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Prevalence and risk factors for drug resistance in patients with lower respiratory infections in Healthcare Associated Infection: a single centre study from Eastern India

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ABSTRACT

Background: Healthcare Associated Infections (HCAI) are associated with longer hospitalisations and increased morbidity and mortality. Lower respiratory infections including Pneumonia is an entity among healthcare associated infections mostly witnessed in nursing home residents, patients on long term care and patients receiving home or hospital based intravenous therapy and undergoing dialysis. Aim of the study to assess the prevalence and risk factors of resistance among the patients developing lower respiratory infections as a consequence of Healthcare Associated Infection.

Methods: The study was conducted as a prospective cohort model. All the eligible patients were subjected to detailed history taking, clinical examination, laboratory and radiological investigations. All the categorical parameters were compared using Fisher's exact test. Continuous parameters were compared using independent t-test. All the statistical analysis was carried out using the software Stata 15.1.

Results: Majority of the patients were older than 60 yrs (73%). Death was significantly seen in persons under 60 years and associated pulmonary consolidation equal to or more than three zones (p<0.05). *Klebsiella spp* (20.95%), and Acinetobacter (6.1%) were most commonly isolated. Multi-drug and extensive drug resistance were encountered among these organisms. Male gender, immune-compromised patients, bilateral pulmonary involvement and hospitalisation for at least 48 hours in preceding 90 days were associated with isolation of MDR organism.

Conclusions: Lower respiratory infection is an important component of healthcare associated infections. It needs targeted antibiotic therapy covering MDR organisms prevalent in the local population. Data from different institutions to corroborate findings regarding antibiotic resistance pattern of the microbes is recommended.

Keywords: Extensive drug resistance, Healthcare, Infections, Klebsiella, Acinetobacter, Multi-drug resistance

INTRODUCTION

Health care reflects a continuum with many traditional inpatient services provided in health care settings due to increase in complicated and chronically ill patients.¹ Healthcare associated infections (HCAI) occur due to spread of infection in health care environment. It is a growing problem in most countries, aggravated by development of resistance to antibiotics and disinfectants. The entity is associated with increased morbidity, longer hospitalization days and mortality.

Lower respiratory infections in HCAI have unique epidemiology and the pathogens are sometimes multidrug

resistant. The increasing population of immunosuppressed patients, device associated infections, instrumentation, support measures, colonization on hands of health care workers and irrational antibiotic therapy are contributory factors of the changes in epidemiology of antimicrobial resistance. The ability to predict multidrug resistant organism (MDRO) in this group of healthcare associated infections and frequency of MDROs has varied significantly.^{2,3} Determining the regional etiology of pneumonia is essential for optimizing patient outcome while minimizing unnecessary broadspectrum antimicrobial use.

The emergence of multidrug resistance among bacterial species is a worldwide public threat that is evolving at an alarming rate. India contributes a major portion of the global burden of antibiotic resistance. A constellation of factors in India includes medical, agricultural, veterinary, social and environmental resulting from unbridled use of antibiotics. The transmission dynamics of antibiotic resistance within a hospital or in persons with easy access to health care setups is well documented. It is known that antibiotic pressure is an established cause of propagation of resistance.^{4,5}

Pathogens, including extended-spectrum beta - lactamase producing (ESBL) and carbapenem-resistant Enterobacteriaceae (CRE), methicillin-resistant Staphylococus aureus (MRSA), Vancomycin-resistant Enterococcus species and multidrug Acinetobacter baumannii pose an ongoing challenge and are associated with health care associated infections. ^{4,5} The spread of infection in healthcare environment is a persistent and growing problem in most countries, aggravated by resistance to antibiotics and disinfectants.

European centre for disease control (ECDC) and Centre for Disease control and prevention (CDC), Atlanta have defined multidrug resistant (MDR), extensive drug resistance (XDR) and pan drug resistant (PDR) bacteria.

Multidrug resistant bacteria is defined as acquired resistance to at least one agent in three or more antimicrobial categories. Extensively drug resistant is defined as bacterial isolate susceptible to only one or two antimicrobial categories. Pan drug resistance is defined as non-susceptibility to all agents in all antimicrobial categories. In the last decade, there has been a dramatic increase worldwide in the number of multidrug resistant Gram neg (MDRGN) bacterial pathogens. Compared with Community acquired pneumonia (CAP) these patients have more severe disease, higher mortality, increased length of hospital stay and greater cost of care.⁶

Aim of this study was to characterize the clinical, radiological and microbiological profile of lower respiratory infections associated with HCAI, to determine the pattern and risk factors for developing drug resistance and to determine the outcome of disease in the study group.

METHODS

The study was conducted at Kalinga Institute of Medical Sciences, KIIT deemed-to- be University, Bhubaneswar, Odisha. The study was designed as a prospective cohort analysis of patients. Study period was from November 2017 to May 2019

Inclusion criteria

All cases admitted as healthcare associated infection with any of the following risk factors with radiological evidence and/or clinical features of lower respiratory tract infection were included in the study:

- Received intravenous therapy at home, wound care
 or specialized nursing care through a healthcare
 agency, family or friends; or had self-administered
 intravenous medical therapy in the 30 days before the
 infection
- Attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the previous 30 days
- Hospitalized in an acute care hospital for 2 or more days in the previous 90 days
- Resided in a nursing home or long-term care facility

Exclusion criteria

- Patients with tuberculosis
- Patients with malignancy

All the eligible patients who consented for the study were subjected to detailed history taking, clinical examination, chest X-ray and/or CT scan of thorax (when needed). Detail laboratory investigations including CBC, procalcitonin, LFT, RFT, electrolytes and blood sugar were obtained. Before initiation of presumptive antimicrobial therapy, sputum samples were collected for Gram stain and aerobic culture. ET aspirate was collected if patient was on ventilator support.

Statistical analysis

All the categorical parameters were presented as frequency and percentage and compared between the two groups using Fisher's exact test. Continuous parameters were presented as mean±SD and compared between the two groups using independent t-test. A p value of <0.05 was considered as statistically significant. All the statistical analysis was carried out using the software Stata 15.1.

RESULTS

Demography

Total 148 patients were included in the study of which 113 were males and 35 females (M:F=3.23:1). The mean age of the patients was 67.75yrs (±12.03). Majority of the patients belonged to the age group 61-75yrs (Table 1).

Table 1: Male and female distribution.

M: F	3.23:1	
Mean age (yrs.)	67.75 (±12.03)	n= 0.967
Male (yrs.)	66.7 (± 11.91)	p= 0.867
Female (yrs.)	67.09 (± 12.46)	

^{*}p< 0.05 is significant

The mean age of male patients was $66.7 \text{yrs} (\pm 11.91)$ while that among females was $67.09 \text{yrs} (\pm 12.46)$ (p= 0.867) (Table 2). Majority of the patients belonged to the 61-75 yrs. age group in both male and female (50.7%) followed by 46-60 yrs and >75 yrs (22.3% each) (Table 2).

Table 2: Age and sex distribution.

Age group	Male	Female	Total
≤45yrs.	5	2	7 (4.7%)
46-60yrs.	26	7	33 (22.3%)
61-75yrs.	57	18	75 (50.7%)
>75yrs.	25	8	33 (22.3%)
Total	113	35	148

Prior antibiotics in the preceding 30 days was the most common comorbid status criterion for developing pneumonia (49.3%), 22.97% patients had been hospitalized within 90 days prior to the current admission while 18.2% had chronic medical renal disease and were on hemodialysis (Table 3).

Table 3: Risk factors status.

Risk factor	No. of cases
Prior antibiotic therapy	73(49.3%)
Chronic dialysis	27(18.2%)
Hospitalization for at least 48hrs in preceding 90 days	34(22.97%)
Resided in nursing home / extended care facility	13(8.78%)
Home infusion therapy/ home wound care	1(0.6%)

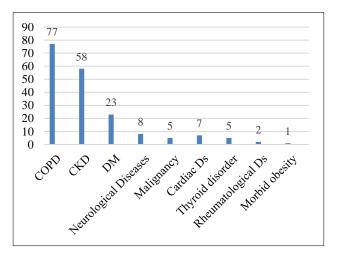


Figure 1: Associated co-morbidities.

Of the study population 77 (52.03%) had Chronic Obstructive Pulmonary Disease. Chronic medical renal disease, diabetes mellitus, malignancy and rheumatological disorders were noted in 39.19%, 15.5%, 3.38% and 1.35% patients respectively (Figure 1).

Clinical characteristics of the patients

Cough was the most common complaint among 125 (84.46%) patients followed by difficulty in breathing 116 (78.38%) and fever in 38 (25.7%) cases (Figure 2).

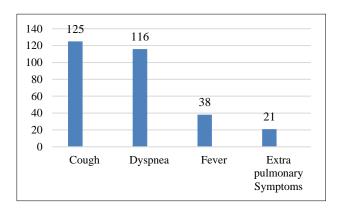


Figure 2: Clinical characteristics of the patients.

Duration of illness

Majority of the patients had a history of ≤ 1 week (67.57%) (Figure 3).

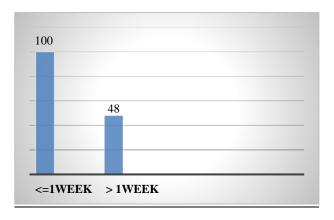


Figure 3: Duration of illness.

Laboratory parameters

The mean WBC count, serum urea and creatinine and serum procalcitonin levels were higher. The mean serum procalcitonin level was 11.8 (Table 4).

Correlation of various parameters with outcome

Out of 148 patients included in the study there were 138 survivors; 6 patients died; 4 cases left against medical advice. Risk factors of death were investigated after correlation with various parameters. Death was

significantly seen in persons less than 60 years and associated with pulmonary consolidation equal to and less than three zones (p<0.05) (Table 5).

Outcome of reports of culture specimens

The microbiologic diagnosis of pneumonia was most often established by sputum culture (27.7%) in non-ICU cases followed by endotracheal aspirate (18.9%) and blood culture in ICU cases (10.8%) (Table 6). Out of the total 91 cases, pathogens were isolated in 55 cases.

Table 4: Mean laboratory parameters.

Laboratory investigation	Mean value
Total leucocyte count (cells/mm ³)	14542.28 (±5708.07)
Hemoglobin (mg/dl)	11.0488 (±2.5495)
Fasting blood sugar (mg/dl)	136.11 (±61.65)
S. Urea (mg/dl)	61.76 (±45.07)
S. Creatinine (mg/dl)	1.97 (±2.1966)
S. Bilirubin (mg/dl)	1.635 (±8.67)
S. Procalcitonin	11.8 (±17.238)

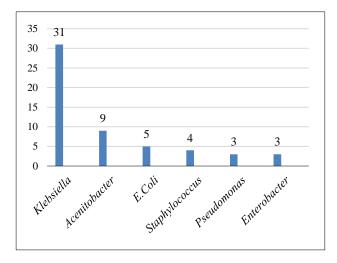


Figure 4: Pattern of organism isolated.

Pattern of organisms isolated

Klebsiella spp. was the most common organism isolated (20.95%) followed by *Acinetobacter* (6.1%) and *E.coli* (3.38%) (Figure 4).

Table 5: Correlation of various parameters with outcome.

Parameter	Survivor	Death	р		
1. Sex	Duivivoi	Death	_		
Male	107	4	0.6205		
Female	31	2			
2. Age					
<60yrs	28	4	p= 0.0227		
≥60yrs	110	2			
Total Leucocyte Cou	nt (cells/mm	³)			
≤ 11000	47	1	P = 0.6637		
>11000	91	5			
4.Hemoglobin (mg/d	1)				
<9	30	1	p= 1.00		
≥9	88	5			
5.Fasting Blood Suga	ar (mg/dl)				
<150	76	5	p= 1.00		
≥ 150	29	1			
6. S. Urea (mg/dl)					
< 50	71	3	p = 0.69		
≥ 50	50	3			
7.S. Creatinine (mg/c	11)				
<2	86	5	p= 1.00		
≥ 2	32	1			
8.Total Bilirubin (mg					
< 1	57	4	p= 0.5748		
≥1	10	1			
9.Radiological evidence of Consolidation					
≤ 3 zones	135	0	p= 0.0001		
>3 zones	7	6			

^{*}p< 0.05 is significant

Organism wise distribution in clinical specimens

In the distribution of pathogens, *Klebsiella* was isolated from sputum in the majority of cases. Endotracheal aspirate contributed to isolation of *Klebsiella spp*, *Acinetobacter*, *E. Coli*, *Staphylococcus*, *Pseudomonas* and *Enterobacter* species. Bacteremia was mostly witnessed in *Klebsiella* and *Acinetobacter* infection (Table 7).

Incidence of drug resistance among isolated organisms.

Among the resistant organism, MDR and XDR pattern was most common among the *Klebsiella*. Similarly, MDR was seen in *Acinetobacter* pathogens (Table 8).

Table 6: Outcome of reports of culture specimens (n=91).

Sample	Total n-91		Positiv	Positive n-55		wth n-36	
		ICU	NON-ICU	ICU	NON-ICU	ICU	NON-ICU
Sputum	41		41		18		23
Et aspirate	28	28		21	-	7	-
Blood	22	20	2	16		4	2
Total	91	48	43	37	18	11	25

Table 7: Organism wise distribution in clinical specimens.

	Klebsiella	Acinetobacter	E. coli	Staphylococcus	Pseudomonas	Enterobacter
Sputum	10	3	1	2	1	1
Et Aspirate	6	5	4	2	2	2
Blood	15	1				
Total	31	9	5	4	3	3

Table 8: Incidence of drug resistance among isolated organisms (n=29).

Organism	MDR	XDR	PDR
Klebsiella	8	8	1
Acinetobacter	4	1	-
E. coli	2	-	-
Staphylococcus	-	2	-
Pseudomonas	1	1	-
Enterobacter	-	1	-
Total	15	13	1

Table 9: Risk factors for resistance (n=29).

Factor	MDR n=15		
Age (yrs.)			
≤60	7	4	0
>60	8	9	1
Gender			
Male	13	10	1
Female	2	3	0
Hospitalisation in last 30 days	5	4	1
Immuno-compromised status	12	9	1
Place of Hospitalisation			
Non-ICU	7	5	
ICU	8	8	1
Radiology			
≤ 3zones	9	3	
>3 zones	6	10	1
CURB 65 score			
≤ 3	10	5	
>3	3	8	1
Ventilator Support			
NIV	2	8	1
Invasive ventilation	5	5	

Risk factors for resistance

Analysis of risk factors for resistance among the pathogens revealed that elderly more than 60 years, male gender, previous hospitalization, immunocompromised state, pulmonary consolidation more than 3 zones and

mechanical ventilation in ICU were more commonly associated as risk factors. CURB 65 score had no significant association (Table 9).

DISCUSSION

Author wanted to elucidate, the clinical, laboratory and radiological presentation, the microbial etiological study with its resistance pattern and clarify the risk factors for drug resistance and the outcome.

This prospective study shows that these patients who were currently hospitalized with pneumonia had recent contact with health care system provided through hemodialysis, hospitalization for intercurrent illness or residents in nursing homes. Empirical antibiotic therapy was administered in 49.3% cases before admission. The appropriateness of antibiotic therapy may not be effective in all cases.⁷

Out of 58 cases having chronic kidney disease, 27 were on hemodialysis. Hemodialysis status in this series (18.2%) may be associated with recent hospitalization or nursing home residence that may have contributed to risk of HAI, and ultimately pneumonia. Two large retrospective study showed high disease burden and mortality of pneumonia in hemodialysis patients, which may not be necessarily related to hemodialysis as the only illness.^{8,9}

Majority of the patients were elder than 60 years (73%). In most studies patients were older when compared with patients diagnosed with CAP. ¹⁰⁻¹³ The gender distribution was not statistically significant.

Many patients had multiple co-morbidities, majority having immunocompromised illness including CKD, diabetes mellitus or malignancy. They had altered sensorium as extrapulmonary symptoms that could predispose them risk of aspiration. Similar observation were made by Caratala J et al. ¹⁴

Cough, dyspnoea and fever were predominant pulmonary presentations. Majority presented with less than 7 days duration as evidenced by raised mean leucocyte count, procalcitonin level, renal and hepatic impairment. Bilateral lung lesions on radiography were also common features.¹⁵

Correlation of various parameters with outcome among non-survivors reveals bilateral consolidation was mostly seen that was statistically significant (p=0.0001). Pathogens were isolated among 55 out of 91 available cases; others could be due to viral aetiology which were not evaluated due to lack of invasive procedure necessary to establish the diagnosis. The real incidence of pathogenic cause could be underestimated. Bacteraemia occurred in 16 patients.

Klebsiella spp (20.95%), Acinetobacter (6.1%) and E.Coli (3.38%) were the most commonly isolated whereas Staphylococcus aureus was the only gram positive

organism isolated. Multidrug and extensive drug resistance was encountered among the Klebsiella and Acinetobacter spp. D'Agata EM found 0.55%-17% prevalence of infections caused by pathogens possessing extended spectrum b-lactamases.¹⁷ Infection colonization due to carbapenem resistant Enterobacteriaceae (CRE) is emerging as an important challenge particularly in high risk patients due to widespread use of carbapenems. The Centres for Disease Control And Prevention (CDC) have responded to the rising peril by classifying CRE as an urgent threat to public health. 18 The prevalence of CRE colonization in hospitalized patients ranges from 3-7% but can be higher in patients admitted to critical care units (CCU). 19,20 In an Indian study it was found that the prevalence of CRE in CCU ranges between 13-51%.²¹ Among the recent emergence of carbapenem - resistant Klebsiella species, three carbapenem hydrolysing betalactamase variants(KPC-1-KPC-3) have been reported.²²⁻ ²⁴ These enzymes confer moderate to high level resistance to all agents in the carbapenem class. Some of the plasmids that carry the genes responsible for carbapenem resistance also carry genes encoding extended-spectrum beta lactamases; in addition, many of the isolates also carries determinants of resistance to aminoglycosides and are fluoroquinolone resistance, thus making these strains resistant to multiple classes of antimicrobial agents.²⁵

Acinetobacter baumannii has emerged globally as an important pathogen in hospitalized patients, causing high morbidity and mortality. It can cause pneumonia, bacteremia, meningitis, urinary tract infections and skin and soft tissue infections. This organism accounts for around 10% of all gram-negative isolate identified in Brooklyn, New York.²⁶

The spread of Gram- negative bacteria resistance to carbapenems is an urgent public threat and a critical priority according to World Health Organisation.²⁷ The variability of MDRO prevalence may be based on geographic location and patient population. Thus, treatment choice should be guided by local microbial epidemiology. This studies on microbial resistance are consistent with studies by Chalmers JD, Aliberti S et al.^{28,29}

Device Associated infections such as Ventilator associated pneumonia, central line associated blood stream infections, catheter associated urinary tract infections and surgical site infections account for most of the health care associated infections that contributes to the growing antimicrobial resistance with resultant morbidity, mortality and adverse outcomes.^{30,31}

Multiple risk factors for resistance were identified. Male gender, immune compromised diseases (CKD, DM, malignancy), bilateral pulmonary involvement and hospitalization for at least 48 hours in preceding 90 days were associated with isolation of MDRO. 32-34 Pneumonia in CKD was associated with increased duration of intravenous antibiotics which could be predictive of

increased hospitalization days. A proactive approach by active surveillance and a strong compliance with infection control measures would be needed to prevent spread of CRE transmission.³⁵

CONCLUSION

The prevalence of healthcare-associated lower respiratory infections in HCAI settings were more in elderly male patients who were on prior empiric antibiotic therapy, chronic dialysis, previous hospitalization or resident in nursing home. COPD, Immune compromised illness including CKD, DM, and malignancy were important comorbid illnesses. Non survivors had bilateral consolidation that was statistically significant. Septicaemia was noticeable among the ICU cases. *Klebsiella pneumoniae*, *Acinetobacter* and *E. coli* were the important gramnegative pathogens. MDR and XDR was seen among Klebsiella and Acinetobacter pathogens.

Infection control, antibiotic prescribing audit as a policy to thwart antimicrobial resistance need to be strengthened in each hospital in the country.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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