics. Indiscriminate use of antibiotics is the key factor influencing the prevalence and distribution of drug resistance in any community or nosocomial setting. **Aims and Objectives:** The objectives of the study are as follows: (1) To know the antibiotic susceptibility pattern of commonly isolated non-lactose fermenters. (2) To know the prevalence of multidrug resistant *P. aeruginosa* and *A. baumannii*. **Materials and Methods:** Clinical samples from various departments were processed using standard isolation and identification procedures. Only non-lactose fermenting colonies were processed further and only those isolates that were identified as *P. aeruginosa* and *A. baumannii*. were considered and their antibiotic susceptibility testing by disk diffusion method was carried out. Results were tabulated and analyzed. **Results:** Among 558 non-lactose fermenting Gram-negative bacilli isolates, *P. aeruginosa* (355) and *A. baumannii*. (203) were the most common isolates. Resistance to commonly used drugs such as aminoglycosides, cephalosporins and inhibitor combinations, and fluoroquinolones ranged from 40% to 65%. Carbapenem resistant isolates were around 24–25%. Multidrug resistant isolates and extensively drug resistant accounted for 17.4% and 9.1%, respectively. **Conclusion:** Increasing multidrug resistance and extensive drug resistance resistance among non-fermenters are on the rise leaving a very small window of treatment options. This is an alarming situation that needs strict antibiotic policy and a robust antimicrobial resistance management plan.

Key words: *Pseudomonas aeruginosa*; *Acinetobacter baumannii*.; Non-lactose fermenters; Multidrug resistant; Extensively drug resistant; Antimicrobial resistance; Nosocomial infections; Antimicrobial susceptibility testing

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INTRODUCTION

Non-fermenting Gram-negative bacilli (NFGNB) are aerobic, non-motile, non-lactose fermenting, oxidase-negative, and catalase-positive organisms posing a major threat in health-care facilities as they contribute significantly to mortality and morbidity especially in immune compromised patients.[1] NFGNB such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*, are important nosocomial pathogens causing a wide spectrum of diseases such as blood stream infections, wound infections, ventilator associated pneumonia, meningitis, urinary tract infections (UTI), and surgical site infections.[2] Immunosuppression, neutropenia, mechanical ventilation, cystic fibrosis, indwelling catheters, and invasive diagnostic and therapeutic techniques have been identified as major risk factors.[3] These non-fermenters have emerged as a very tough organisms in the health-care set up due to their ability to survive in environment on a wide variety of surfaces including instruments and human skin surface.[4] As

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a result of this survival nature of these organisms, they are easily transferred from patient to patient through fomites or the hands of health care workers leading to health-care associated infections.[5] They account for around 15% of all bacterial isolates from clinical samples and routinely they are identified in laboratories but speciating Acinetobacter is a bit tedious procedure.[6] They are also known to cause resistant infections leaving a small window of options to choose relevant antibiotics. Clinicians worldwide are struggling to choose the effective drugs in the management of critically ill patients. Main reasons for this issue could be the easy/over the counter availability of most of the antibiotics followed by inadvertent use of higher antibiotics leading to their remarkable evolution of resistance mechanisms. These organisms are intrinsically resistant to many drugs such as Ampicillin, Amoxicillin, Amoxckav, Cefotaxim, Ceftriaxone, Cefazolin, Ertapenem, Tetcyclins, Trimethoprim, and Chloramphinecol.[7] This has led to use of Carbapenems (Imipenem, Meropenem etc.), Aminoglycosides, β-lactam/lactamase inhibitors, Quinolones, Polymixins, and Monobactams as drugs of choice for treating infections caused by *Pseudomonas* and *Acinetobacter* spp. Over a period of time, due to the inadvertent use of these penems, the organisms have evolved as much more resistant strains by adapting various mechanisms such as carbapenemase production, decreased permeability due to loss of porin channels, overexpression of efflux pump, and changes in penicillin binding proteins.[8] These further added up by biofilm production as an adaptive resistance mechanism has really pushed the clinicians to look for alternative reserved drugs such as tigecycline, doripenem, and colistin. *P. aeruginosa* and *A. baumannii* are among the main pathogens targeted by colistin and the Clinical and Laboratory Standards Institute has published minimum inhibitory concentration interpretation guidelines only for these organisms.[9] Along with colistin and tigecycline, a newer semi synthetic glycycline, is being used. Moreover, for MDR *P. aeruginosa*, Doripenem is being used. A bigger therapeutic challenge is when extensively drug resistant (XDR) strains are encountered. Thus, the increasing emergence of multidrug resistant (MDR) and XDR strains has limited the treatment options globally.

Aims and objectives

The present study aims to determine the prevalence of MDR *P. aeruginosa* and *Acinetobacter baumannii*. in our tertiary care center and also their susceptibility pattern to various antibiotics.

The objectives of the study are as follows:

1. Isolation and identification of non-lactose fermenters (NLFs)
2. To determine susceptibility pattern of NLFs such as *P. aeruginosa* and *A. baumannii*.
3. To know the prevalence of MDR and XDR *P. aeruginosa* and *A. baumannii*.

MATERIALS AND METHODS

This cross-sectional and prospective study was conducted at SS Institute of Medical Sciences and Research Centre, Davangere which is a tertiary care hospital. It was carried out from December 2020–May 2022. Ethical clearance from the Institutional Ethics and Review Board (IERB) was obtained to carry out this study. Samples which were sent to microbiology laboratory for culture and sensitivity from various departments were included in this study. After receiving the samples, standard microbiological techniques (by manual method) were used for the isolation and identification of bacteria. All the samples except urine were inoculated onto blood agar/chocolate agar and MacConkey agar plates using a sterile wire loop. Urine samples were inoculated onto CLED agar and the inoculated agar plates were incubated aerobically at 37°C for 18–24 h. After 18–24 h of incubation, culture plates were examined for growth of bacteria. Each isolate was identified using standard colony morphology, microscopy, and biochemical reactions. Out of 1968 samples, 558 NLFs were identified as *P. aeruginosa* (355) and *A. baumannii* (203) were included in this study.

Antimicrobial susceptibility testing

Antimicrobial susceptibility test was put up on Mueller-Hinton agar (Hi-Media) by Kirby-Bauer disk diffusion method and interpretation was done according to the Clinical Laboratory Standards Institute (CLSI) 2022 guidelines.[9] Inoculum (Bacterial isolate suspension) was made by emulsifying bacterial colonies with 3–4 mL of normal saline, to achieve 0.5% McFarland standard. Lawn culture was done on Muller-Hinton agar plates. Once it dried, a set of standard antimicrobial disks were placed aseptically and plates were incubated aerobically at 37°C for 24–48 h. Following antibiotics procured from Hi-Media Zones of inhibition were measured and interpreted according to recent CLSI guidelines. Zones were reported as sensitive, intermediate, and resistant.

Inclusion criteria

Only those isolates that turned out to be *P. aeruginosa* and *A. baumannii*. were included in this study.

Exclusion criteria

NLF isolates other than *Pseudomoas aeruginosa* and *A. baumannii* were excluded from this study.

RESULTS

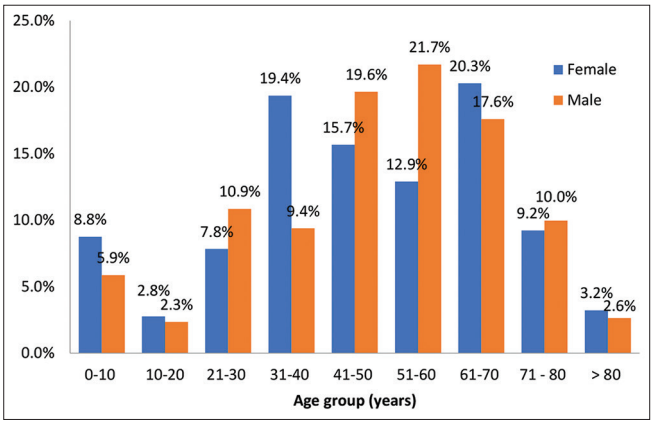
Out of 1968 samples that were processed, 558 isolates were confirmed as non-lactose fermenters (NLFs). Out

of 558, 355 were identified as *P. aeruginosa* and 203 isolates as *A. baumannii*. As *P. aeruginosa* and *A. baumannii*. were the predominant species isolated, other species of *Pseudomonas* and *Acinetobacter* were not considered for the present study.

Data were entered in the excel spread sheet. Descriptive statistics of the explanatory and outcome variables were calculated by frequency and proportions for qualitative variables. Statistical Package for the Social Sciences (SPSS) version 20 was used to perform the statistical analysis (Graph 1 and Tables 1-4).

DISCUSSION

In the recent years, NLFGNB have emerged as important nosocomial pathogens and their resistance to antimicrobials as well as their epidemiological complexity has made them very remarkable organisms.[10] Most of the isolates were from inpatients (49%) whereas the rest were from outpatient (29%) followed by intensive care unit (ICU) (22%). This shows their wide spread both at community level as well as in the hospital set up. Sample-wise distribution of isolates shows that the maximum isolates were from PUS (38%) which is very similar to study by Malini[11] and also other studies.[12,13] Endotracheal secretion (23%) and blood(19%) were the next common samples from which NLFGNB were isolated**.** Among non-fermenters, *P. aeruginosa* was the most common isolate (63.6%) followed by *A. baumannii*. (36.3%). This finding is similar to studies done by many others.[14] Samples from inpatient (275, 49%) are more compared to samples from outpatients (159, 29%). Samples from different ICUs accounted for 22% (124 isolates) only. Resistance pattern of these nosocomial pathogens shows wide variation not only from country to country but also within the same country over a period of time. Thus, it is very important that each hospital should have its own antibiotic policy based on the geographical distribution of the strains and also extensive data on susceptibility patterns. For cephalosporins and inhibitor combination, 43–49% of isolates were resistant. This is in contrast to other studies where they show 60–70% resistance.[12] About 45–57% of our isolates exhibited resistance to fluoroquinolones such as ciprofloxacin, ofloxacin, and levofloxacin, being similar to results put forth by Chmielarczyk et al.[15] Only 20% of psudomonas isolates were resistant to Piperacillin-Tazobactum combination proving it to be one of the therapeutic options. They also showed very less



Graph 1: The frequency distribution of gender and age of the patients from various departments from whom the samples were collected

Table 1: The frequency and percentage of isolates from various sections

Ward	*P. aeruginosa*		*A. baumannii*		Total	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
ICUs	56	15.8	68	33.5	124	22.2
Inpatient	171	48.2	104	51.2	275	49.3
Outpatient	128	36.1	31	15.3	159	28.5
Total	355	100.0	203	100.0	558	100.0

ICUs: Intensive care units. *P. aeruginosa: Pseudomonas aeruginosa, A. baumannii.: Acinetobacter baumannii*

Table 2: Sample-wise distribution of isolates

Sample	*P. aeruginosa*		*A. baumannii.*		Total	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
PUS	174	49.0	40	20	214	38
Blood	58	16.3	49	24	106	19
Urine	53	14.9	18	9	71	13
ET	42	11.8	87	43	129	23
Sputum	13	3.7	4	2	17	3
Tissue	8	2.3	3	1	11	2
BAL	7	2.0	1	0	8	1
CSF	0	0	1	0	1	0
Total	355	100.0	203	100	558	100

ET: Endotracheal secretion, BAL: Bronchoalveolar lavage, CSF: Cerebrospinal fluid. *P. aeruginosa: Pseudomonas aeruginosa, A. baumannii: Acinetobacter baumannii*

Table 3: Antibiotic susceptibility pattern of both *P. aeruginosa* and *A. baumannii.*

Antibiotic	Sensitivity pattern	*P. aeruginosa*		*A. baumannii.*		Total	
		Frequency	Percent	Frequency	Percent	Frequency	Percent
Ak	S	241	67.9	72	35.5	313	56.1
	I	18	5.1	2	1.0	20	3.6
	R	96	27.0	129	63.5	225	40.3
GEN	S	236	66.5	69	34.0	305	54.7
	I	23	6.5	4	2.0	27	4.8
	R	96	27.0	130	64.0	226	40.5
CPM	S	200	56.3	67	33.0	267	47.9
	I	4	1.1	20	9.9	24	4.3
	R	151	42.5	116	57.1	267	47.8
CAZ	S	184	51.8	42	20.7	226	40.5
	I	0	0.0	3	1.5	3	0.5
	R	171	48.2	158	77.8	329	59.0
CIS	S	178	50.1	108	53.2	286	51.3
	I	3	0.8	27	13.3	30	5.4
	R	174	49.0	68	33.5	242	43.4
CIP	S	151	42.5	31	15.3	182	32.6
	I	10	2.8	2	1.0	12	2.2
	R	194	54.6	170	83.7	364	65.2
LE	S	167	47.0	90	44.3	257	46.1
	I	20	5.6	19	9.4	39	7.0
	R	168	47.3	94	46.3	262	47.0
OF	S	160	45.1	55	27.1	215	38.6
	I	3	0.8	18	8.9	21	3.8
	R	192	54.1	130	64.0	322	57.7
COT	S	118	33.2	38	18.7	156	28.0
	I	0	0.0	9	4.4	9	1.6
	R	237	66.8	156	76.8	393	70.4
PIT	S	185	52.1	37	18.2	222	39.8
	I	41	11.5	22	10.8	63	11.3
	R	72	20.3	105	51.7	177	31.7
IPM	S	290	81.7	85	41.9	375	67.2
	I	21	5.9	28	13.8	49	8.8
	R	44	12.4	90	44.3	134	24.0
MRP	S	303	85.4	82	40.4	385	69.0
	I	7	2.0	29	14.3	36	6.5
	R	45	12.7	92	45.3	137	24.6
NIT	S	27	7.6	11	5.4	38	6.8
	I	306	86.2	186	91.6	492	88.2
	R	22	6.2	6	3.0	28	5.0
NX	S	25	7.0	11	5.4	36	6.5
	I	306	86.2	186	91.6	492	88.2
	R	24	6.8	6	3.0	30	5.4
	Total	355	100.0	203	100.0	558	100.0

Ak: Amikacin (30 µg), GEN: Gentamicin (10 µg), CPM: Cefepime (30 µg), CAZ: Ceftazidime (30 µg), CIS: Ceftriaxone-Sulbactam (30/15 µg), CIP: Ciprofloxacin (5 µg), LE: Levofloxacin (5 µg), OF: Ofloxacin (5 µg), COT: Co-Trimoxazole (25 µg), PIT: Piperacillin-Tazobactam (100/10 µg), IPM: Imipenem (10 µg), MRP: Meropenem (10 µg), NIT: Nitrofurantoin (300 µg), NX: Norfloxacin (10 µg). *P. aeruginosa: Pseudomonas aeruginosa, A. baumannii: Acinetobacter baumannii*

resistance 12% and13% to Imipenem and Meropenem, respectively. Urinary isolates showed 6%–7% resistance to nitrofurantoin and norfloxacin implicating that these drugs can be used for UTI caused by *P. aeruginosa.*

A. baumannii. was the most common *Acinetobacter* spp. isolated in our present study which is concordant with other studies too.[5,11] In the recent decades, *A. baumannii.* has become one of the most difficult nosocomial pathogens to control and treat, with a mortality rate of 30%. Even in our study, we observed that the isolates showed about 64% resistance to aminoglycosides like Amikacin and Gentamicin which is showing the rising trend but less than the other studies.[5,11] Even with 64% of isolates showing resistance, aminoglycosides can still be given for severe infections where injectable antibiotics are called for. It was observed that for Cephalosporins and inhibitor combination, resistance of our isolates varied between 34% and 78%. Least resistance (34%) was for Cetriaxone and sulbactam combination and maximum was for Ceftazidime. This shows that combination of β lactamase inhibitors is better than the cephalosporins alone. Our findings are concordant with study done by Taneja.[16] Among fluoroquinolones, maximum resistance was shown

Table 4: MDR and XDR

Strain	*P. aeruginosa* (n=355)		*A. baumannii.* (n=203)		Total (n=558)	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
MDR	59	16.6	38	18.7	97	17.4
XDR	17	4.8	34	16.7	51	9.1

P. aeruginosa: Pseudomonas aeruginosa, A. baumannii: Acinetobacter baumannii

for Ciprofloxacin (84%) followed by least resistance to levofloxacin (46%). About 77% of our *A. baumannii.* isolates were resistant to Cotrimoxazole. On the other hand, Piperacillin-Tazobactam seemed to be quite a promising drug of choice for Acinetobacter infections as only 51% of isolates were resistant which is much less than the resistance accounted by Lu et al.[17] Similarly, less resistance was seen to Carbapenems like imipenem (44.3%) and Meropenem (45.3%). Thus, in our results, we found that Cephalosporins and inhibitor combination along with Piperacillin-Tazobactam and Carbapenems are more effective than the other drugs for treating a wide variety of infections caused by *A. baumannii.* Colistin and tigecycline are the drugs of choice for resistant infections caused by these non-fermenters. However, we could not test colistin due to lack of facility to test the drug by broth microdilution method in our set up.

These non-fermenters not only are widespread in environment causing a wide spectrum of infections but also they show intrinsic resistance to a number of antibiotics and leave a small window of therapeutic options as proved by many studies including ours. In the recent decades, they have become a big challenge to health-care facilities from the infection prevention and control point of view. Their remarkable ability to thrive in the environment and easy transferable property from one patient to another as well as the emerging array of resistance mechanisms to a number of drugs has made them one of the deadliest organisms being encountered in health-care facilities across the globe. Thus, their resistance pattern to multiple drugs making them multidrug resistant (MDR) and emerging XDR is a big and serious issue of concern. In our study, 17.4% of isolates (*P. aeruginosa* – 16.6 % and *A. baumannii.* – 18.7%) were MDR strains while 9.1% (*P. aeruginosa* – 4.8% and *A. baumannii.* – 16.7%) were XDR. Details are shown in Table 4. As per another study done by Jayakumar and Appalraju, 22% of *P. aeruginosa* were MDR which is just a slight high rate than our study result.[18] Increased use of carbapenems to treat infection of third generation cephalosporin-resistant Gram-negative bacilli resulted in emergence of carbapenem-resistant *P. aeruginosa* and *Acinetobacter* spp. A surveillance study done in Korea over a decade shows that imipenem-resistant *P. aeruginosa* and *Acinetobacter* spp. increased from 17% to 26% and 1–51%, respectively.[19] A recent review of 30 studies in Saudi Arabia showed full or high resistance of *A. baumannii* to penicillins, cephalosporins, and carbapenems; variable degree of resistance to aminoglycosides, ciprofloxacin, and tigecycline; and low resistance to colistin.[20,21] The prevalence rate of MDR strains of the non-fermenters observed in our study was higher than the prevalence rates documented by Gill et al.,[22] (India, 50%). Considering the different data collected in the recent decades emphasis should be made on the seriousness of increasing resistance trend in non-fermenter especially *P. aeruginosa* and *A.baumannii.* Globally, health-care facilities are facing challenges in mitigating the spread of these organisms as well as their treatment especially in immune compromised and critically ill patients. Adding up to this problem, the burden is also on the patient regarding the cost of treating infections by resistant NFGNB which could be devastating for unaffordable patients, health-care system, and community at large. Thus, it is very important to realize the importance of tackling this burning issue of rising MDR and XDR non-fermenters. This could be possible only when the policy makers ban the sales of over-the-counter antibiotics and implement a robust and workable national antimicrobial resistance plan.[23]

Limitations of the study

1. Complete data on the previous consumption of antibiotics before admission to our hospital was not done in an extensive manner for all the inpatient cases. This might have helped us to document whether MDR and XDR strains were really prevalent in our tertiary care.
2. We could not test colistin as we did not have facility and man power to carry out broth microdilution for all the isolates.
3. We also could not test Doripenem and Tigecycline due to inconsistent availability and supply by the local suppliers in our geographical area.

CONCLUSION

Non-fermenters such as *P. aeruginosa* and *A. baumannii.* have evolved and emerged as dynamic duo due to their remarkable ability to survive in health-care facilities. Their resistance mechanisms are posing a threat and challenging the management of infections as we do have just a handful of antibiotics. Although our data on MDR and XDR are not so high as compared to many other studies, we need to look deep into the issue by conducting more studies and

collecting data from various aspects and for a longer period too. Thus, it is very important to have a proper antibiotic policy and carry out proper screening of non-fermenters, regular assessment of their antibiotic susceptibility profiles and judicious use of antibiotics to effectively manage the infections caused by them and also to limit the emergence of multidrug resistance in these organisms. In our tertiary care center, antibiotic stewardship is still in its infancy and hence we need to improve our policies and protocols in this regard.

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VM- Concept and design, data collection, first draft of manuscript, literature review, and correspondence with editor. **SVR-** Concept and design, review of literature, data collection, and compilation and interpretation. **AB**- Data tabulation, data analysis, statistical tests, and literature review. **JVL-** Financial and technical support, proof reading, and revision of manuscript.

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