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EDITORIAL

Revolutionizing the Treatment of Tuberculosis: The Promise of BPaL and BPaLM Regimens

Bipul Kanti Biswas

[Chest Heart J. 2023; 47(2) : 74-75]
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Proper treatment for tuberculosis (TB), including its drug-resistant strains, entails taking multiple medications together for an adequate amount of time. Conventional treatment protocols for multidrug-resistant tuberculosis (MDR-TB; defined as tuberculosis resistant to both isoniazid and rifampicin; referred to as MDR/RR-TB) and rifampicin-resistant tuberculosis (RR-TB) were long and laborious, using painful injectable medications. The length of treatment for RR-TB was around three times longer than that of drug-susceptible TB, and it came with a significantly higher pill burden and risk of side effects, both during and after treatment. Treatment was even more challenging for persons with RR-TB and fluoroquinolone resistance (pre-XDR-TB), as well as those with extensively drug-resistant TB (XDR-TB, defined as pre-XDR-TB plus resistance to at least one of bedaquiline or linezolid).

Since the 1990s, numerous studies and initiatives have been carried out to explore more efficient and innovative treatment regimens, utilizing contemporary and reinvented medicines, in response to the dire need for more effective treatment regimens to benefit people with RR-TB, MDR-TB, and those with even more extensive patterns of drug resistance. The World Health Organization (WHO) has consistently studied novel information regarding the utilization of specific drug compositions and combinations of regimens with varying periods of time. Most recently, emerging data have contributed to a significant improvement in the recommended course of treatment for patients with MDR/RR-TB and pre-XDR-TB[1].

The incorporation and prioritization of a new all-oral 6-month regimen is the main modification in the most recent WHO recommendations. Bedaquiline (B), pretomanid (Pa), linezolid (L), and moxifloxacin (M) constitute the regimen known as BPaLM for patients with MDR/RR-TB; for those with pre-XDR-TB, the combination can be used without moxifloxacin (BPaL). Even in the context of resource-poor setting like our country, the shorter duration, more affordable price, lower pill burden, and high potency of this breakthrough regimen should facilitate much better management and treatment outcomes for individuals with MDR/RR-TB or pre-XDR-TB. Furthermore, it should help our healthcare systems to treat a greater number of patients.

The TB-PRACTECAL randomized controlled trial provided the data that served as the foundation for the updated recommendations[2]. Compared to earlier standard-of-care regimens, this trial's 6-month BPaLM regimen demonstrated significantly higher treatment success rates (52% vs 89%) and reduced rates of treatment failure, fatalities, and loss to follow-up. People with RR-TB were randomized to receive regimens of bedaquiline, pretomanid, and daily linezolid at four alternative dosage schedules in a second trial known as ZeNiX-TB[3]. Both TB-PRACTECAL and ZeNiX-TB trial data suggested that a 600 mg linezolid dose achieved good efficacy but resulted in fewer side effects.

The implementation of the BPaLM/BPaL regimen has several restrictions. This recommendation currently only applies to adults and adolescents 14 years of age and above owing to the absence of safety data on pretomanid in children under 14

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years of age. Enrolling individuals with CD4 counts below 100 cells/mm3 requires considerable caution, even if the guideline is applicable to everyone, regardless of HIV status. Pregnant and nursing women should consider alternative treatment options as the safety of pretomanid at these stages of life is uncertain. While the BPaLM/BPaL regimen is appropriate for the majority of tuberculosis cases, it isn't recommended for cases of extrapulmonary tuberculosis involving the central nervous system (CNS), osteoarticular TB and disseminated (miliary) TB.

A strong "Call to Action" was issued on World TB Day 2023 by the WHO, donor community and other stakeholder to quickly expand global access to the BPaLM/BPaL regimen[4]. As soon as the guidelines were released, the WHO also announced the setting up of a worldwide BPaLM accelerator platform. This platform served as a forum for technical debates and information exchange aimed at addressing issues related to the implementation of the BPaLM/BPaL regimen[5].

In conclusion, the introduction of the BPaL and BPaLM regimens represents a significant milestone in the fight against tuberculosis. These innovative treatment approaches offer new hope to patients with drug-resistant TB and have the potential to revolutionize TB treatment globally. However, concerted efforts are needed to overcome implementation challenges and ensure equitable access to these life-saving therapies. With continued investment in research, healthcare infrastructure, and global collaboration, we can strive towards a world free from the burden of tuberculosis.

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ORIGINAL ARTICLE

Importance of Fractional Exhaled Nitric Oxide in the Differentiation of Asthma-COPD Overlap (ACO), Asthma and COPD

Muhammad Humayoun Kabir[1], Md Ezazul Karim[2], H.M. Aminur Rashid[3], Prottush Kumar Mondal[4], Mohammad Mostafizur Rahman[4], Abdullah Al Mujahid[4], S M Abdur Razzaque[5]

Abstract:

Background: *Chronic obstructive pulmonary disease (COPD) and asthma are the most common inflammatory airway diseases. Some individuals share features of both asthma and COPD called asthma-COPD overlap (ACO) syndrome (ACOS). Fractional exhaled nitric oxide (FeNO) is an easy, sensitive, reproducible, and noninvasive marker of eosinophilic airway inflammation. Accordingly, FeNO is extensively used to diagnose and manage asthma. Patients with COPD who share some of the features of asthma have a condition called asthma–COPD overlap syndrome (ACOS).*

Aims: *To evaluate the importance of fractional exhaled nitric oxide (FeNO) in the differentiation of asthma-COPD overlap (ACO), asthma and COPD.*

Materials & Methods: *This cross sectional observational study conducted at the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital from January 2019 to December 2019. A total of 117 patients with asthma-COPD overlap (ACO), asthma and COPD were enrolled in this study. Statistical analyses of the results were obtained by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-23).*

Results: *Out of 117 patients with asthma-COPD overlap (ACO), asthma and COPD. Out of which 50 patients were asthma, 52 were COPD and 15 were asthma-COPD overlap (ACO) group. Age, sex and BMI were not statistically significant when compared Asthma, COPD and ACO group. However, smoker 12(240%) patients were smoker in asthma group, 48(92.3%) in COPD group and 13(86.7%) in ACO group, that was statistically significant ($p<0.05$). Mean FVC, FEV^1, post-bronchodilator FEV_1/FVC and FEF 25-75 were also statistically significant ($p<0.005$) when compared Asthma, COPD and ACO group. Mean FeNO was found 42.9±18.9 ppb in Asthma group, 12.0±5.4 ppb in COPD group and 25.2±9.3 ppb in ACO group, which indicated that FeNO level was significantly ($p<0.05$) increased in Asthma group than COPD and ACO group. Based on the receiver-operator characteristic (ROC) curves FeNO level had area under curve 0.560. Receiver-operator characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value e"20.5 ppb, with 60.0% sensitivity and 52.9% specificity for prediction of ACO.*

Conclusion: *In conclusion, the present study has demonstrated that smoker, FVC, FEV_1, post-bronchodilator FEV_1/FVC, FEF 25-75 and FeNo were statistically significant when compared Asthma, COPD and ACO group. Using ROC best cut off value of FeNO e"20.5 ppb for prediction of ACO.*

Keywords: Asthma-COPD Overlap (ACO), Asthma, COPD, Fractional Exhaled Nitric Oxide (FeNO)

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Introduction:

Asthma and COPD are common diseases of airways and lungs and share some common clinical characteristics. Asthma, a chronic disorder of the airways, is associated with two main characteristics: airway hyperresponsiveness (AHR) and airway inflammation. The airflow limitation is reversible.[1] Meanwhile, COPD is a disease characterized by persistent, progressive airflow limitation and is also an inflammatory disease.[2]

Fractional exhaled nitric oxide (FeNO) is an easy, sensitive, reproducible and noninvasive marker for directly detecting eosinophilic airway inflammation.[3] Given the airway inflammation can be assessed through FeNO measurement, the American Thoracic Society clinical practice guideline recommends the use of FeNO to diagnose and monitor asthma.[4] Some patients with COPD have the features of asthma; FeNo values are elevated in this specific category of patients with COPD, and this condition is called asthma-COPD overlap (ACO).[5]

ACO was proposed by the science committees of both Global Initiative for Asthma (GINA) and Global Initiative for Obstructive Lung Disease (GOLD) in 2015.[6] However, the exact role of FeNO in patients with ACO remains to be defined. Corticosteroids are known to increase the risk for pneumonia and other diseases in COPD patients, but ACO patients positively respond to treatment with inhaled corticosteroids. FeNO could differentiate ACO from COPD and could offer additional advantages for the management of COPD patients. FeNO measurement is an easy, sensitive, noninvasive and reproducible method for directly detecting airway inflammation. In the present study, we performed a cross sectional-observational study that aimed to evaluate the diagnostic performance of FeNO, which may be able to indicate airway eosinophilic inflammation in patients with COPD and to differentiate ACO from COPD.

Materials and methods

This cross sectional observational study conducted at the Department of Respiratory Medicine of National Institute of the Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka from January 2019 to December 2019.

Inclusion criteria:

Asthma, Asthma-COPD overlap (ACO), and COPD patients defined as per GOLD and GINA guideline who were willing to participate in the study

Exclusion criteria:

- Bronchiectasis
- Cystic fibrosis
- Obliterative bronchiolitis
- Reactive airway dysfunction syndrome
- Used any oral corticosteroid in the previous 4 weeks

Operational definition:

FeNO

Fractional exhaled breath (FENO) is a quantitative, noninvasive, simple, and safe method of measuring airway inûammation that provides a complementary tool to other ways of assessing airways disease, including asthma.

Asthma

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of the respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airway limitation.[6]

COPD

COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[6]

Asthma-COPD overlap syndrome (ACOS) or Asthma-COPD overlap:

Asthma-COPD overlap syndrome (ACOS) or Asthma-COPD overlap is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACO is therefore identified in clinical practice by the features that it shares with both asthma and COPD.

Study procedure

A total of 117 patients with asthma, asthma-COPD overlap (ACO), and COPD attending in outpatient

department of NIDCH were selected as per inclusion & exclusion criteria. Purposive sampling was done in this study. In case, information about patients was obtained after getting consent. Consent from the patient was obtained after discussing with patient about study procedure. Enrolled patients were then evaluated properly by taking history, physical examination and investigations like full blood count and Chest X ray assay. Data were recorded by a standard proforma (History and clinical examination details). The relevant socio-demographic characteristics and history of the smoking were collected by face to face interview using predesigned interveiw schedule. After complection of interview the patient was examined physically all information and findings were recorded in the preformed proforma. After selection of the patient, spirometry was performed in each case to exclude the restrictive airway diseases. A rapport was built up individually with each patient. All subjects were asked to undergo spirometry in a reproducible way, and the best values were retained. FeNO level was measured according to the American Thoracic Society recommendations. Patients were instructed to inhale NO-free air to total lung capacity and immediately exhale fully into the device at a flow rate of 50 mL/s for 10 seconds. The collected data of each patient was recorded systematically. All data were analyzed by using computer based SPSS -23 (statistical package for social sciences). Data were presented in frequency, percentage and mean and standard deviation as applicable. Chi square test was used for categorical variables. ANOVA test was used for continuous variables. Receiver-operator characteristic (ROC) curve of FeNO level was used for prediction of ACO. P value of less than 0.05 was considered as significant.

Observations and results

This cross sectional observational study was carried out in the Department of Respiratory Medicine, NIDCH, Dhaka from January 2019 to December 2019. One hundred and seventeen (117) patients with asthma, asthma-COPD overlap (ACO), and COPD were included in this study based on inclusion and exclusion criteria. Out of which 50 patients were asthma, 52 were COPD and 15 were asthma-COPD overlap (ACO) group.

In this study half (50.0%) patients belonged to age 51-70 years in asthma group, 33(63.5%) in COPD group and 8(53.3%) in ACO group. The mean age was found 54.9±15.0 years in asthma group, 60.7±12.6 years in COPD group and 62.3±14.3 years in ACO group. Majority (70.0%) patients were male in asthma group, 42(80.8%) in COPD group and 12(80.0%) in ACO group. Two third (66.0%) patients were BMI 18.5-24.9 kg/m^2 in asthma group, 37(71.2%) in COPD group and 14(93.3%) in ACO group. The mean BMI was found 22.9±3.6 kg/m^2 in asthma group, 21.5±3.0 kg/m^2 in COPD group and 22.7±2.8 kg/m^2 in ACO group. There were no significant different regarding age, sex and BMI among three groups (Table-I). 12(240%) patients were smoker in asthma group, 48(92.3%) in COPD group and 13(86.7%) in ACO group. The differences were statistically significant ($p<0.05$) among three groups (Table-II). Mean FVC was found 2.42±0.92 L in asthma group, 1.80±0.56 L in COPD group and 2.35±0.50 L in ACO group. The mean FEV_1 was found 1.85±0.77 L in asthma group, 0.89±0.37 L in COPD group and 1.38±0.26 L in ACO group. Mean post-bronchodilator FEV_1/FVC was found 83.7±6.9 percent in asthma group, 48.1±10.0 percent in COPD group and 63.6±2.3 percent in ACO group. The differences were statistically significant ($p<0.05$) among three groups (Table-III). Mean FEF 25-75 was found 2.12±1.0 L/sec in asthma group, 0.58±0.46 L/sec in COPD group and 1.58±0.19 L/sec in ACO group. Mean FeNO was found 42.9±18.9 ppb in asthma group, 12.0±5.4 ppb in COPD group and 25.2±9.3 ppb in ACO group. The differences were statistically significant ($p<0.05$) among three groups (Table-IV).

Based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.947. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value e"21.5 ppb, with 92.0% sensitivity and 86.6% specificity for prediction of asthma (Table-V & Figure-1). Based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.030. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value e"15.5 ppb, with 30.8% sensitivity and 4.62% specificity for prediction of COPD (Table-VI & Figure-2). Based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.560. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value e"20.5 ppb, with 60.0% sensitivity and 52.9% specificity for prediction of ACO (Table-VII & Figure-3)

Table I

Demographic characteristics of the study subjects (n=117)

Demographic characteristics	Asthma (n=50)		COPD (n=52)		ACO (n=15)		*P* value
	n	%	n	%	n	%	
Age (years)							
≤30 3	6.0	1	1.9	0	0.0		
31-50	16	32.0	10	19.2	3	20.0	
51-70	25	50.0	33	63.5	8	53.3	
>70	6	12.0	8	15.4	4	26.7	
Mean±SD	54.9	±15.0	60.7	±12.6	62.3	±14.3	0.060^{ns}
Range (min-max)	20.0	-85.0	28.0	-90.0	34.0	-86.0	
Sex							
Male	35	70.0	42	80.8	12	80.0	0.413^{ns}
Female	15	30.0	10	19.2	3	20.0	
BMI (kg/m^2)							
<18.5	5	10.0	8	15.4	0	0.0	
18.5-24.9	33	66.0	37	71.2	14	93.3	
25.0-29.9	10	20.0	7	13.5	0	0.0	
≥30.0	2	4.0	0	0.0	1	6.7	
Mean±SD	22.9	±3.6	21.5	±3.0	22.7	±2.8	0.079^{ns}
Range (min-max)	16.7	-31.0	16.5	-28.9	19.7	-30.8	

ns= not significant; P value reached from ANOVA test; P value reached from chi square test

Table II

Distribution of the study patients according to smoking (n=117)

Smoker	Asthma (n=50)		COPD (n=52)		ACO (n=15)		*P* value
	n	%	n	%	n	%	
No 38	76.0	4	7.7	2	13.3	0.001^{s}	
Yes 12	24.0	48	92.3	13	86.7		
If yes							
<20 (pack/yr)	10	83.3	12	25.0	3	23.1	
≥20 (pack/yr)	2	16.7	36	75.0	10	76.9	

s= significant; P value reached from chi square test

Table-III

Distribution of the study patients according to FVC, FEV_1 and post-bronchodilator FEV_1/FVC (n=117)

	Asthma(n=50) Mean±SD	COPD(n=52) Mean±SD	ACO(n=15) Mean±SD	*P* value
FVC (L)	2.42±0.92	1.80±0.56	2.35±0.50	0.001^{s}
Range (min-max)	0.76-5.55	0.91-2.93	1.64-2.90	
FEV_1 (L)	1.85±0.77	0.89±0.37	1.38±0.26	0.001^{s}
Range (min-max)	0.64-4.08	0.40-1.62	1.01-1.70	
Post-bronchodilator FEV_1/FVC (%)	83.7±6.9	48.1±10.0	63.6±2.3	0.001^{s}
Range (min-max)	71.6-97.0	33.0-69.4	61.0-67.0	

s= significant; P value reached from ANOVA test

Table IV

Distribution of the study patients according to FEF 25-75 (n=117)

	Asthma(n=50) Mean±SD	COPD(n=52) Mean±SD	ACO(n=15) Mean±SD	*P* value
FEF 25-75 (L/sec)	2.12±1.0	0.58±0.46	1.58±0.19	0.001[s]
Range (min-max)	0.35-5.04	0.17-2.23	1.34-1.85	
FeNO (ppb)	42.9±18.9	12.0±5.4	25.2±9.3	0.001[s]
Range (min-max)	19.0-85.0	3.0-22.0	13.0-41.0	

s= significant; P value reached from ANOVA test

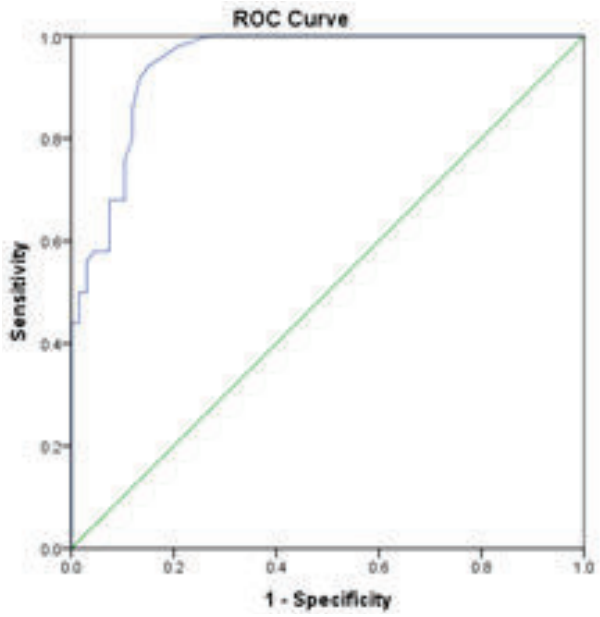

Figure 1: *Receiver-operating characteristic curves of FeNO level for prediction of asthma*

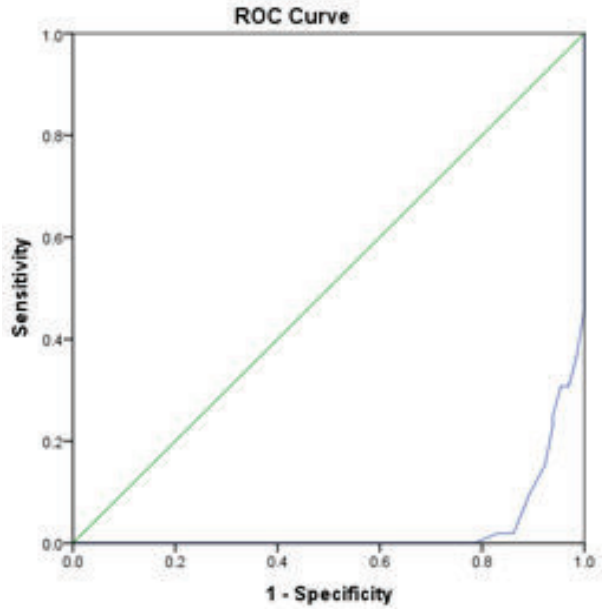

Figure 2: *Receiver-operating characteristic curves of FeNO level for prediction of COPD*

Table V

Receiver-operating characteristic (ROC) curve of FeNO level for prediction of asthma

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI) Lower bound	Upper bound
	≥19.5	98.0	79.1			
	≥20.5	94.0	85.1			
	≥21.5	92.0	86.6			
FeNO level	≥22.5	86.0	88.1	0.947	0.910	0.983
	≥23.5	82.0	88.1			
	≥24.5	80.0	88.1			
	≥25.5	76.0	89.6			

Table VI

Receiver-operating characteristic (ROC) curve of FeNO level for prediction of COPD

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI) Lower bound	Upper bound
	≥13.5	36.5	1.54			
	≥15.5	30.8	4.62			
FeNO level	≥17.5	23.1	6.15	0.030	0.005	0.055
	≥18.5	15.4	7.69			
	≥20.5	1.9	13.85			

Table-VII

Receiver-operating characteristic (ROC) curve of FeNO level for prediction of ACO

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI) Lower bound	Upper bound
	≥16.5	73.3	38.2			
	≥18.5	66.7	43.1			
	≥19.5	60.0	47.1			
FeNO level	≥20.5	60.0	52.9	0.560	0.445	0.674
	≥21.5	53.3	53.9			
	≥23.5	53.3	59.8			
	≥25.5	46.7	62.7			

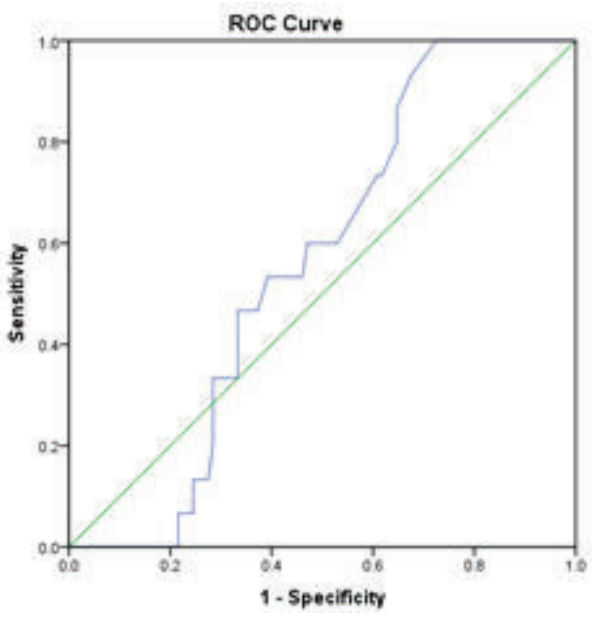

Figure 3: *Receiver-operating characteristic curves of FeNO level for prediction of ACO*

Discussion:

This cross sectional observational study was carried out with an aim to evaluate the importance of fractional exhaled nitric oxide (FeNO) in the differentiation of asthma-COPD overlap (ACO), asthma and COPD. A total of 117 patients with asthma-COPD overlap (ACO), asthma and COPD were attending in the Department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period from January 2019 to December 2019 were included in this study. Asthma, Asthma-COPD overlap (ACO), and COPD patients defined as per GOLD and GINA guideline were enrolled in this study.

In this study it was observed that half (50.0%) patients belonged to age 51-70 years in asthma group, 33 (63.5%) in COPD group and 8(53.3%) in ACO group. The mean age was found 54.9±15.0 years in asthma group, 60.7±12.6 years in COPD

group and 62.3±14.3 years in ACO group. The mean age was not statistically significant (p>0.05) among three groups. In a study of Chen et al.[7] found that the mean age was 41.92±15.23 years in asthma group, 63.52±9.58 years in COPD group and 63.17±9.17 years in ACOS group. Shi et al.[8] reported that the mean age was 62.2±5.9 years in asthma group, 65.4±7.0 years in COPD group and 64.8±6.5 years in ACO group, the difference was not statistically significant among three groups. Takayama et al.[9] demonstrated that the mean age was 72.3±9.8 years in COPD group and 72.3±7.8 years in ACO group, the difference was not statistically significant between two groups. Another study conducted by Colak et al.[10] documented that mean age was 60 years, 68 years and 68 years in asthma, COPD and ACO group respectively. The reason for the difference of age at presentation in various regions of the world may be due to geographic/ ethnic influence.

In this present study it was observed that majority (70.0%) patients were male in asthma group, 42(80.8%) in COPD group and 12(80.0%) in ACO group. Female was 15(30.0%), 10(19.2%) and 3(20.0%) in asthma, COPD and ACO group respectively. The differences were not statistically significant (p>0.05) among three groups. Almost similar study observed by Shi et al.[8] which showed that male was 11(68.8%) in asthma group, 21(84.0%) in COPD group and 13(68.4%) in ACO group. The differences were not statistically significant among three groups. Chen et al.[7] consisted that male was found 215(43.0%) in asthma group, 109(82.6%) in COPD group and 37(64.9%) in ACOS group. Female was 285(57.0%), 23(17.4%) and 20(35.1%) in asthma, COPD and ACOS group respectively. Takayama et al.[9] in their study found that the male was 54(83.1%) in COPD group and 42(75.0%) in ACO group. Female was 11(16.9%) and 14(25.0%) in COPD and ACO group respectively. The differences were not statistically significant (p>0.05) between two groups. Another study conducted by Colak et al.[10] where they observed that male patients was 142(32.0%) in asthma group, 220(54.0%) in COPD group and 58(42.0%) in ACO group. This difference across various studies may be due to different demographic and geographic distribution of the population.

In this study it was observed that 12(240%) patients were smoker in asthma group, 48(92.3%) in COPD group and 13(86.7%) in ACO group. The differences were statistically significant (p<0.05) among three groups. In a study of Chen et al.[7] which showed that smoking history was 129(25.80%) in asthma group, 98(74.24%) in COPD and 23(40.35%) in ACOS patients. Takayama et al.[9] documented that current smoker was 14(21.5%) in COPD group and 12(21.4%) in ACO group. Ex-smoker was 48(73.9%) and 40(71.4%) in COPD and ACO group respectively. Mean pack-year was 56.0±31.6 in COPD group and 46.4±30.0 in ACO group. The mean pack-year was statistically significant between two groups. Shi et al. (2018) have found that there were more smokers in the ACO group (57.9%) than in the Asthma group (25.0%, *p*=0.037). Another study documented by Colak et al.[10] where they observed smoker was 55(12.0%), 100(25.0%) and 40(29.0%) in asthma, COPD and ACO group respectively. This difference across various studies may be due to different demographic and geographic distribution of the population.

Our study showed that two third (66.0%) patients were BMI 18.5-24.9 kg/m^2 in asthma group, 37(71.2%) in COPD group and 14(93.3%) in ACO group. The mean BMI was found 22.9±3.6 kg/m^2 in asthma group, 21.5±3.0 kg/m^2 in COPD group and 22.7±2.8 kg/m^2 in ACO group. The mean BMI were not statistically significant (p>0.05) among three groups. Similarly, Shi et al.[8] had found that mean BMI was 24.0±2.0 kg/m^2 -asthma group, 23.0±3.7 kg/m^2 in COPD group and 22.9±1.9 kg/m^2 in ACO group. The differences were not statistically significant (p>0.05) among three groups. Takayama et al.[9] reported that the mean BMI was 23.0±3.7 kg/m^2 in COPD group and 22.6±5.6 kg/m^2 in ACO group, The mean BMI were not statistically significant (p>0.05) between two groups. Colak et al.[10] also documented that mean BMI was 25 kg/m^2 in asthma group, 25 kg/m^2 in COPD group and 26 kg/m^2 in ACO group. This difference across various studies may be due to different demographic and geographic distribution of the population.

In this study it was observed that mean FVC was found 2.42±0.92 L in asthma group, 1.80±0.56 L in COPD group and 2.35±0.50 L in ACO group. The mean FEV_1 was found 1.85±0.77 L in asthma group, 0.89±0.37 L in COPD group and 1.38±0.26 L in ACO group. The differences were statistically

significant (p<0.05) among three groups. In a study of Shi et al.[8] which showed mean FVC was 3.49±0.51 L in asthma group, 2.57±0.76 L in COPD group and 5.50±0.50 L in ACO group. The mean FEV_1 was 2.59±0.37 L, 1.47±0.56 L and 1.39±0.35 L in asthma, COPD and ACO group respectively. The differences were statistically significant (p<0.05) among three groups. Takayama et al.[9] in their study found that mean FVC was 3.15±0.80 L in COPD group and 3.04±0.77 L in ACO group. The differences were not statistically significant between two groups. The mean FEV_1 was 1.72±0.56 L in COPD group and 1.55±0.51 L in ACO group. The differences were not statistically significant (p>0.05) between two groups. Another study conducted by Chen et al.[7] which consisted that mean FVC was 96.99±15.59 % predicted in asthma group, 75.80±17.73% predicted in COPD group and 77.42±17.56% predicted in ACOS group. Mean FEV_1 was 88.49±19.38% predicted in asthma group, 50.81±19.30% predicted in COPD group and 51.01±18.64% in predicted ACOS group.

In my study showed that mean post-bronchodilator FEV_1/FVC was found 83.7±6.9 percent in asthma group, 48.1±10.0 percent in COPD group and 63.6±2.3 percent in ACO group. The differences were statistically significant (p<0.05) among three groups. In a study of Chen et al.[7] demonstrated that mean post-bronchodilator FEV_1/FVC was 76.89±11.37% in asthma group, 51.44±12.37% in COPD group and 51.88±11.70% in ACOS group. Another study documented by Shi et al.[8] where they found mean FEV_1/FVC was 74.37±2.25 % in asthma group, 53.65±10.93 % in COPD group and 55.39±6.28 % in ACO group. The differences were statistically significant (p<0.05) among three groups.

Our study showed that mean FEF 25-75 was found 2.12±1.0 L/sec in asthma group, 0.58±0.46 L/sec in COPD group and 1.58±0.19 L/sec in ACO group. The differences were statistically significant (p<0.05) among three groups. In a study of Donohue et al.[11] where they showed mean FEF 25-75% was 0.759±0.6898 L/Sec with range from 0.12 to 3.87 L/sec.

In this study it was observed that mean FeNO was found 42.9±18.9 ppb in asthma group, 12.0±5.4 ppb in COPD group and 25.2±9.3 ppb in ACO group. The differences were statistically significant (p<0.05) among three groups. Almost similar study conducted by Miskoff et al.[12] which showed that the mean FeNO (ppb) level in patients with an initial diagnosis of asthma, COPD, ACOS, and without a diagnosis was 40.5 (ppb), 19.48 (ppb), 28.19 (ppb), and 12.38 (ppb), respectively. Takayama et al.[9] in their study found that the FeNO levels were higher in patients with ACO than in patients with COPD (median 24.5 ppb [14.0–39.5 ppb] vs 16.0 ppb [12.0–20.0 ppb], respectively; P<0.01). Shi et al.[8] also observed their study that the FeNO levels of ACO (37.7±16.5 ppb) and asthma group (36.3±17.7 ppb) were higher in the COPD (21.9±10.3 ppb), while there was no significant difference between ACO and asthma groups (p=0.833). All subjects in ACO group had FeNO levels of >20 ppb, except for two patients; these patients had FeNO level of 15 and 18 ppb. 10 (52.6%) of total 19 in ACO group had FeNO levels of >35 ppb. Furthermore, the proportion of subjects with an elevated FeNO level also had significant differences among the three groups (p<0.001). Pillai[13] reported that mean FeNO in ACO group and COPD was 40.13 ± 17.2 ppb and 12.35 ± 4.19 ppb (p<0.001). Donohue et al.[11] consisted that the mean FeNO level for all patients was 15.3±17.2 parts per billion (ppb).

In this study it was observed that based on the receiver-operating characteristic (ROC) curves FeNO level had area under curve 0.560, 0.030 and 0.947 for prediction of ACO, COPD and asthma respectively. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value e"20.5 ppb, with 60.0% sensitivity and 52.9% specificity for prediction of ACO. Receiver-operating characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value e"15.5 ppb, with 30.8% sensitivity and 4.62% specificity for prediction of COPD. Receiver-operator characteristic (ROC) was constructed by using FeNO level, which gave a best cut off value e"21.5 ppb, with 92.0% sensitivity and 86.6% specificity for prediction of asthma. In a study of Chen et al.[7] where they constructed ROC curve defines the optimal cutoff value for FeNO level and was used to differentiate ACOS from COPD. The ROC AUC was estimated to be 0.783 for FeNO. The optimal diagnostic cutoff point was 22.5 ppb (with 70% sensitivity and 75% specificity). FeNO is a good predictor for differentiating ACOS from COPD, with an ROC AUC of 0.783. Taking

22.5 ppb as a cut-off point to diagnose ACOS, FeNO measurement indicated a sensitivity of 70% and a specificity of 75%, which agreed with previous studies. Donohue et al.[11] (2014) showed an FeNO level of 20 ppb in COPD patients with a previous diagnosis of asthma. Some authors have observed that patients with a cutoff point of 35 ppb can be classified as ACOS, whether or not they have allergic rhinitis.[14] Corticosteroids are known to increase the risk for pneumonia and other diseases in COPD patients[15], but ACOS patients positively respond to treatment with inhaled corticosteroids. Given that FeNO could differentiate ACOS from COPD, FeNO could offer additional advantages for the management of COPD patients. Takayama et al.[9] reported that ROC curve analysis demonstrated that 21.0 ppb was the best diagnostic cutoff value of FeNO for differentiating ACO from COPD (AUC: 0.671). The sensitivity and specificity at 21.0 ppb for the diagnosis of ACO were 62.5% and 75.4%, respectively. Among patients naïve to ICS, the AUC for FeNO was calculated to be 0.726, and the optimal diagnostic cut-off level was 25.0 ppb, with 60.6% sensitivity and 87.7% specificity for differentiating ACO from COPD. Chen et al6 reported that the best diagnostic cutoff level of FeNO was 22.5 ppb, with 70.2% sensitivity and 75.0% specificity for differentiating ACO from COPD. Four studies showed that FeNO can be useful to differentiate ACO(S) from COPD and introduced optimal cut-off values of 19, 22.5, 23, and 29 ppb with a sensitivity of 68, 70, 73, 80%, and specificity of 75, 75, 68.2, and 73%, respectively. The area under the curve (AUC) for the cut-off 19, 22.5, 23 and 29 ppb was 0.79, 0.78, 0.74, and 0.85, respectively.[7,16,17,18] This combination of cutoff values, which showed such high specificity, could be useful for preventing the inappropriate use of ICS in patients without an asthmatic component.

Conclusion:

In conclusion, the present study has demonstrated that smoker, FVC, FEV_1, post-bronchodilator FEV_1/FVC, FEF 25-75 and FeNo were statistically significant when compared asthma, COPD and ACO group. Using ROC best cut off value of FeNO e"20.5 ppb for prediction of ACO. Fractional exhaled nitric oxide (FeNO) is a simple, reproducible, and a noninvasive marker of inflammation which may be used as one piece of data to help the clinician better assess the patients true underlying pulmonary disorder and potentially change the treatment plan. Measurement of FeNO provides useful information to evaluate the airway calibre and responsiveness, and may indicate the management of patients with asthma, COPD and ACO. Although the primary purpose of this study was to help more accurately diagnose the patient, the true value of FeNO may be in regards to treatment. Therefore, further studies are needed to better understand FeNO and its applicability across the clinical spectrum. Furthermore, we simply focused the initial FeNO levels, and didn't follow-up serial FeNO levels regularly. It would be of interest to evaluate the role of FeNO monitoring the treatments of older patients with ACO.

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ORIGINAL ARTICLE

Bacteriological Profile and Antibiotic Sensitivity Pattern Among Ventilator-Associated Pneumonia Patients in Intensive Care Unit of NIDCH and Factors Contributing Antibiotic Resistance

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Abstract

Background: *Ventilator-associated pneumonia (VAP) is the most frequent intensive careunit (ICU) acquired infection and is associated with significant mortality, morbidity andcosts. The etiology and antimicrobial susceptibility pattern of VAP is variable and thereis scarcity of data. So, this study aimed to track the bacteriological profile of pneumoniaand their current local antibiotic susceptibility pattern among ICU patients (VAP) and toidentify factors responsible for antibiotic resistance.*

Objective: *To determine the spectrum of bacteria that causes Ventilator-associated pneumonia (VAP) by tracheal aspirates culture and the antibiotic sensitivity admitted in ICU.*

Materials and Methods: This was a cross-sectional descriptive type of observational study was conducted at the National Institute of Diseases of the Chest and Hospital (NIDCH) from 01.07.2019 to 30.06.2020. Total 46 diagnosed cases of VAP were included in this study. Following informed written consent, clinical and demographical history were taken, physical examination and relevant investigations were done for all patients. In all cases, ethical issues and health issues were maintained properly and collected data were analyzed by SPSS 23.

Results: *Among 46-VAP patients, average age of the study population was 54.26±12.01 SD (years), ranging from 31 to 90 years. Male female distribution showed male predominance with 76.1% male and 23.9% female. Regarding risk factors, 78.3% had history of smoking, 60.9% had self-medication, 41.3% history of steroid taking. 100% patients had mechanical ventilation, 56.5% had history of taking farm meat, 86.9% patients had history of previous antibiotic use, 63% had history of taking inadequate dose and duration of antibiotic and 21.7% had nasogastric aspiration.*

Bacteriological profile showed that 60.9% patients were infected by single organism. Of all organisms Acinetobacter baumannii had 37% and Enterobacter species had 37%.

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Streptococcus species 21.7%, Candida species 15.2%, Escherichia coli 13%, Pseudomonas aeruginosa 10.9% and Neisseria bacterial growth 4.3%.

Acinetobacter baumannii, 88.24% were resistant to amoxicilin+clavulonic acid, cefixime, cefuroxine whereas 100% were sensitive to aztreonam, colistin, tigecycline and doxycycline. Enterobacter species, 100% were resistant to cefixime, cefuroxime and amikacin with 100% were sensitive to moxifloxacin, aztreonam, colistin, tigecycline and doxycycline. Streptococcus species 100% were resistant to gentamycin with 100% were sensitive to azithromycin and linezolid.

Conclusion:*This study found that more than half of VAP patients were infected by single organism and by Acinetobacter baumannii and Enterobacter species were the major common causative organism. The factors most responsible for resistance are multi drug resistant pathogen, Inadequate dose and duration of antibiotic use, overuse of antibiotic and eating farm meat. However, further larger study is recommended to validate these findings.*

Keyword: *VAP, ICU, Antibiotic Resistance,NIDCH*

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Introduction:

Ventilator Associated Pneumonia (VAP) are the most common nosocomical infections acquired in people receiving mechanical ventilation. VAP is defined as pneumonia occurring more than 48 h after endotracheal intubation/initiation of mechanical ventilation or pneumonia developing even after extubation[1]. Ventilator Associated Pneumonia is divided into two groups based upon mechanical ventilation duration; early onset VAP (takes place after 2 to 4 days) and late onset VAP (taking place after day 5)[2].

VAP which is early-onset, usually less severe, mostly caused by antibiotic-sensitive bacteria and with a better prognosis, whereas late-onset VAP develops five or more days after the initiation of mechanical ventilation and is due to multidrug-resistant (MDR) pathogens and is usually associated with increased morbidity and mortality[3].

Ventilator-associated pneumonia (VAPs) are the most common infections acquired in the hospital with the highest prevalence in intensive care units (ICUs)[4,5] .Depending on the case definition and study population incidence of HAP is usually between 5 and 15 cases per 1000 hospital admissions but incidence of VAP in patents on mechanical ventilation is 6–20 fold greater [6,7,8]These infections negatively impact important patient outcomes and the health-care system because VAP significantly prolong treatment, escalate health care costs and are leading cause of death attributed to hospital infections [9,10,11]

VAP are caused by an imbalance between normal host defenses and the ability of microorganisms to colonize and then invade the lower respiratory tract. Although a wide spectrum of bacterial pathogens can cause VAP the most frequent causative agents are aerobic Gram-negative bacilli, especially Pseudomonas aeruginosa (P. aeruginosa), Acinetobacter spp, Klebsiella pneumoniae, Escherichia coli as well as Gram-positive cocci like Staphylococcus aureus [12,13]. Bacteria which cause VAP are often resistant to various antibiotics, but exact susceptibility profile depends on hospital or ICU, patient population and previous exposure to antibiotics. It is not static, but changes over time.

Many infections are polymicrobial and caused by multi-drug resistant (MDR) pathogens. Since early initiation of appropriate empiric antibiotic therapy is of vital importance for the patient, good knowledge of local prevalence of pathogens and their drug susceptibility patterns is essential. In some developing countries, the etiologic agents of VAP and their susceptibility to antibiotics are not systematically followed, making choice of empiric therapy difficult.

The aim of this study was to investigate prevalence of bacterial pathogens isolated from patients with VAP in an ICU and to reveal their susceptibility rates and to identify factors responsible for antibiotic resistance in order to establish a basis for empirical antibiotic therapy.

The main objective of this study is as follows-

- To know the spectrum of bacteria that causes Ventilator Associated Pneumonia by tracheal aspirates culture and the antibiotic sensitivity admitted in ICU
- To identify common bacteria isolated from tracheal aspirates that causes Ventilator Associated Pneumonia in ICU
- To observe antibiotic sensitivity of pathogenic bacteria.
- To identify the pattern of antibiotics resistance to bacteria.
- To explore the possible factor responsible for resistance.

Materials and Methods:

This cross-sectional, method validation studywas conducted in the Intensive care unit, National Institute of Diseases of the chest and Hospital Mohakhali, Dhaka, Bangladesh from July 2019 to June 2020.

Inclusion Criteria:

1) Patients with Ventilator-associated pneumonia admitted to ICU,

2) Patients with age 18 Years and older (Adult, Older Adult).

Exclusion criteria:

1) Patients unwilling to be included in study.

Patients diagnosed as VAP cases were approached for this study and 46 patients were selected according to the inclusion and exclusion criteria. Following informed written consent from each of the patient's attendent, history and clinical records was taken about age, gender, date of admission into ICU, duration of hospitalization, duration of mechanical ventilation, details of antibiotic therapy, history of surgery, underlying diseases, use of steroids, presence of neurological disorders and impairment of consciousness. Endotracheal aspirate was obtained with sterile precaution using a 22-inch, No. 14 Fr suction catheter and collected in a sterile container and sample was collected within 2 to 4 days. A length of approximately 24 cm of the catheter was passed through the endotracheal tube, and secretions were aspirated without instilling saline. After the catheter was withdrawn, 10-fold serial dilution of ETA was done with 0.9% normal saline and then plated for quantitative culture and Gram stain.

ETA was mechanically homogenized using sterile glass beads and were centrifuged for 1 min. The samples were then serially diluted in 0.9% sterile saline solution with final dilutions of 10"2, 10"3, and 10"4 and plated on sheep blood agar, chocolate agar, MacConkey agar and two Saboraud's dextrose agar (SDA) by using 2 mm nichrome wire loop, which holds 0.005 ml of solution. All plates were incubated overnight aerobically at 37°C except one SDA plate which was kept at room temperature. The plates for bacterial culture were incubated up to 48 h and SDA plates up to 1 week. For definitive diagnosis of VAP, quantitative culture threshold of >105 CFU/ml was considered significant. And growth of any organism below 105 CFU/ml was assumed to be due to colonization or contamination. Any significant growth was identified based on standard microbiological techniques. Antimicrobial susceptibility was performed for all the isolates with positive quantitative cultures. All relevant information was recorded in a predesigned case record form. After collection of data,they were processed and analyzed using SPSS (Statistical Package for Social Sciences) software version 23. Continuous scale data were presented as mean standard deviation and Categorical data were presented as frequency and percentage.

Results:

Table 1 shows majority of patients are within 40-60 years (56.5 %) and the mean age was found 54.26 ± 12.01 years with range from 31-90 years. Majority patients were male (76.1 %) and female was (23.9 %). Male to female ratio was 3.1: 1. The majority 31 (67.4 %) came from rural area, service holder and business were 21 (45.6 %). Majority of patients was SSC 15 (32.6 %). Middle class status was 31 (69.6 %).

In this study 6 risk factors were used. Table 2 shows major part of the patients had history of smoking (78.3%), Mechanical ventilation (100%). (41.3%) patients had h/o steroid taking. (86.9%) patients had h/o previous antibiotic use, self-medication (60.9%) and nasogastric aspiration (21.7%).

Table 3 showsClinical spectrum of different disease from the primary diagnosis.

Table 4 shows about 73.9% of the patients had COPD. 50% of the patients had DM (21.7%) and/or HTN (28.3%), 13% had CVD, 6.5% had CKD, 2.2% had malignancy.

Table-I

Demographic Characteristics of the study patients. (n=46)

Demographic Characteristics	Number of Patients	Percentage
Age		
<40 years	6	13 %
40-60 years	26	56.5 %
>60 years	14	30.4 %
Mean age (years)	54.26 ± 12.01 years	
Range (min-max)	31-90 years	
Sex		
Male	35	76.1 %
Female	11	23.9 %
Resident		
Rural	31	67.4 %
Urban	15	32.6 %
Occupation		
Service	7	15.2 %
Business	14	30.4 %
Day laborer	8	17.4 %
Retired	7	15.2 %
House hold	10	21.7 %
Education		
Under SSC	11	23.9 %
SSC	15	32.6%
HSC	11	23.9 %
Graduation and above	9	19.6 %
Socio Economics Status		
Higher	5	8.7 %
Middle	31	69.6 %
Lower	10	21.7 %

Table-II

Risk factors for developing VAP. (n=46)

Factors	Frequency	Percentage
H/o smoking	36	78.3
H/o steroid taking	19	41.3
H/o previous antibiotic use	40	86.9
Taking antibiotic without doctor's prescription (Self-medication)	28	60.9
Nasogastric aspiration	10	21.7
Mechanical ventilation (MV)	46	100

Table-III

Clinical spectrum of different disease (Primary diagnosis)

Primary Diagnosis	Number of patients	Percentage
COPD with type-II respiratory failure	28	60.8
COPD with corpulmonale	6	13.04
ILD with ARDS	4	8.69
Bilateral plural effusion with pneumothorax	2	4.34
Encysted plural effusion	1	0.21
Hydropneumothorax	2	4.34
Lung abscess with septicemia	1	0.21
Post TB fibrosis with corpulmonale	1	0.21
Lung cancer	1	0.21

Table-IV

Co-morbidities among patients. (n=46)

Co-morbidities	Frequency	Percent (%)
DM	10	21.7%
HTN	13	28.3%
COPD	34	73.9%
CKD	3	6.5%
CVD	6	13.0%
Malignancy	1	2.2%
	1	0.21

Figure 1 presents the Pattern of organism distribution among patients where sample size n=46. According to the Figure most of the patients were infected by single organism (60.9%).

Table 5 shows that the majority (74%) patients were infected by Acinetobacter baumannii (37%) and Enterobacter species (37%). Among rest, Streptococcus species (21.7%), Candida species (15.2%), Escherichia coli (13%), Pseudomonas aeruginosa (10.9%) and Neisseria bacterial growth (4.3%).

Figure 2 presents the Spectrum of Organism where the majority (74%) patients were infected by Acinetobacter baumannii (37%) and Enterobacter species (37%).

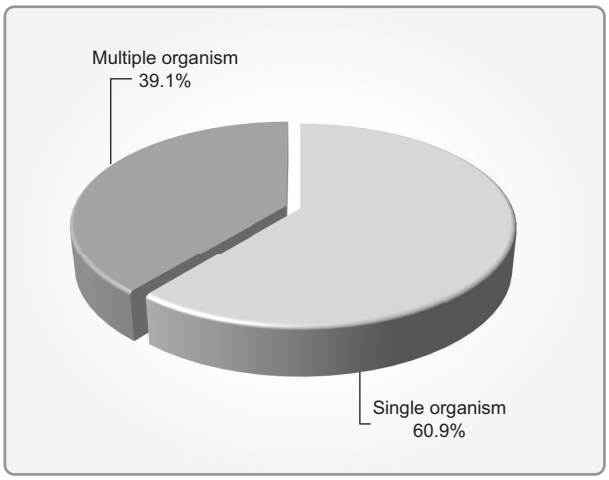

Figure 1: *Pattern of organism distribution among patients. (n=46)*

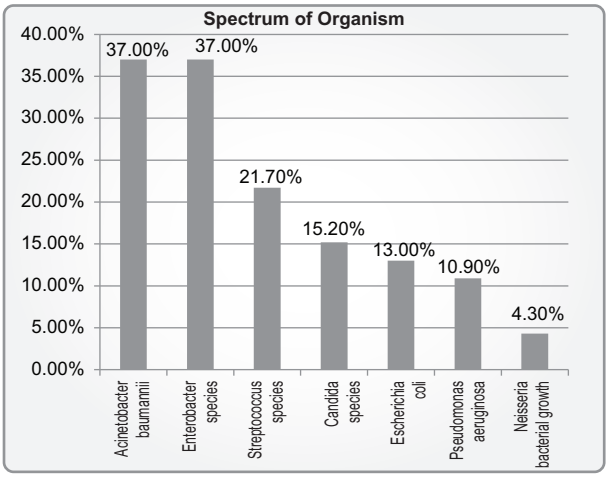

Figure 2: *Spectrum of Organism*

Table 6 shows maximum patients were infected by Gram-negative organisms (82.4 %) and rest of the patients (17.6%) were infected by Gram-positive organism.

Table 7 shows that out of 17 Acinetobacter baumannii 88.24% (15) were resistant to amoxicilin + clavulonic acid, cefixime and cefuroxime whereas 100% were sensitive to aztreonam, colistin, tigecycline and doxycycline.

Table 8 shows that out of 17 Enterobacter species 100% were resistant to cefixime, cefuroxime and amikacin whereas 100% were sensitive to moxifloxacin, aztreonam, colistin, tigecycline and doxycycline.

Table 9 shows that out of 10 Streptococcus species 100% were resistant to cefixime, cefuroxime and gentamycin whereas 100% were sensitive to azithromycin, linezolid, aztreonam, colistin, tigecycline and doxycycline.

Table 10 shows that out of 7 Candida species 100% were resistant to ceftriaxone, cefixime, cefuroxime, cefotaxime, cotrimoxazole, amikacin, vancomycin, linezolid, meropenem, nalidixic acid, imipenem, ertapenem, piperacillin+tazobactum, aztreonam, colistin, tigecycline and doxycycline.

Table 11 shows that out of 6 Escherichia coli 100% were resistant to amoxicilin+clavulonic acid, ceftriaxone, ciprofloxacin, cefixime, cefuroxime, cefotaxime and cotrimoxazole whereas 100% were sensitive to aztreonam, colistin, tigecycline and doxycycline.

Table 12 shows that 5 Pseudomonas aeruginosa 100% were resistant to amoxicilin+clavulonic acid, ceftriaxone, ciprofloxacin, cefixime, cefuroxime, cefotaxime, ceftazidime, cotrimoxazole, cefoperazone+sulbactum and nalidixic acid whereas 100% were sensitive to imipenem, ertapenem, piperacillin+tazobactum, aztreonam, colistin, tigecycline and doxycycline.

Table 13 shows that major Organism isolates were sensitive to Aztreonam, Collistin, Tigecycline, Doxycycline. But resistant to remaining common antibiotics Cefexime, Cefuroxime Amoxicilin+clavulonic acid, Amikacin, Ceftriaxone, Gentamicin, Ciprofloxacin, Cefotaxime, Co-trimoxazole.

Table 14 shows that major Registant Antibiotic (Cefexime, Cefuroxime Amoxicilin+clavulonic acid, Amikacin, Ceftriaxone, Gentamicin, Ciprofloxacin, Cefotaxime, Co-trimoxazole).Major Sensitive Antiobiotic (imipenem, ertapenem, piperacillin+tazobactum, aztreonam, colistin, tigecycline, linezolid, and doxycycline).

In this study 6 factors were found. Table 15 shows major part of the patients had MDR pathogen (100%). (39.1%) had H/o antibiotic overuse, H/o taking inadequate dose and duration of antibiotic (63%), self-medication (60.9%) and H/o taking farm meat (56.5%).

Table-V

Identification of VAP organisms (Spectrum).

Organism	Group	Frequency	Percent (%)
Acinetobacter baumannii	Gram (-) ve	17	37.0%
Enterobacter species	Gram (-) ve	17	37.0%
Streptococcus species	Gram (+) ve	10	21.7%
Candida species	Fungus	7	15.2%
Escherichia coli	Gram (-) ve	6	13.0%
Pseudomonas aeruginosa	Gram (-) ve	5	10.9%
Neisseria bacterial growth	Gram (-) ve	2	4.3%

Table-VI

Organisms Group.

Organisms Group	Frequency	Percentage
Gram (-) ve	47	82.4 %
Gram (+) ve	10	17.6%

Table-VII

Antibiotics sensitivity pattern of Acinetobacter baumannii among patients (n=17)

Antibiotic	Sensitive	Resistant
Amoxicilin+clavulonic acid	2 (11.76%)	15 (88.24%)
Levofloxacin	9 (52.94%)	8 (47.06%)
Moxifloxacin	10 (58.82%)	7 (41.18%)
Ceftriaxone	5 (29.41%)	12 (70.59%)
Ciprofloxacin	0 (0.00%)	17 (100%)
Cefixime	2 (11.76%)	15 (88.24%)
Cefuroxime	2 (11.76%)	15 (88.24%)
Cefotaxime	6 (35.29%)	11 (64.71%)
Ceftazidime	0 (0.00%)	17 (100%)
Co-trimoxazole	10 (58.82%)	7 (41.18%)
Cefoperazone+sulbactum	5 (29.41%)	12 (70.59%)
Gentamycin	3 (17.65%)	14 (82.35%)
Amikacin	2 (11.76%)	15 (88.24%)
Azithromycin	17 (100%)	0 (0.00%)
Vancomycin	12 (70.59%)	5 (29.41%)
Linezolid	13 (76.47%)	4 (23.53%)
Meropenem	5 (29.41%)	12 (70.59%)
Nalidixic acid	8 (47.06%)	9 (52.94%)
Imipenem	0 (0.00%)	17 (100%)
Etrapenem	4 (23.53%)	13 (76.47%)
Pipericillin+Tazobactam	5 (29.41%)	12 (70.59%)
Aztreonam	17 (100%)	0 (0.00%)
Collistin	17 (100%)	0 (0.00%)
Tigecycline	17 (100%)	0 (0.00%)
Doxycycline	17 (100%)	0 (0.00%)

Table-VIII

Antibiotics sensitivity pattern of Enterobacter species among patients (n=17)

Antibiotic	Sensitive	Resistant
Amoxicilin+clavulonic acid	3 (17.65%)	14 (82.35%)
Levofloxacin	14 (82.35%)	3 (17.65%)
Moxifloxacin	17 (100%)	0 (0.00%)
Ceftriaxone	3 (17.65%)	14 (82.35%)
Ciprofloxacin	6 (35.29%)	11 (64.71%)
Cefixime	0 (0.00%)	17 (100%)
Cefuroxime	0 (0.00%)	17 (100%)
Cefotaxime	3 (17.65%)	14 (82.35%)
Ceftazidime	5 (29.41%)	12 (70.59%)
Co-trimoxazole	9 (52.94%)	8 (47.06%)
Cefoperazone+sulbactum	6 (35.29%)	11 (64.71%)
Gentamycin	9 (52.94%)	8 (47.06%)
Amikacin	0 (0.00%)	17 (100%)
Azithromycin	14 (82.35%)	3 (17.65%)
Vancomycin	14 (82.35%)	3 (17.65%)
Linezolid	17 (100%)	0 (0.00%)
Meropenem	6 (35.29%)	11 (64.71%)
Nalidixic acid	9 (52.94%)	8 (47.06%)
Imipenem	3 (17.65%)	14 (82.35%)
Etrapenem	6 (35.29%)	11 (64.71%)
Pipericillin+Tazobactam	6 (35.29%)	11 (64.71%)
Aztreonam	17 (100%)	0 (0.00%)
Collistin	17 (100%)	0 (0.00%)
Tigecycline	17 (100%)	0 (0.00%)
Doxycycline	17 (100%)	0 (0.00%)

Table-IX

Antibiotics sensitivity pattern of Streptococcus species among patients (n=10)

Antibiotic	Sensitive	Resistant
Amoxicilin+clavulonic acid	2 (20%)	8 (80%)
Levofloxacin	3 (30%)	7 (70%)
Moxifloxacin	7 (70%)	3 (30%)
Ceftriaxone	2 (20%)	8 (80%)
Ciprofloxacin	2 (20%)	8 (80%)
Cefixime	0 (0.00%)	10 (100%)
Cefuroxime	0 (0.00%)	10 (100%)
Cefotaxime	3 (30%)	7 (70%)
Ceftazidime	2 (20%)	8 (80%)
Co-trimoxazole	6 (60%)	4 (40%)
Cefoperazone+sulbactum	5 (50%)	5 (50%)
Gentamycin	0 (0.00%)	10 (100%)
Amikacin	2 (20%)	8 (80%)
Azithromycin	10 (100%)	0 (0.00%)
Vancomycin	7 (70%)	3 (30%)
Linezolid	10 (100%)	0 (0.00%)
Meropenem	5 (50%)	5 (50%)
Nalidixic acid	5 (50%)	5 (50%)
Imipenem	2 (20%)	8 (80%)
Etrapenem	4 (40%)	6 (60%)
Pipericillin+Tazobactam	7 (70%)	3 (30%)
Aztreonam	10 (100%)	0 (0.00%)
Collistin	10 (100%)	0 (0.00%)
Tigecycline	10 (100%)	0 (0.00%)
Doxycycline	10 (100%)	0 (0.00%)

Table-X

Antibiotics sensitivity pattern of Candida species among patients (n=7)

Antibiotic	Sensitive	Resistant
Amoxicilin+clavulonic acid	0 (0%)	7 (100%)
Levofloxacin	0 (0%)	7 (100%)
Moxifloxacin	0 (0%)	7 (100%)
Ceftriaxone	0 (0%)	7 (100%)
Ciprofloxacin	0 (0%)	7 (100%)
Cefixime	0 (0%)	7 (100%)
Cefuroxime	0 (0%)	7 (100%)
Cefotaxime	0 (0%)	7 (100%)
Ceftazidime	0 (0%)	7 (100%)
Co-trimoxazole	0 (0%)	7 (100%)
Cefoperazone+sulbactum	0 (0%)	7 (100%)
Gentamycin	0 (0%)	7 (100%)
Amikacin	0 (0%)	7 (100%)
Azithromycin	0 (0%)	7 (100%)
Vancomycin	0 (0%)	7 (100%)
Linezolid	0 (0%)	7 (100%)
Meropenem	0 (0%)	7 (100%)
Nalidixic acid	0 (0%)	7 (100%)
Imipenem	0 (0%)	7 (100%)
Ertapenem	0 (0%)	7 (100%)
Pipericillin+Tazobactam	0 (0%)	7 (100%)
Aztreonam	0 (0%)	7 (100%)
Colistin	0 (0%)	7 (100%)
Tigecycline	0 (0%)	7 (100%)
Doxycycline	0 (0%)	7 (100%)

Table-XI

Antibiotics sensitivity pattern of Escherichia coli among patients (n=6)

Antibiotics	Sensitive	Resistant
Amoxicilin+clavulonic acid	0 (0.00%)	6 (100%)
Levofloxacin	4 (66.67%)	2 (33.33%)
Moxifloxacin	4 (66.67%)	2 (33.33%)
Ceftriaxone	0 (0.00%)	6 (100%)
Ciprofloxacin	0 (0.00%)	6 (100%)
Cefixime	0 (0.00%)	6 (100%)
Cefuroxime	0 (0.00%)	6 (100%)
Cefotaxime	0 (0.00%)	6 (100%)
Ceftazidime	0 (0.00%)	6 (100%)
Co-trimoxazole	0 (0.00%)	6 (100%)
Cefoperazone+sulbactum	2 (33.33%)	4 (66.67%)
Gentamycin	2 (33.33%)	4 (66.67%)
Amikacin	4 (66.67%)	2 (33.33%)
Azithromycin	6 (100%)	0 (0.00%)
Vancomycin	2 (33.33%)	4 (66.67%)
Linezolid	2 (33.33%)	4 (66.67%)
Meropenem	4 (66.67%)	2 (33.33%)
Nalidixic acid	2 (33.33%)	4 (66.67%)
Imipenem	4 (66.67%)	2 (33.33%)
Etrapenem	4 (66.67%)	2 (33.33%)
Pipericillin+Tazobactam	2 (33.33%)	4 (66.67%)
Aztreonam	6 (100%)	0 (0.00%)
Collistin	6 (100%)	0 (0.00%)
Tigecycline	6 (100%)	0 (0.00%)
Doxycycline	6 (100%)	0 (0.00%)

Table-XII

Antibiotics sensitivity pattern of Pseudomonas aeruginosa among patients (n=5)

Antibiotic	Sensitive	Resistant
Amoxicilin+clavulonic acid	0 (0.00%)	5 (100%)
Levofloxacin	5 (100%)	0 (0.00%)
Moxifloxacin	5 (100%)	0 (0.00%)
Ceftriaxone	0 (0.00%)	5 (100%)
Ciprofloxacin	0 (0.00%)	5 (100%)
Cefixime	0 (0.00%)	5 (100%)
Cefuroxime	0 (0.00%)	5 (100%)
Cefotaxime	0 (0.00%)	5 (100%)
Ceftazidime	0 (0.00%)	5 (100%)
Co-trimoxazole	0 (0.00%)	5 (100%)
Cefoperazone+sulbactum	0 (0.00%)	5 (100%)
Gentamycin	5 (100%)	0 (0.00%)
Amikacin	5 (100%)	0 (0.00%)
Azithromycin	5 (100%)	0 (0.00%)
Vancomycin	5 (100%)	0 (0.00%)
Linezolid	5 (100%)	0 (0.00%)
Meropenem	5 (100%)	0 (0.00%)
Nalidixic acid	0 (0.00%)	5 (100%)
Imipenem	5 (100%)	0 (0.00%)
Ertapenem	5 (100%)	0 (0.00%)
Pipericillin+Tazobactam	5 (100%)	0 (0.00%)
Aztreonam	5 (100%)	0 (0.00%)
Colistin	5 (100%)	0 (0.00%)
Tigecycline	5 (100%)	0 (0.00%)
Doxycycline	5 (100%)	0 (0.00%)

Table-XIII

Antibiotics sensitivity pattern of bacterial isolates (n=46)

Antibiotic	Acinetobacter baumannii	Enterobacter species	Streptococcus species	Escherichia coli	Pseudomonas aeruginosa
Amoxicilin+clavulonic acid	2 (11.76%)	3 (17.65%)	2 (20%)	0 (0.00%)	0 (0.00%)
Levofloxacin	9 (52.94%)	14 (82.35%)	3 (30%)	4 (66.67%)	5 (100%)
Moxifloxacin	10 (58.82%)	17 (100%)	7 (70%)	4 (66.67%)	5 (100%)
Ceftriaxone	5 (29.41%)	3 (17.65%)	2 (20%)	0 (0.00%)	0 (0.00%)
Ciprofloxacin	0 (0.00%)	6 (35.29%)	2 (20%)	0 (0.00%)	0 (0.00%)
Cefixime	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cefuroxime	2 (11.76%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cefotaxime	6 (35.29%)	3 (17.65%)	3 (30%)	0 (0.00%)	0 (0.00%)
Ceftazidime	0 (0.00%)	5 (29.41%)	2 (20%)	0 (0.00%)	0 (0.00%)
Co-trimoxazole	10 (58.82%)	9 (52.94%)	6 (60%)	0 (0.00%)	0 (0.00%)
Cefoperazone+sulbactum	5 (29.41%)	6 (35.29%)	5 (50%)	2 (33.33%)	0 (0.00%)
Gentamycin	3 (17.65%)	9 (52.94%)	0 (0.00%)	2 (33.33%)	5 (100%)
Amikacin	2 (11.76%)	0 (0.00%)	2 (20%)	4 (66.67%)	5 (100%)
Azithromycin	17 (100%)	14 (82.35%)	10 (100%)	6 (100%)	5 (100%)
Vancomycin	12 (70.59%)	14 (82.35%)	7 (70%)	2 (33.33%)	5 (100%)
Linezolid	13 (76.47%)	17 (100%)	10 (100%)	2 (33.33%)	5 (100%)
Meropenem	5 (29.41%)	6 (35.29%)	5 (50%)	4 (66.67%)	5 (100%)
Nalidixic acid	8 (47.06%)	9 (52.94%)	5 (50%)	2 (33.33%)	0 (0.00%)
Imipenem	0 (0.00%)	3 (17.65%)	2 (20%)	4 (66.67%)	5 (100%)
Etrapenem	4 (23.53%)	6 (35.29%)	4 (40%)	4 (66.67%)	5 (100%)
Pipericillin+Tazobactam	5 (29.41%)	6 (35.29%)	7 (70%)	2 (33.33%)	5 (100%)
Aztreonam	17 (100%)	17 (100%)	10 (100%)	6 (100%)	5 (100%)
Collistin	17 (100%)	17 (100%)	10 (100%)	6 (100%)	5 (100%)
Tigecycline	17 (100%)	17 (100%)	10 (100%)	6 (100%)	5 (100%)
Doxycycline	17 (100%)	17 (100%)	10 (100%)	6 (100%)	5 (100%)

Table-XIV

Antibiotic resistance pattern of organisms among patients (n=46)

Antibiotic	Organism				
Cefexime	*Acinetobacter* baumannii	*Enterobacte* r species	*Streptococcus* species	*Escherichia* coli	*Pseudomonas* aeruginosa
Cefuroxime	*Acinetobacter* baumannii	*Enterobacte* r species	*Streptococcus* species	*Escherichia* coli	*Pseudomonas* aeruginosa
Amoxicilin+clavulonic acid	*Acinetobacter baumannii*			*Escherichia coli*	*Pseudomonas aeruginosa*
Amikacin		*Enterobacter species*			
Ceftriaxone				*Escherichia* coli	*Pseudomonas* aeruginosa
Gentamycin			*Streptococcus species*		
Ciprofloxacin	*Acinetobacter* baumannii			*Escherichia* coli	*Pseudomonas* aeruginosa
Cefotaxime				*Escherichia* coli	*Pseudomonas* aeruginosa
Co-trimoxazole				*Escherichia* coli	*Pseudomonas* aeruginosa

Table-XV
Factor responsible for antibiotic resistance among patients.

Factors	Frequency	Percentage
Multiple drug resistance pathogen	46	100
H/o taking inadequate dose of antibiotic	15	32.6
H/o taking inadequate duration of antibiotic	14	30.43
H/o antibiotic overuse	18	39.1
Self-Medication of antibiotic	28	60.9
H/o taking farm meat (Broiler hen)	26	56.5

Discussion:

In our study 46 tracheal aspirates from 46 patients with a clinical diagnosis of VAP were analyzed and a total of 64 pathogenic microbial strains were isolated from these samples (Table 5). Mean age of all patients of our study was 54.26±12.01 years (range: 31-90 years). Age is a leading factor that plays a significant role in an individual life because with increasing age resistance power is reduced and elderly people are more susceptible to numerous infections. It is important to mention that most of the patients 56.5% were 40-60 years old. The incidence of VAP was more in males 76.1% as compared to females 23.90%.

Major part of the patients had history of smoking 78.3%, self-medication 60.9%, history of steroid taking 41.3%. 100% patients had mechanical ventilation, 56.5% had history of taking farm meat, 86.9% patients had history of previous antibiotic use, 63% had history of taking inadequate dose and duration of antibiotic and 21.7% had nasogastric aspiration.

Among the primary diseases 73.9% of the patients had COPD, 8.69% had ILD, 8.68%. had pneumothorax with plural effusion. 60.86% were complicated with respiratory failure and 13.04% with corpulmunale. Regarding co-morbidities 28.3% patients had HTN, 21.7% had DM, 13% had CVD and 6.5% had CKD.

Most of the patients of our study were infected by single organism 60.9% and rest 39.1% were by multiple organisms. Similarly, 58% of mono-microbial infection were reported in other study[14].

Most of the patients of our study were infected with Gram (-) ve organisms 82.4% as shown in Table 6. Of all organisms Acinetobacter baumannii had 37% and Enterobacter species had 37%. Streptococcus species 21.7%, Candida species 15.2%, Escherichia coli 13%, Pseudomonas aeruginosa 10.9% and Neisseria bacterial growth 4.3% (Table 5). The similar findings were seen in another study [15].

This study revealed that more than 90% organisms were resistant to cefixime and cefuroxime whereas 100% were sensitive to aztreonam, colistin, tigecycline and doxycycline. Beside these antibiotic sensitivity pattern, Acinetobacter baumannii 88.24% were resistant to amoxicilin+clavulonic acid whereas Enterobacter species 100% were resistant to amikacin with 100% were sensitivity to moxifloxacin, Streptococcus species 100% were resistant to gentamycin with 100% were sensitivity to azithromycin and linezolid. Escherichia coli 100% were resistant to amoxicilin+clavulonic acid, ceftriaxone, ciprofloxacin, cefotaxime and cotrimoxazole whereas Pseudomonas aeruginosa 100% were resistant to amoxicilin+clavulonic acid, ceftriaxone, ciprofloxacin, cefotaxime, ceftazidime, cotrimoxazole, cefoperazone+sulbactum and nalidixic acid with 100% were sensitive to imipenem, ertapenem and piperacillin+ tazobactum.

Data showed that the proportion of fungal isolates was present in our ICU. Candida species is main fungal isolates (15.21%) in endotracheal aspirates of mechanical ventilated patients in our ICU and this might be due to presence of DM and use of steroids and broad-spectrum antibiotic. Growth of Candida species from respiratory secretions usually indicate colonization and rarely required treatment. In our study we did sample analysis from VAP patients. They were not categorized as early-onset or late-onset VAP. Many studies found

that prior prolonged incomplete or excessive usage of antibiotics had an influence on the selection of antibiotic resistance strains. In various studies a linear relationship was reported between bacterial resistance and delay in initiating effective antibiotic treatment. In our study it was impossible to make one to one comparison because resistant and sensitive strains were not compared.

These microbial profiles of pathogens causing VAP may differ between hospitals and ICU settings, even within the same institution between different ICUs. Antibiotic choices based on published guidelines may be ineffective if local microbial flora shows different susceptibility patterns. Therefore, this study helped to find out most common pathogen associated with VAP in ICUs and its antibiotic sensitivity pattern which might be useful to modify antibiotic policy of VAP in our hospital ICUs to reduce emergence of multidrug-resistant organisms and morbidity, mortality associated with VAP. This study recommends aztreonam, colistin, tigecycline, and doxycycline as empirical antibiotic in our ICU.

From the study it is observed that, 100% pathogens are resistance to most of the antibiotic. So, the main factors of antibiotic resistance are Multi Drug Resistant pathogens.

Conclusion:

This study found that more than half of VAP patients were infected by single organism and by Acinetobacter baumannii and Enterobacter species were the most common causative organism. The antibiotics most resistant are cefexime, cefuroxime, ceftriaxone, ciprofloxacin and sensitive antibodies are astreonam, linezolid, tigecycline. The factors most responsible for resistance are multi drug resistant pathogen, Inadequate dose and duration of antibiotic use, overuse of antibiotic and eating farm meat.

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ORIGINAL ARTICLE

Effect of Oral Azithromycin Three Times Per Week on Reduction of Asthma Exacerbations in Adults with Persistent Asthma

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Abstract

Background: *Asthma exacerbation is a cause of major financial burden on any country. Many asthma patients remain symptomatic despite optimum treatment. Controlling the inflammatory response using a macrolide can be novel approach as one of the core underlying mechanisms in asthma is inflammation. This study evaluated the effect of oral azithromycin three times per week on reduction of asthma exacerbations in adults with persistent asthma.*

Aim: *To evaluate the efficacy of azithromycin in reducing asthma exacerbations in persistent asthma patients.*

Materials & Methods: *An open label randomized clinical trial was conducted in National Institute of diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka from 2018 to 2019 for one year. A total of 70 patients older than of 12 years suffering from persistent asthma who fulfilled the inclusion and exclusion criteria were recruited. Eligible patients were allocated randomly into group A (Azithromycin group) who were given azithromycin 500 mg three times on alternate days for 24 weeks in addition to standard asthma medications and group B (Standard Asthma treatment group) who received only standard asthma therapy. The patients of both groups were evaluated at base line, during and at the end of 24 weeks. A total of 60 patients who completed the study were analyzed. Asthma exacerbation (moderate vs severe), number of exacerbations, symptomatic improvement and adverse events were monitored during study period. Trial was registered at International Traditional Medicine Clinical Trial Registry ISRCTN (registry number 14464685).*

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Results: *In our study, number of exacerbation was significantly reduced in azithromycin group (Group A) in comparison to conventional group (Group B). In group A, 53% patients did not suffer any exacerbation whereas 46% patients from Group B suffered one exacerbation during study period which is statistically significant ($p<0.05$). In reduction of type of exacerbation, out of the 14 exacerbations in group A, 13(92.9%) had moderate exacerbations, 1(7.1%) had severe exacerbations. In group B, 20(83.3%) had moderate exacerbation and 4 (16.7%) had severe exacerbation. But the difference was not statistically significant ($p>0.05$).*

Conclusion: *Oral azithromycin 500 mg three times a week on alternate days can reduce exacerbation; improve asthma symptoms, and asthma control status in patients with persistent asthma.*

Key words: Persistent asthma, Exacerbation, Azithromycin, Bangladesh

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Introduction:

Asthma is an important public health problem worldwide with wide differences in prevalence and severity throughout the world. The World Health Organization (WHO) estimates that 235 million people currently suffer from asthma (Fact sheet of asthma, 2022) and by 2025 it has been estimated that a further 100 million will be affected. Asthma accounts for one in every 250 deaths worldwide and 1% of all disability.[1] Psychological distress and feelings of decreased control are high in people with asthma and strongly associated with physical health. [2]

The exact etiology of asthma is still unknown but a number of epidemiological studies have identified some risk factors for asthma, including sensitization to perennial aeroallergens such as house dust mites, family history of asthma, infections with respiratory syncytial virus, dietary habits, in utero smoking, residence in urban areas, and reduced exposure to other children. [3,4]

The First National Asthma Prevalence Study (NAPS) in 1999 showed that about 7 million people (5.2% of the population) were suffering from asthma in Bangladesh and prevalence was more in rural area than in metropolitan area. [5]

Asthma severity is determined by current impairment (as evidenced by impact on day-to-day activities) and risk of future exacerbations (as evidenced by frequency of oral systemic corticosteroid use), and allows categorization of disease as intermittent, mild persistent, moderate persistent, and severe persistent asthma. [6]

Pharmacological options for long term treatment of asthma fall into the three main categories like reliever medications, controller, preventer medications and add on therapies for patient with severe asthma. They are the mainstay of drugs for the acute relief of asthma symptoms, symptoms relieve during maintenance treatment of asthma and protection against exercise -induced asthma.[7]

Asthma exacerbations can occur despite maintenance treatment with conventional medications resulting in a need for additional treatment options in uncontrolled persistent asthma.[8,9] Macrolide antibiotics have combined antibacterial, antiviral, and anti-inflammatory effects. It has been reported to be beneficial in both eosinophilic and also non-eosinophilic asthma subtypes. [10-12] Initial systematic reviews of various randomized controlled trials using azithromycin in asthma reported benefits of macrolides on asthma symptoms but were unable to draw conclusions. It was due to many factors such as lack of data, heterogeneity of results, and inadequate study design and sample size. [13-16]

Patients with persistent asthma have limited treatment options. The use of other add-on treatments are limited by factors such as side effects, poor availability and cost. Considering the major socio economic impact of asthma exacerbations on patients and the community, we evaluated the effect of oral azithromycin on reduction of asthma exacerbations in adults with persistent asthma.

Materials and Methods:

This open label randomized controlled trial was carried out at National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka

from June 2018 to June 2019. All men and women aged more than 12 years attending the out and inpatient department of of National Institute of diseases of the Chest and Hospital (NIDCH), who fulfilled the inclusion criteria were recruited as study sample.

A total of 70 patients were recruited and were divided into Group A (Azithromycin group) and Group B (Standard asthma treatment group) with 35 patients in each group. Allocation by randomization was done by block randomization. Group A received Azithromycin 500 mg three times per week in addition to conventional asthma medication for 24 weeks whereas Group B received conventional asthma medication alone for 24 weeks. Patients with emphysema, current and ex smokers, patients with hearing impairment, prolonged QTc interval in ECG, bronchiectasis and hypersensitivity to azithromycin were excluded from the study. Reduction of total number of asthma exacerbations were considered as primary outcome variable whereas reduction of types of exacerbation (moderate, severe), change in self reported asthma symptoms, adverse effects occurring in patients were considered as ssecondary outcome variables. A structured questionnaire was used to collect data from patients on the basis of objective of study.

Those who fulfilled the GINA 2018 diagnostic criteria for asthma in adults were labelled as having asthma.[7]

Progressive increase in shortness of breath, cough, wheezing or chest tightness over a short period of time that is sufficient to require a change in treatment were labelled as asthma exacerbation (GINA 2018). [7] It was again subdivided into -

Severe exacerbation: Worsening of asthma symptoms that led to one of the following: at least 3 days of systemic corticosteroid treatment (e"10 mg/day) or a temporary increase in a stable oral corticosteroid maintenance dosage of at least 10 mg/day for at least 3 days; an asthma-specific hospitalization; or emergency department visit requiring systemic corticosteroids. [17]

Moderate exacerbation: Any temporary increase in inhaled corticosteroids or antibiotics in conjunction with a deterioration in asthma symptoms or both, or any increase in â2 agonist use for at least 2 days, or an emergency department visit not requiring systemic corticosteroids.[17]

Persistent Asthma: Patients who fulfilled the criteria as per National guidelines for Asthma & COPD 2016 was labelled as persistent asthma patients. [18]

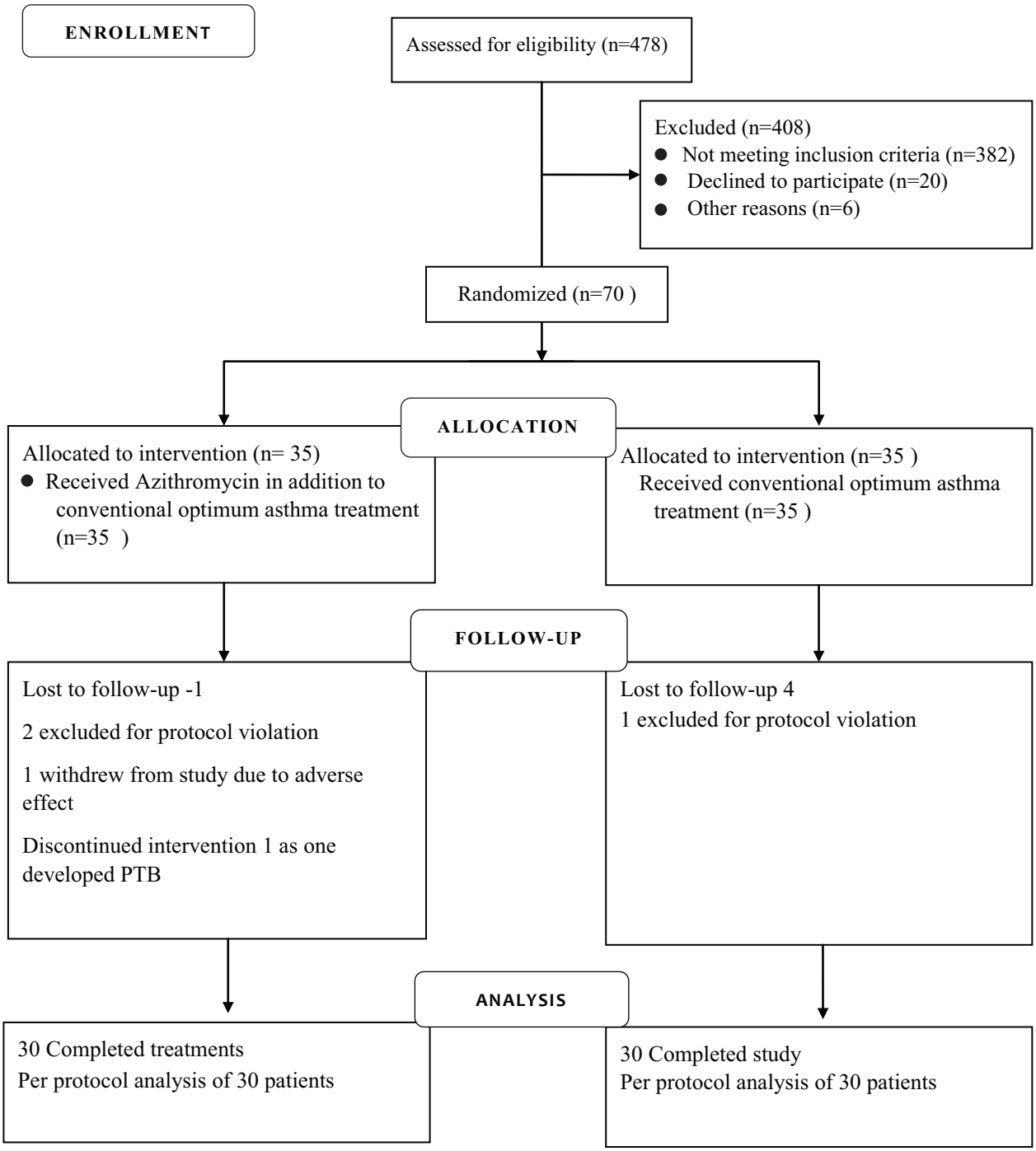
Each subject was evaluated based on history and examination and necessary baseline investigations (CBC with ESR, Serum electrolytes, Chest X-ray, RBS, ECG, Sputum for AFB etc.) were done. Spirometry (obtained with a computerized system (MEDGRAPHICS spirometry machine) with reversibility and ECG were obtained before starting treatment. Drugs were supplied by a GMP certified company. Drugs were packaged as per standardized protocol with specific batch number.

Patients were advised to maintain a dairy in which they recorded their symptoms and use of medications. Adherences to the medications were checked by interviewing the study subjects and also by return of the empty case of medicine containing same serial number of marked package. Patients were monitored for 24 weeks and assessment was done at weeks 4, 12, 24. At each visits assessment of symptoms, medication use, asthma exacerbations, adherence, adverse events (including self-reported respiratory infections) were done. Telephone assessments were done if a patient was unable to attend/ missed a follow up. Finally results were analyzed.

Data were processed manually and analyzed with the help of SPSS (Statistical package for social sciences) for windows version 22. Quantitative data were expressed as mean and standard deviation; and comparison done by paired and unpaired t-test. Qualitative data were expressed as frequency and percentage and association was carried by Chi-square ($\div^2$) Test. 95% confidence limit was taken. A probability value (p) of less than 0.05 was considered to indicate statistical significance.

Ethical clearance was obtained from Institutional Review Board (IRB) of NIDCH to undertake the current study. Informed written consent was obtained from each subject who voluntarily provide consent to participate in this study.

Consort Flow Diagram of study



Results:

Between June, 2018, and December, 2018, 478 patients were screened for participation, and 70 were randomly assigned. The reasons for screen failure were incorrect inhaler technique use, inconsistent use of medication by patient. We allocated 35 (50%) to azithromycin treatment group and 35 (50%) to control group. The trial was completed by 60 (85%) patients. There were similar numbers of trial withdrawals in each group. Per protocol analysis was done.

Demographic and some laboratory parameter analysis of patients were done. It included age, sex, occupational status, pre treatment of FEV_1, BMI, blood eosinophil count and atopy. It showed both groups had similar characteristics (Table I).

Table II showed majority 16(53.3%) patients had no exacerbation in azithromycin treatment group (Group A) and 6(20.0%) patients had one exacerbation who received standard asthma treatment group (Group B). In group A, 3(10.0%) had two exacerbations whereas 10 (33.3%) patients had two episode of exacerbation in group B. The difference was statistically significant ($p<0.05$) between two groups. Table III showed moderate exacerbations was found 13(92.9%) in group A and 20(83.3%) in group B. One patient (7.1%) had an episode of severe exacerbation in group A and 4 (16.7%) had severe exacerbation in group B. The difference was not statistically significant ($p>0.05$) between two groups.

Table IV shows in pre treatment, shortness of breath was found 28(93.3%) in group A and 26(86.6%) in group B. In post treatment, shortness of breath was present in 11(36.7%) in group A and 21(70.0%) in group B. Shortness of breath was not found 9(30.0%) in azithromycin treatment group and 3(10.0%) in standard asthma treatment group. In post treatment, reduced shortness of breath was found in 10(33.3%) in azithromycin treatment group and 6(20.0%) in standard asthma treatment group. In post treatment, reduction of shortness of breath was statistically significant ($p<0.05$) between two group.

Table V shows that in pre treatment, cough was found 28(93.3%) and 30(100%) in azithromycin treatment group and standard asthma treatment

Table-I

Baseline characteristics of the study subjects (n=60)

	Azithromycin Treatment Group (n=30)		Standard Asthma Treatment Group (n=30)	
Age (years)				
Mean±SD		40.6±13.8	44.1±12.6	
Sex (n, %)				
Male	17	56.7	22	68.6
Female	13	43.3	08	31.4
Occupational status (n, %)				
Businessman	1	3.3	5	11.4
Day labour	2	6.7	3	2.9
Farmer	5	16.7	3	11.4
Fisher man	0	0.0	2	2.9
Housewife	4	22.9	11	31.4
Retired	1	13.3	6	11.4
Shop keeper	1	3.3	4	0.0
Service holder	11	36.7	0	25.7
Vendor	4	13.3	6	2.9
Student	1	8.6	0	0.0
Mean pre treatment FEV_1 (%, SD)	53.3	±13.8	48.2	±14.5
Mean BMI (kg/m^2)	23.2	±13.8	25.0	±6.2
Mean Eosinophil count ($/mm^3$)	224.9	±70.3	218.1	±126.0
Atopy				
Present (n, %)	21	70.0	27	88.6
Absent (n, %)	9	30.0	3	11.4

Azithromycin Treatment group(Group A) = Oral azithromycin three times weekly along with other asthma medications for 24 weeks

Standard asthma treatment group (Group B) = Conventional asthma medications for same duration

Table-II

Number of exacerbations among the patients (n=60)

Number of exacerbations	Azithromycin Treatment Group (n=30)		Standard Asthma treatment Group (n=30)		P value
	n	%	n	%	
None	16	53.3	6	20.0	
One	11	36.7	14	46.7	0.013[s]
Two	3	10.0	10	33.3	

s= significant
P value reached from chi square test

Table-III

Type of exacerbations among the study population (n=38)

Type of exacerbations	Azithromycin Treatment Group (n=14)		Standard Asthma treatment Group (n=24)		P value
	n	%	n	%	
Moderate	13	92.9	20	83.3	0.312[ns]
Severe	1	7.1	4	16.7	

ns= not significant
P value reached from chi square test

Table-IV

Shortness of breath in different follow up (n=60)

Shortness of breath	Azithromycin Treatment Group (n=30)		Standard Asthma treatment Group (n=30)		P value
	n	%	n	%	
Pre treatment					
Present	28	93.3	26	86.6	[a]0.694[ns]
Absent	2	6.7	4	13.4	
Post treatment					
Present	11	36.7	21	70.0	
Absent	9	30.0	3	10.0	[b]0.028[s]
Reduced	10	33.3	6	20.0	

s= significant, ns= not significant
[a]P value reached from fisher exact test
[b]P value reached from chi square test

Table-V

Cough in different follow up (n=60)

Cough	Azithromycin Treatment Group (n=30)		Standard Asthma treatment Group (n=30)		P value
	n	%	n	%	
Pre treatment					
Present	28	93.3	30	100.0	[a]0.246[ns]
Absent	2	6.7	0	0.0	
Post treatment					
Present	7	23.3	15	50.0	
Absent	11	36.7	4	13.3	[b]0.045[s]
Reduced	12	40.0	11	36.7	

s= significant, ns= not significant
[a]P value reached from fisher exact test
[b]P value reached from chi square test

group respectively. In post treatment, cough was found in 7(23.3%) in azithromycin treatment group and 15(50.0%) in standard asthma treatment group. In post treatment, reduced cough was found in 12(40.0%) in azithromycin treatment group and 11(36.7%) in standard asthma treatment group. In post treatment, reduction of cough was statistically significant ($p<0.05$) between two groups.

Table VI shows in pre treatment, sputum productions was found 17(56.7%) in azithromycin treatment group and 24(80.0%) in standard asthma treatment group. Sputum productions was not found 13(43.3%) in azithromycin treatment group and 6(20.0%) in standard asthma treatment group. In post treatment, sputum productions was present in 6(6.7%) and 12(40.4%) in azithromycin treatment group and standard asthma treatment group respectively. No sputum production was found in 15(50%) in azithromycin treatment group and 12(40%) standard asthma treatment group. In post treatment, reduction of sputum production was statistically significant ($p<0.05$) between two groups.

Table VII shows in pre treatment, rhonchi was found 30(100.0%) in azithromycin group and 29(96.7%) group standard asthma treatment group. In post treatment, rhonchi was present in 16(53.3%) in azithromycin group and 21(70.0%) in standard asthma treatment group. In post treatment, reduced rhonchi was found in 9(30.0%) and 7(23.3%) patients in azithromycin group and standard asthma treatment group respectively. The differences were not statistically significant ($p>0.05$) between two groups.

Table VIII shows in azithromycin group, majority 8(26.7%) patients had palpitations, 8(26.7%) had

Table-VI

Sputum productions in different follow up (n=60)

Sputum productions	Azithromycin treatment Group (n=30)		Standard asthma treatment Group (n=30)		P value
	n	%	n	%	
Pre treatment					
Present	17	56.7	24	80.0	0.052^{ns}
Absent	13	43.3	6	20.0	
Post treatment					
Present	2	6.7	12	40.0	
Absent	15	50.0	12	40.0	0.007^{s}
Reduced	13	43.3	6	20.0	

s= significant, ns= not significant

P value reached from chi square test

Table-VII

Rhonchi in different follow up (n=60)

Rhonchi	Azithromycin treatment Group (n=30)		Standard asthma treatment Group (n=30)		P value
	n	%	n	%	
Pre treatment					
Present	30	100.0	29	96.7	$^{a}0.754^{ns}$
Absent	0	0.0	1	3.3	
Post treatment					
Present	16	53.3	21	70.0	
Absent	5	16.7	2	6.7	$^{b}0.331^{ns}$
Reduced	9	30.0	7	23.3	

ns= not significant

[a]P value reached from fisher exact test

[b]P value reached from chi square test

Table-VIII

Adverse events in study population (n=60)

Adverse events	Azithromycin treatment Group (n=30)		Standard asthma treatment Group (n=30)		P value
	n	%	n	%	
Palpitations	8	26.7	7	23.3	0.766^{ns}
Diarrhoea	5	16.7	2	6.7	0.212^{ns}
Vertigo	1	3.3	4	13.3	0.177^{ns}
Tinnitus	4	13.3	3	10.0	0.500^{ns}
Nausea	8	26.7	3	10.0	0.095^{ns}
Others*	3	10.0	5	16.7	0.353^{ns}

ns= not significant

P value reached from chi square test

*Others - Headache, Rash, Abdominal discomfort

Table-IX

Multivariate Regression Analysis to Predict the Number of Exacerbations

Variable	Unstandardized Coefficient	Standard Error	Standardized Coefficient	t statistic	P value
BMI	-0.029	0.017	-0.213	-1.736	0.088
Presence or absence of atopy	-0.082	0.240	-0.044	-0.343	0.733
Baseline FEV1	0.012	0.007	0.215	1.675	0.100
Peripheral blood eosinophil count	-0.001	0.001	-0.175	-1.392	0.170
Azithromycin therapy status	-0.679	0.188	-0.454	-3.606	0.001

nausea, 5(16.7%) had diarrhea, 4(13.3%) had tinnitus. In standard asthma medication group, 7(23.3%) had palpatations, 5(16.7%) had others adverse events, 4(13.3%) had vertigo. The difference were not statistically significant ($p>0.05$) between two groups.

Multivariate regression analysis was carried out to predict the number of exacerbations of asthma over 6 months from BMI, the presence or absence of atopy, baseline FEV1, peripheral blood eosinophil count and the status of azithromycin therapy. This revealed that only the status of azithromycin therapy added significantly ($p=0.001$) to the model (Table IX).

Discussion:

This study was conducted to explore the efficacy and safety of oral azithromycin as an add on with conventional therapy in reducing exacerbations in of persistent asthma patients. Eligible patients were allocated randomly into two groups. Total 35 patients in group A received oral azithromycin in addition to conventional asthma medication whereas group B patients also consisting of 35 patients received conventional asthma medication. Efficacy of azithromycin to reduce overall asthma exacerbations with type of exacerbations were assessed (severe vs moderate). Improvement of asthma related symptoms, adverse events were also assessed. A total of 60 patients who completed the study were finally analyzed.

In this study, baseline characteristics of the 60 patients were analyzed. It showed that in both groups majority were at or below 40 years of age. Similar finding was reported by Chen et al., and Schatz et al. [19,20,21] Our study showed that percentage of males (53.01%) is higher than female 46.99%. In our study, the mean BMI found was 23.2±3.9 kg/m^2 in azithromycin group and 25.0±6.6 kg/m^2 in patients who received standard asthma treatment group. In our study, majority 70.0% patients had atopy in azithromycin group and 90.0% in standard asthma treatment group. Our findings are similar to the study conducted by Brusselle et al., and Gibson et al. [17,22]

Asthma can be phenotypically classified in non-eosinophilic (mainly neutrophilic) and eosinophilic asthma. If blood eosinophil is e" 300 mm^3, it is eosinophilic asthma. [23] In our study, the mean eosinophil count was found 207.2±70.3 mm^3 in group azithromycin group and 218.5±133.5 mm^3 in standard asthma treatment group. In our study, most patients had eosinophil count in < 350 mm^3 making them non eosinophil phenotype. Analysis of mean blood eosinophils count in another case control study showed that mean blood eosinophils count was 280 mm^3, and 200mm^3. [8] In another study mean blood eosinophil count was 186 mm^3 and 208 mm^3. [17,22]

In our study, both frequency type of exacerbation were reduced by azithromycin. In Azithromycin group, 53.3% patients were exacerbation free, whereas only 20% were exacerbation free in conventional asthma treatment group. Number of exacerbation was significantly reduced in azithromycin group ($p<0.05$) (36% vs 46.7%). In reduction of type of exacerbation, out of the 14 exacerbations in azithromycin group, 13(92.9%) had moderate exacerbations, 1(20.83%) had severe exacerbations. In standard asthma treatment group, 20(83.3%) had moderate exacerbation and 4 (16.7%) had severe exacerbation. The difference was not statistically significant ($p>0.05$). Our results are in accordance with another study where significant reduction in the incidence of total (moderate and severe combined) asthma exacerbations in the azithromycin-treated group was observed. In their study, placebo group experienced 1·86 exacerbations per person-year (95% CI 1·54–2·18), whereas the azithromycin-treated group experienced 1·07 exacerbations per person-year (0·85–1·29). The placebo group experienced 1·07 severe asthma exacerbations per person-year whereas the azithromycin treated group experienced 0·61 severe asthma exacerbations per person-year. [17] In our study, most of the exacerbations were mild to moderate but as our study period was six months, we could not draw any similar conclusion from our study. Two other studies, one using azithromycin 600 mg weekly for 12 weeks and another study using 200 mg azithromycin in a did not show any superiority to placebo group. [22, 24] This may be explained by the dosage and duration difference (500 mg vs 200 mg; 24 vs 12 weeks). But they did report that add-on treatment with azithromycin significantly decreased the rate of primary endpoints and of severe exacerbations in the subgroup of patients with non-eosinophilic severe asthma. [22,24] There have been reports of induction of Churg– Strauss syndrome in patients with eosinophilic asthma receiving add-on treatment with azithromycin. The exact mechanism of this causation is not known but an underlying immune dysregulation, eosinophil chemokine dysfunction has been postulated. [25] We did not observe any similar effects in our study.

Self reported asthma symptoms such as shortness of breath, cough, sputum productions were noted and improvement in azithromycin group was statistically significant in comparison to control group ($p<0.05$) (Table IV, V, VI, VII). Another study using azithromycin reported an overall reduction in breathlessness, cough, and sputum production in patients which is similar to our study results. [17] Though in our study the overall asthma symptom was reduced, our major limitation was we did not use any standardized validated tool for assessment of these symptoms whereas a visual analogue scale and, sputum production with a defined as a score of at least 6 were used in the other study. [17] Brusselle et al., reported that there was a significant improvement in the AQLQ score in the azithromycin group (0.32 ± 0.89; 95% CI, 0.08 0.57, P = 0.011) compared with a non significant trend in the placebo group but there was no significant reduction of asthma symptoms.[22] Although Hahn et al., indicated no obvious improved AQLQ score from baseline after azithromycin treatment, they detected improvement of overall asthma symptoms (cough, wheeze, shortness of breath, sleep disturbance due to asthma) in the azithromycin group (+0.55) and worsened symptoms in the placebo treated group ("0.13), suggesting a statistically significant difference ($P < 0.04$). [24] A Cochrane review by Kew et al., (2015) found that there was some evidence that macrolides led to some improvement on symptom scales (SMD -0.35, 95% CI - 0.67 to 0.02). But improvement was not significant. [13] Another review by Tian et al. revealed no statistically significant benefit for lung function (FEV1, PEF), airway inflammation or life quality (ACQ, AQLQ). [26] In our study, reduction of rhonchi found on auscultation in pre treatment period was reduced

in post treatment period as well. But the difference among two groups were not statistically significant ($p>0.05$).

Analysis of adverse effects showed that in azithromycin group, 8(26.7%) patients had palpitations, 8(26.7%) had nausea, 5(16.7%) had diarrhoea, 4(13.3%) had tinnitus. In standard asthma treatment group, 7(23.3%) had palpitations, 5(16.7%) had others adverse events, 4(13.3%) had vertigo. The difference in the overall frequency and type of serious adverse events between azithromycin and standard asthma treatment groups were not statistically significant ($p>0.05$). A study reported diarrhoea being most common side effects using 500 mg azithromycin where 34% patients had diarrhoea. [17] Another study did not show any definite pattern of side effects when they used 200 mg azithromycin. [22] Two meta analysis also concluded that oral azithromycin did not cause any of serious side effects of and the treatment was mostly well tolerated. [13,26] A multivariate regression analysis was carried out to predict the number of exacerbations of asthma over 6 months from BMI, the presence or absence of atopy, baseline FEV1, peripheral blood eosinophil count and the status of azithromycin therapy. This revealed that only the status of azithromycintherapy added significantly ($p < 0.001$) to the model.

In conclusion, 500 mg azithromycin three times weekly on alternate days for 24 weeks causes reduced exacerbations, improvements in overall asthma symptoms without causing any significant adverse effects case of adults with persistent asthma.

Conflict of Interest: None

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ORIGINAL ARTICLE

Pattern of Antibiotic Susceptibility of Bacteria Isolated from Patients of COPD Treated in ICU of NIDCH

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Abstract

Background: *Chronic Obstructive Pulmonary Disease (COPD) patients in the ICU pose challenges due to microbial infections leading to exacerbations and mortality. Selecting antibiotics requires understanding susceptibility patterns, emphasizing the need for customized guidelines.*

Objective: This study aimed to investigate the antibiotic susceptibility pattern of bacteria isolated from COPD patients in the ICU at the National Institute of Diseases of the Chest and Hospital (NIDCH).

Method: *A cross-sectional observational study conducted from June 2019 to August 2020 involved 100 COPD cases in the ICU. Samples were collected with aseptic precautions, tested for Culture/Sensitivity, and additional relevant tests were performed. Statistical analysis employed SPSS version 23.0, utilizing Chi-square and Fisher's exact tests.*

Results: *Out of 100 respondents, the age of the patients ranged from 47 years to 77 years, with a mean of 63.0 ± 7.8 years. A majority (86 86%) were male. Out of 100 samples, 91% had growth of organisms in culture. A significant association was found between smoking and organism growth (p-value 0.033). Gram-negative bacteria were predominant (79, 86.8%), most common was Klebsiella (27, 29.67%) followedby Acinetobacter (23, 25.27%), Enterobacter (12, 13.2%), Streptococcus (11, 12.1%),Pseudomonas (8, 8.8%), E. coli (4, 4.4%), Moraxella (3, 3.3%) and others (3, 3.3%). Regarding antibiotic sensitivity, Colistin was 94.8% sensitive for gram-negativebacteria, Tigecycline was 85.2% sensitive for both gram-negative and gram-positive, and Linezolid was 100% sensitive for gram-positive bacteria.*

Conclusion:*Bacterial infection was high among the patients with COPD in ICU and was caused mainly by gram-negative bacteria. Isolated bacterial strains were highly resistant to most groups of antibiotics. Sensitivity was high to Colistin, Tigecycline, and Linezolid. Smoking was found to be associated with the growth of organisms.*

Keywords: *COPD, ICU, Antibiotic Susceptibility, Gram-negative Bacteria, Smoking.*

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Introduction:

Chronic Obstructive Pulmonary Disease (COPD) stands as a global health challenge, characterized by persistent respiratory symptoms and airflow limitation, often resulting from prolonged exposure to noxious particles or gases[1]. The World Health Organization (WHO) predicts that COPD will emerge as the third-leading cause of death worldwide by 2030, necessitating a comprehensive understanding of its epidemiology, impact, and effective management strategies [2].

In 2016, the Global Burden of Disease Study reported a staggering prevalence of 251 million COPD cases worldwide, with over 90% of COPD-related deaths occurring in low- and middle-income countries [3]. This disease burden is not uniform across nations, and individual countries grapple with unique challenges in managing COPD. Bangladesh, for instance, faces a significant burden, with the Burden of Obstructive Lung Disease (BOLD) study reporting a 21.6% prevalence of COPD in individuals over 40, totaling an estimated 6 million cases. The overall prevalence in the general population was 4.32%, with a substantial proportion affecting individuals aged 40 to 50 (42%) [4].COPD has become a significant public health concern globally, ranking as the fourth leading cause of death in 2012, resulting in over 3 million deaths and accounting for 6% of all global fatalities [5]. This trajectory is expected to worsen in the coming decades, underscoring the urgency of effective COPD management and preventive measures [6].

A critical aspect of COPD management involves addressing acute exacerbations, which significantly impact both individual health and healthcare systems. The Global Initiative for Chronic Lung Disease (GOLD) defines Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) as an event marked by increased dyspnea, cough, and sputum production, requiring a change in management [7]. Exacerbations are associated with a heightened economic burden and increased mortality, particularly in ICU settings [8]. In India, COPD affects 30% of outpatient department attendees and contributes to 1-2.5% of inpatient cases [9].Microbial triggers, both infectious and noninfectious, contribute significantly to COPD exacerbations. Respiratory tract infections, air pollution, temperature changes, allergen exposure, and medication interruptions all play roles in exacerbation occurrence [10]. In up to 30% of cases, the exact cause of AECOPD remains unknown, highlighting the complexity of COPD exacerbations. However, bacterial pathogens are isolated in 40–60% of AECOPD cases, emphasizing the role of bacteria in exacerbation events [11].

Streptococcus pneumoniae, Haemophilusinfluenzae, and Moraxella catarrhalis are commonly implicated bacterial strains in AECOPD, with respiratory tract infections contributing to 50%-80% of cases [12]. Understanding the microbial etiology of AECOPD is crucial for guiding antibiotic treatment. Over 90% of AECOPD patients treated with antibiotics experience a shift in the drug-resistant pattern of organisms, necessitating the importance of selecting appropriate treatment protocols [13].The association between lung function impairment and the causative bacterial pathogen in exacerbations has also been observed. Enterobacteriaceae and Pseudomonas are often isolated from patients with significant pulmonary function impairment (FEV1 <50% of predicted) [14]. Hospitalized patients, who tend to have more severe lung function compromise, may present with a different spectrum of causative organisms for AECOPD.

The impact of antibiotic resistance further complicates the management of COPD exacerbations. Antibiotics have significantly reduced short-term mortality, treatment failure, and sputum purulence in AECOPD patients with signs of bacterial infection [15]. However, in an era of rising antibiotic resistance and limited development of new antimicrobials, the judicious use of antibiotics becomes paramount.Multi-drug resistant (MDR) gram-negative organisms, in particular, pose a substantial threat, leading to increased morbidity, mortality, prolonged hospitalizations, and heightened healthcare expenses [16]. The economic impact of antibiotic resistance is significant, affecting both healthcare costs and society at large. The dire consequences of antibiotic-resistant bacteria, often referred to as "nightmare bacteria," are especially pronounced in low- and middle-income countries[17].

Routine screening and understanding the local antibiotic resistance patterns are crucial in

addressing the spread of resistant organisms in the community. Various factors contribute to antibiotic resistance, including prescribing behaviors, patients' demands, dosages, and durations of prescribed drugs [18]. As antibiotic resistance continues to rise, it becomes imperative to identify resistant pathogens to plan effective treatment strategies, ultimately reducing both morbidity and mortality in critical settings such as the ICU.This study aims to fill this critical knowledge gap by investigating the bacteriological profile and antibiogram of COPD patients admitted to the ICU. The findings of this research are expected to contribute valuable insights into the optimal use of antibiotics, guide treatment protocols, and enhance antimicrobial stewardship in managing COPD exacerbations.

Objectives

General Objective

- To observe the pattern of bacteria isolated and their susceptibility to antibiotics in patients of COPD in the ICU of NIDCH.

Specific Objectives

- To identify the common bacteria isolated from samples obtained from patients of COPD in ICU of NIDCH.
- To see the pattern of antibiotic sensitivity of bacteria among the patients of COPD in ICU of NIDCH.
- To see the pattern of resistance of bacteria to antibiotics among the patients of COPD in ICU of NIDCH.

Material and Methods

Study Design

This study employed a cross-sectional observational design to investigate bacterial growth, antibiotic sensitivity, and resistance patterns in COPD patients admitted to the Intensive Care Unit (ICU) at the National Institute of Diseases of the Chest and Hospital (NIDCH), Dhaka, Bangladesh. The research spanned from June 2019 to August 2020, involving 100 known COPD cases meeting specific inclusion criteria. Data were collected through structured questionnaires, clinical evaluations, and laboratory investigations, followed by descriptive and inferential statistical analyses using SPSS version 23.0.

Inclusion criteria

- Patients admitted to the ICU department of NIDCH diagnosed as a case of COPD.

Exclusion criteria

- Patients transferred from another ICU and stayed there for more than 48 hours.
- Patient received antibiotics within the last 48 hours of hospital admission.
- Patient has other known respiratory diseases.

Data Collection

Data collection encompassed comprehensive assessments of COPD patients admitted to the NIDCH, Dhaka, Bangladesh ICU. Eligible patients underwent history-taking, physical examinations, and relevant investigations, including complete blood counts, biochemical analyses, and arterial blood gas measurements. Additionally, culture and sensitivity testing samples were collected using sterile containers and aseptic techniques. Data were recorded through structured questionnaires and clinical forms, ensuring accuracy and completeness for subsequent analysis.

Data Analysis

Data analysis involved meticulously examining collected information from COPD patients using descriptive and inferential statistics. The statistical package for social science (SPSS) version 23.0 was employed for thorough analysis. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized using means and standard deviations. Chi-squared tests determined associations between bacterial culture results and specific categorical variables. The significance level was set at p-value < 0.05.

Ethical Consideration

The research protocol was approved by the Institutional Review Board of the National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh, prior to the commencement of the study. All patients/legal guardians were briefed about the study in an understandable way. Informed written consent was taken from all participants. Confidentiality and

privacy were maintained throughout the study. The participant's refusal and withdrawal from the study was accepted.

Results:

This cross-sectional observational study was carried out in the Department of ICU, NIDCH, Dhaka, from June 2019 to August 2020. One hundred patients with COPD were included in this study based on inclusion and exclusion criteria. One hundred samples, collected from 100 patents, were tested for C/S. The findings obtained from data analysis are presented:

Table-I

Distribution of the study patients according to age (n=100)

Demographic characteristics	Frequency	Percentage
Age(years)		
40-49	1	1
50-59	38	38
60-69	35	35
70-79	26	26
Mean± SD63.0±7.8		
Range(min-max)	47.0-77.0	

Table 1 shows that the maximum patients (38%) were in the age range 50-59 years whereasthe mean age was 63±7.8 years with range from 47 to 77 years.

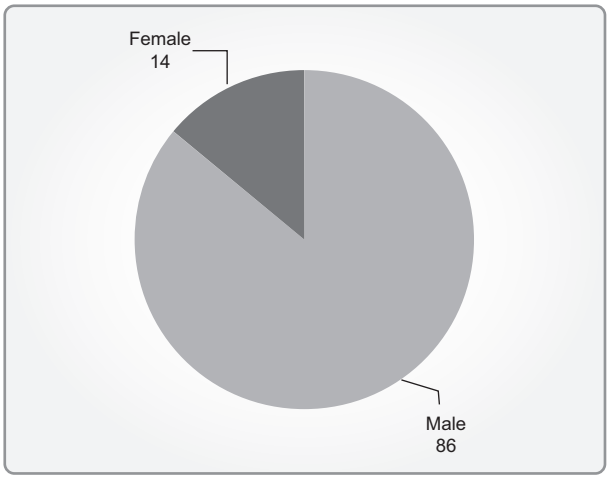

Figure 1: *Distribution of study patients according to gender (n=100)*

Table-II

Distribution of the study patients according to smoking status (n=100)

History of exposure to risk factors	Frequency	Percentage
Smoker		
Yes		
<20 (pack year)	28	28
≥20 (pack year)	63	63
No	9	9

Table 2 shows that smoker was 91(91%), among them majority 63(63%) patients taken e • 20 pack year.

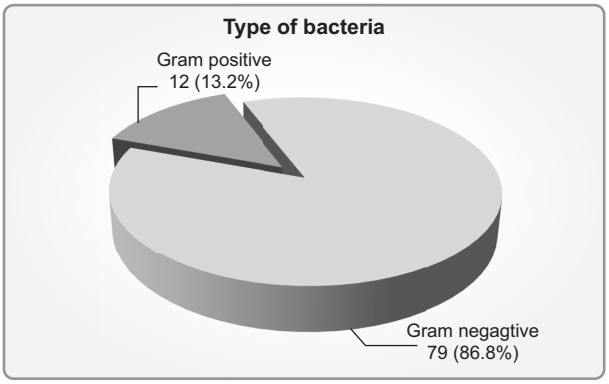

Figure 2: *Distribution of patients according to type of bacteria (n=91)*

Pie chart showing majority 79(86.8%) patients had growth of gram-negative bacteria.

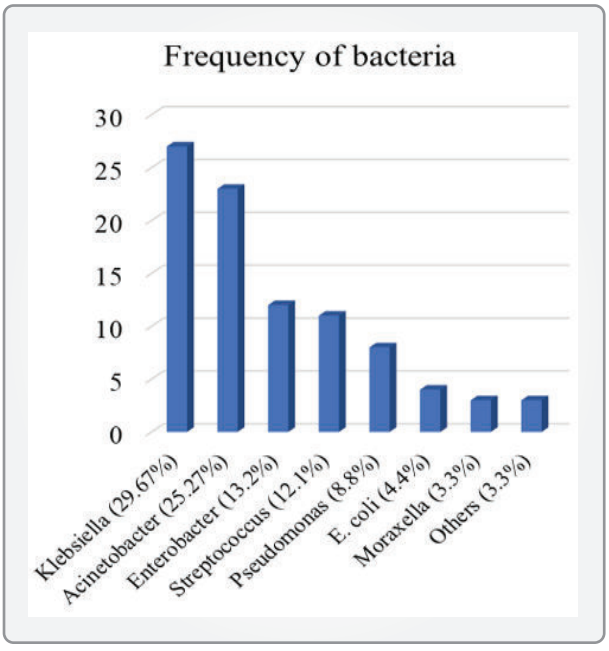

Figure 3: *Frequency of different bacteria of the study patients (n=91)*

Table-III

Antibiotic sensitivity pattern of Klebsiella

Antibiotic	Total	Sensitive		Resistant	
	27	N	%	N	%
Amoxicillin + Clavulanic acid	27	1	3.7	26	96.3
Levofloxacin	6	0	0.0	6	100.0
Ceftriaxone	27	2	7.4	25	92.6
Ceftazidime	27	2	7.4	25	92.6
Cefepime	27	2	7.4	25	92.6
Amikacin	27	2	7.4	25	92.6
Meropenem	26	2	3.8	24	96.2
Imipenem	27	1	3.7	26	96.3
Piperacillin + Tazobactam	27	1	3.7	26	96.3
Colistin	27	27	100.0	0	0.0
Gentamycin	27	2	7.4	25	92.6
Tigecycline	27	27	87.5	0	0.0

Table-IV

Antibiotic susceptibility pattern

Antibiotic	SensitiveN (%)	ResistantN (%)	Total	Notdone
Colistin	73 (94.8)	4(5.2)	77	14
Tigecycline	75(85.2)	13(14.8)	88	3
Amikacin	15(19.5)	62(80.5)	77	14
Gentamycin	18(22)	64(78)	82	9
Amoxicillin + Clavulanic acid	5(7.8)	59(92.2)	64	27
Cefoperazone + Sulbactam	4(5.4)	70(94.6)	74	17
Cefixime	4(6.3)	59(93.7)	63	28
Ceftazidime	6(8.1)	68(91.9)	74	37
Ceftriaxone	7(7.9)	82(92.1)	89	2
Cefuroxime	4(6.6)	57(93.4)	61	30
Ciprofloxacin	13(16.3)	67(83.8)	80	11
Levofloxacin	9(33.3)	18(66.7)	27	64
Linezolid	14(100)	0	14	77
Meropenem	15(20)	60(80)	75	16
Imipenem	11(14.3)	66(85.7)	77	14
Piperacillin + Tazobactam	15(20)	60(80)	75	16
Clindamycin	11(78.6)	3(21.4)	14	77
Vancomycin	6(50)	6(50)	12	79

Table-V

Association between growth of organisms with smoking status (n=100)

Smoking status	Growth of organism				p-value
	Yes (N=91)		No (N=9)		
	N	%	N	%	
Yes	85	93.4	6	6.6	0.033
No	6	66.7	3	33.3	

Figure 3 showing among the isolated bacteria *Klebsiella* was 27(29.67%), *Acinetobacter*23(25.27%), *Enterobacter*12(13.2%), *Streptococcus* 11(12.1%), *Pseudomonas* 8(8.8%), *E. coli* 4(4.4%), *Moraxella* 3(3.3%) and others *(MRSA, Citrobacter, Prevotella*) 3(3.3%).

Table 3 shows that Klebsiella was found in 27 patients. Among them, 100% antibiotic sensitivity was found for Colistin and 87.5% antibiotic sensitivity for Tigecycline. 100.0% antibiotic resistance was found for Levofloxacin, and 96.3% resistance was found for Amoxicillin + Clavulanic acid, Imipenem and Piperacillin + Tazobactam. 96.2% resistance for Meropenem, 92.6% resistance for Ceftriaxone, Ceftazidime, Cefepime, Amikacin and Gentamycin.

Table 4 shows the overall susceptibility of antibiotics to bacteria. Colistin was tested in 77 patients and found 73(94.8%) sensitivity, Tigecycline was sensitive for 75(85.2%) out of 88, Linezolid sensitivity found 14(100%), Clindamycin was sensitive for 11(78.6%) out of 14 patients. Ceftriaxone was resistant in 82(92.1%) out of 89, Cefoperazone + Sulbactam 70(94.6%) out of 74, Ceftazidime 68(91.9%) out of 74, Cefixime 59(93.7%) out of 63, Cefuroxime 57(93.4%) among 61, Co-amoxiclav 59(92.2%) out of 64, Meropenem 60(80%) among 75, Imipenem 66(85.7%) among 77, Piperacillin + Tazobactam 60(80%) out of 75, Amikacin 62(80.5%) out of 77, Gentamycin 64(78%) among 82, Ciprofloxacin 67(83.8%) among 80, Levofloxacin 18(66.7%) among 27 patients.

Table 5 shows a statistically significant association between the organism's growth and the patient's smoking status, as the p-value was 0.033.

Discussion

The cross-sectional study aimed to investigate the antibiotic susceptibility patterns of bacteria isolated from 100 known patients with chronic obstructive pulmonary disease (COPD) admitted to the Intensive Care Unit (ICU) at the National Institute of Diseases of the Chest and Hospital (NIDCH) in Mohakhali, Dhaka, Bangladesh.Demographic characteristics revealed that most (38%) of patients fell within the 50-59 age group, ranging from 47 to 77 years (mean 63.0±7.8 years). This aligns with findings by those who reported a mean age of 65±8.06 years in a similar patient population[19]. The study comprised predominantly male participants (86%), consistent with other investigationsbut varied from studies with a higher female representation[20].

Smoking was a prevalent risk factor, as 91% of patients were smokers, with the majority (63%) having a smoking history of e™ 20 pack years. This is comparable to findings by those who reported a mean pack year of 60 among smokers. Additionally, a high proportion of patients (71%) reported antibiotic use in the last 6 months, while 63% had used systemic corticosteroids. These rates suggest potential issues with the judicious use and prescription practices of these medications in the country[21].Comorbidities were observed, with 27% having diabetes mellitus, 23% having hypertension, 12% ischemic heart disease, and 7% chronic kidney disease. Blood sugar levels were predominantly normal in 80% of cases. The study's metabolic and cardiovascular comorbidity rates align with those reported by COPD patients[22].

Physiological parameters, including low pH (76%), low PaO2 (93%), and elevated PaCO2 (with a mean of 82.7±22 mmHg), indicated severe respiratory distress. Tracheal aspirate (58%) and sputum (40%) were the primary sample types collected. The majority (91%) of cultures yielded bacterial growth, consistent withwho reported positive cultures in 94% and 41.12% of cases, respectively.Gram-negative organisms predominated (86.8%), with Klebsiella (29.67%) and Acinetobacter (25.27%) being the most frequently isolated. This distribution aligns with studies byemphasizing the significance of these pathogens in COPD-related infections[23,24].Antibiotic susceptibility patterns were assessed for major bacterial isolates. Klebsiella exhibited high sensitivity (100%) to Colistin and Tigecycline, with resistance observed (>92%) for other antibiotics. Acinetobacter demonstrated sensitivity (86.9%) to Colistin and Tigecycline but resistance to multiple antibiotics, emphasizing the limited therapeutic options. Enterobacter, Streptococcus, and Pseudomonas also showed variable susceptibility patterns.

Overall, Colistin, Tigecycline, and Linezolid demonstrated notable efficacy across various isolates, while several commonly prescribed antibiotics, including cephalosporins, fluoroquinolones, and aminoglycosides, exhibited

high resistance rates. This challenges the conventional treatment approaches and emphasizes the need for targeted antibiotic therapies.The study identified smoking as significantly associated with bacterial growth (p-value 0.033). However, age, steroid or antibiotic use, and biochemical parameters like RBS and serum creatinine did not significantly correlate with bacterial growth.This study provides valuable insights into the antibiotic susceptibility patterns of bacteria in COPD patients admitted to the ICU. The high prevalence of Gram-negative organisms and multidrug-resistant strains highlights the challenges in managing infections in this population. The findings underscore the importance of judicious antibiotic use, considering the susceptibility patterns revealed in this study, and advocate for ongoing surveillance to guide effective treatment strategies. Further research and interventions are warranted to address the complex interplay of risk factors and microbiological characteristics influencing the outcomes of COPD patients in ICU settings.

Conclusion:

This study underscores the prevalence of gram-negative bacteria, particularly Klebsiella, in ICU-admitted COPD patients at NIDCH. High antibiotic resistance was observed, emphasizing the limited efficacy of commonly used antibiotics. Sensitivity to Colistin, Tigecycline, and Linezolid suggests the importance of targeted therapeutic strategies. Further research is warranted for effective treatment protocols.

Recommendation

- Antibiotic sensitivity patterns should be checked for all patients with COPD in ICU.
- Antibiotics for these patients must be given according to culture and sensitivity patterns.
- Cautious use of antibiotics should be considered for COPD patients in ICU.
- Colistin and Tigecycline could be used as empirical antibiotics for COPD patients in ICU.

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ORIGINAL ARTICLE

Outcome Evaluation in Acute Exacerbation of COPD On the Basis of Serum Gamma-Glutamyl Transferase Level

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Abstract

Background: *Chronic obstructive pulmonary disease (COPD) is a huge burden to the health care facility worldwide that is both substantial and increasing. Exacerbations of COPD have a negative impact on health status, rates of hospitalization and disease progression. However, there is still a lack of effective biomarkers to monitor COPD and its acute exacerbation. One of the most important factors in the pathogenesis of COPD is oxidative stress. GGT (gamma-glutamyl transferase) has been regarded as a novel marker of oxidative stress over the last few years. This aim of the study was to assess serum GGT level during acute exacerbation of COPD and to evaluate its role in monitoring the outcome of COPD exacerbation. We also tried to correlate serum GGT level with severity of COPD, respiratory failure and patients' degree of dyspnoea.*

Materials and Methods: *This was a hospital based longitudinal study and was conducted at the department of Respiratory Medicine, National Institute of Diseases of the Chest & Hospital (NIDCH), Dhaka, Bangladesh over a period of one year. Following informed written consent, total 50 patients with acute exacerbation of COPD were included into the study. All patients were interviewed and they were subjected to do physical examination along with relevant investigations by researcher with a pretested questionnaire. Serum GGT level was detected during admission, on day 3 and the day before discharge or other outcomes. In all cases, ethical issues were maintained properly and collected data were analysed by SPSS 23.*

Results: *Mean GGT was found 141.4±76.3 U/L at admission, 137.4±87.2 U/L on day 3 after admission and 85.5±45.0 U/L on the day before discharge. Negative correlation (r= -0.434; p=0.002) was observed between FEV_1(% predicted) and GGT at admission whereas positive correlation (r= 0.857; p=0.001) was present between PCO_2 and GGT at admission.*

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Mean GGT at admission was found to be higher in those referred to RCU/ICU group than those not requiring referral to RCU/ICU group and the difference was statistically significant (p<0.05). Serum GGT value e"103.5 U/L was associated with acute exacerbation of COPD requiring hospitalization, serum GGT level of e"141.5 U/L displayed a reliable prediction of referral to RCU/ICU and GGT level of e"194.0 U/L could be applied to predict an increased risk of mortality.

Conclusion: *This study demonstrates that serum GGT can be used as an effective biomarker to access the severity and predict the outcome in patients with acute exacerbation of COPD. The monitoring of GGT values can be useful during the progression of COPD exacerbation and assessment of serum GGT should be made readily available and easily accessible at all tertiary level hospitals in our country.*

Key words: *COPD, serum GGT*

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world, and is now one of the top three causes of death worldwide.[1] COPD is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development.[2]

COPD prevalence, morbidity and mortality vary across countries and across different groups within countries. COPD is the result of complex interplay of long-term cumulative exposure to noxious gases and particles, combined with a variety of host factors including genetics, airway hyperresponsiveness and poor lung growth during childhood.[3-5] The prevalence and burden of COPD are projected to increase over the coming decades due to continued exposure to COPD risk factors and aging of the world's population; as longevity increases more people will express the long term effects of exposure of COPD risk factors.[6] A systematic review and meta-analysis, including studies carried out in 28 countries between 1990 and 2004, provided evidence that the prevalence of COPD is appreciably higher in smokers and ex-smokers compared to non-smokers, in those e" 40 years of age compared to those < 40 and in men compared to women.[7] Based on BOLD and other large scale epidemiological studies, it is estimated that the number of COPD cases was 384 million in 2010. In a systematic review and meta-analysis published in 2015, ADELOYE et al.[8] identified 123 surveys with a global prevalence of COPD in 2010 of 11.7% (8.4–15.0%). Globally, there are around three million deaths annually.[9]

COPD results from a complex interaction between genes and the environment. Cigarette smoking is the leading environmental risk factor for COPD, yet even for heavy smokers, fewer than 50% develop COPD during their lifetime.[10] Although genetics may play a role in modifying the risk of COPD in smokers, there may also be involvement of other risk factors like sex, occupational exposure, socioeconomic status and longer life expectancy.

COPD should be considered in any patient who has dyspnea (persistent, progressive and characteristically worse with exercise), chronic cough or sputum production, a history of recurrent lower respiratory tract infection and/or a history of exposure to risk factors for the disease. Spirometry is required to make the diagnosis; the presence of a post-bronchodilator FEV1/FVC<0.7 confirms the presence of persistent airflow limitation.[2] Common complications of COPD include recurrent infective exacerbations, respiratory failure, pulmonary hypertension and cor pulmonale. COPD patients who frequently experience exacerbations have adverse impacts on their life quality, spirometry function and prognosis.[11] Moreover, episodes of exacerbation generate substantial social and financial costs.[12,13] Therefore, effective prevention is important both for the patients and health care providers.

Acute exacerbation of COPD is defined as an event in the course of the disease, characterized by a change in the patient's baseline dyspnea, cough, and/or sputum production, that is beyond normal day-to-day variations, and may warrant a change in regular medication.[14,15] However, there is still a lack of effective biomarkers for COPD and its acute exacerbation.[16]

It is known that the most important factors in the pathogenesis of COPD are inflammation and oxidative stress.[17] Cigarette smoking, the principal aetiology of chronic obstructive pulmonary disease (COPD) in the developed countries, delivers and generates oxidative stress within the lungs. This imbalance of oxidant burden and antioxidant capacity has been implicated as an important contributing factor in the pathogenesis of COPD. Oxidative processes and free radical generation orchestrate the inflammation, mucous gland hyperplasia, and apoptosis of the airway lining epithelium which characterizes COPD.[18]

Glutathione is one of the most abundant proteins in vivo involved in maintaining cellular homeostasis and is essential for the regulation of oxidant stress. Gamma-Glutamyl transferase (GGT) is the first enzyme of the gamma glutamyl cycle that regulates the antioxidant glutathione, hence it is a critical enzyme in glutathione homeostasis. The lung has a large reserve of antioxidant agents such as glutathione and superoxide dismutase to counter oxidants. However, smoking also causes the depletion of antioxidants, which further contributes to oxidative tissue damage. The downregulation of antioxidant pathways has also been associated with acute exacerbations of COPD.[18]

Serum gamma-glutamyl transferase (GGT) is present in high concentrations in the biliary tree and is traditionally used in clinical practice as a biomarker for liver disease.[19.] Since GGT is found in several other organs, including the lungs, it is unlikely to be a specific marker solely for biliary or liver disease.[20] Over the last few years GGT has become regarded as a novel biomarker for oxidative stress, and many studies have shown that GGT values within set reference ranges are predictive of several diseases, including chronic kidney disease, cardiovascular disease, type 2 diabetes, and cancer.[21] Nowadays, serum GGT levels are being applied as a marker for oxidative stress.[22] There are several previous studies on the relationship between GGT and COPD.[23-27] However, their results are not consistent. Bozkus et al.[25] demonstrated that serum GGT may be helpful in grading the severity of COPD while some scientists found serum GGT were similar in patients with different severity of disease.[25] Ermis et al. found significantly higher GGT activity in COPD patients compared to healthy controls,[26] while other scientists found no difference.[24]

Therefore, the present study was aimed to compare the serum levels of GGT at different stages of treatment during acute exacerbation of COPD admitted at a single center. Serum GGT activity and its predictive value in the outcome of acute exacerbation of COPD was also analyzed. Other targets of the study were to investigate relationship of serum GGT with pulmonary function and severity of COPD along with patient's level of dyspnea and development of respiratory failure on the basis of spirometry, mMRC dyspnea scale and ABG analysis respectively. As it is a cheap and easily available investigation all through our country, we can utilize it to predict the outcome of patients who are admitted in hospitals with acute exacerbation of COPD and take necessary steps at an earlier stage of disease to prevent further worsening and to reduce mortality and morbidity.

Methods

This longitudinal study was carried out in the Department of Respiratory Medicine, National Institute of Diseases of the chest and Hospital (NIDCH), Mohakhali, Dhaka. Total study period was 1 year (January 2022 to December 2022).

Inclusion criteria:

1. Patients with age e" 40 years.
2. Current smokers or patients with previous smoking history of 10 pack-years or longer.
3. Patients with the diagnosis of acute exacerbation of COPD according to the criteria established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Exclusion criteria:

- Patients with pulmonary diseases other than COPD, a history of asthma, pulmonary tuberculosis, DPLD, bronchial carcinoma etc.

- Patients with abnormal liver or biliary tract function, neoplastic pathologies, gastrointestinal, renal and endocrine diseases; regular alcohol consumption.
- Patients with severe comorbid diseases, eg acute heart failure, acute coronary syndrome.
- Patients not given written consent.

A total of 64 cases were enrolled on the basis of inclusion and exclusion criteria. All of them were clinically diagnosed cases of COPD of whom spirometry had been done previously. All the spirometry reports were checked and finally 50 patients were selected as study subjects whose spirometry data fulfilled the criteria to be defined as COPD.

All subjects undergoing the study were given necessary information and informed written consent were taken on a predesigned proforma/ data collection sheet. Detailed history was taken from each case and a thorough clinical examination was done including general and local chest examinations and anthropometric measurements.

Routine laboratory investigations including complete blood count (CBC), erythrocyte sedimentation rate (ESR), sputum for culture and sensitivity, sputum for AFB, ECG, Random blood sugar (RBS), liver and renal function tests, and chest X-ray (postero-anterior view) were done. Specific investigations like spirometry and ABG analysis were also performed. As all the patients were admitted with acute exacerbation, spirometry was performed before discharge when patients became clinically stable. Among the 50 study subjects spirometry could be done by 43 patients, remaining 7 patients died in the hospital intensive care unit (ICU) while being treated.

All the patients were treated as per standardized treatment protocol. Serum GGT level was detected during admission, on day 3 and on the day before discharge. The level of GGT was measured by the Vitros-7600 autoanalyzer using the original kits (batch 2021).

Patients' level of dyspnea was determined during admission on the basis of mMRC dyspnea scale. The final outcome of the patients (discharged/ transferred to RCU or ICU/ expired) was noted.

Data was analyzed with computer by SPSS software version 23 on the basis of objective of the study. Participant was volunteered, consent was obtaining after the briefing of the study in local language to all respondents and all answers were kept confidential.

Results:

A total of 64 cases were enrolled on the basis of inclusion and exclusion criteria. All of them were clinically diagnosed cases of COPD and finally 50 patients were selected as study subjects whose spirometry data fulfilled the criteria to be defined as COPD.

Table I shows that mean age was found 64.5±6.9 years with range from 51 to 85 years. Half (50.0%) of the patients belonged to age 61-70 years, 49(98.0%) were male, 26(52.0%) patients had completed school education, 35(70.0%) were unemployed.

Table I

Distribution of the study patients by demographic characteristics (n=50)

Variables	Number of patients	Percentage
Age (years)		
51-60	17	34.0
61-70	25	50.0
71-80		7
14.0		
>80	1	2.0
Mean±SD	64.5	±6.9
Range (min-max)	51	-85
Sex		
Male	49	98.0
Female	1	2.0
Educational status		
Illiterate	18	36.0
School	26	52.0
College	4	8.0
University	2	4.0
Occupational status		
Unemployed	35	70.0
Employee	14	28.0
Housewife	1	2.0

Figure 1 shows that majority 44(88.0%) patients were smoker, 11(22.0%) had low birth weight, 10(20.0%) had undernutrition and 1(2.0%) had history of exposure to biomass gas.

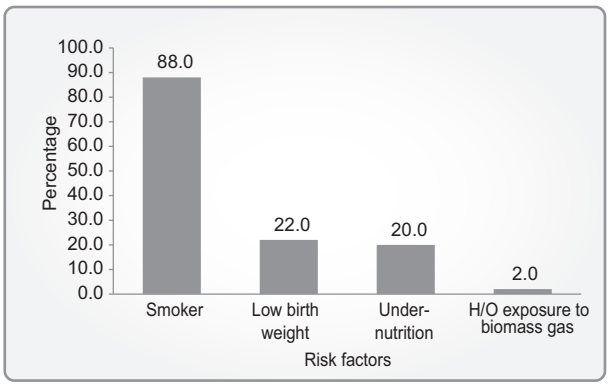

Figure 1: *Bar diagram showing risk factors of the patients (n=50)*

45 (90%) of the study subjects had higher GGT value during their admission. Mean GGT was found 141.4±76.3 U/L at admission, 137.4±87.2 U/L on day 3 after admission and 85.5±45.0 U/L on the day before discharge (Table II).

Table II

GGT in different follow up (n=50)

	Number of patients	Percentage
At admission		
Normal (d"50 U/L)	5	10.0
Abnormal (>50 U/L)	45	90.0
Mean±SD	141.4	±76.3
On day 3		
Normal (d"50 U/L)	7	14.0
Abnormal (>50 U/L)	43	86.0
Mean±SD	137.4	±87.2
Day before discharge	(n=43)	
Normal (d"50 U/L)	11	25.5
Abnormal (>50 U/L)	32	76.2
Mean±SD	85.5	±45.0

Figure 2 shows that majority 43(86%) patients could be discharged and 7(14.0%) were expired.

Table III shows that mean GGT at admission was found 105.0±51.6 U/L in moderate, 186.9±80.8 U/L in severe and 137.7±73.3 U/L in very severe airway obstruction. The difference was statistically significant ($p<0.05$) among three groups.

Figure 3 presents a scatter diagram showing negative correlation (r= -0.815; p=0.001) between pH and GGT at admission.

Figure 4 presents a scatter diagram showing positive correlation (r= 0.857; p=0.001) between PCO_2 and GGT at admission.

Another scatter diagram showing negative correlation (r= -0.434; p=0.002) between FEV_1(% predicted) and GGT at admission (Figure 5).

Table IV shows that mean GGT at admission was found 209.4±64.9 U/L in those referred to RCU/ICU group and 96.0±42.1 U/L in those without being referred to RCU/ICU group. The difference was statistically significant ($p<0.05$) between two groups.

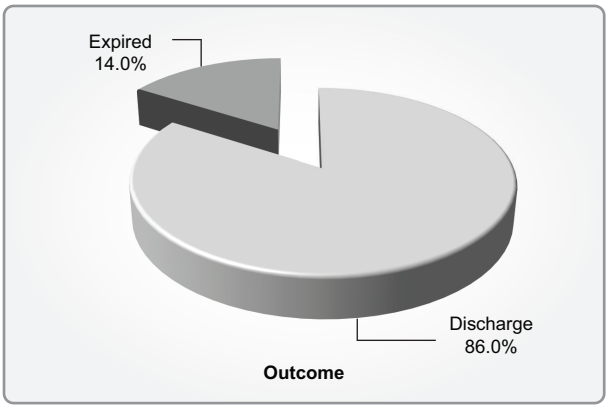

Figure 2: *Pie chart showing outcome of the study patients (n=50)*

Table III

Association between FEV_1(% predicted) with GGT at admission of study patients (n=43)

GGT at admission	FEV_1 (% predicted)						P value
	Moderate(n=26)		Severe (n=12)		Very severe (n=5)		
	N	%	n	%	n	%	
Normal (≤50 U/L)	5	19.2	0	0.0	0	0.0	
Abnormal (>50 U/L)	21	80.8	12	100.0	5	100.0	
Mean±SD	105.0	±51.6	186.9	±80.8	137.7	±73.3	0.001[s]
Range (min-max)	19.0	-196.0	78.0	-338.0	53.0	-181.0	

s= significant; P value reached from ANOVA test

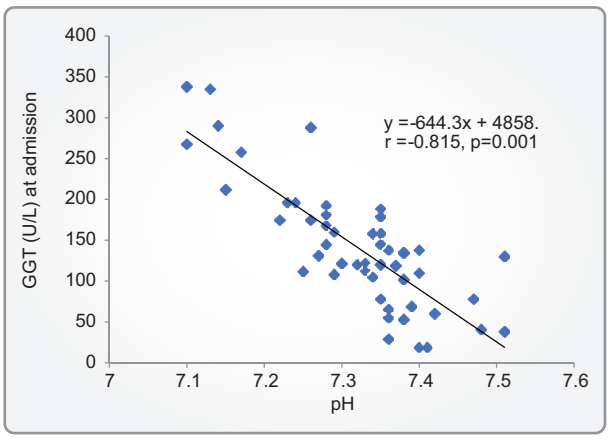

Figure 3: *Scatter diagram showing negative correlation (r= -0.815; p=0.001) between pH and GGT at admission.*

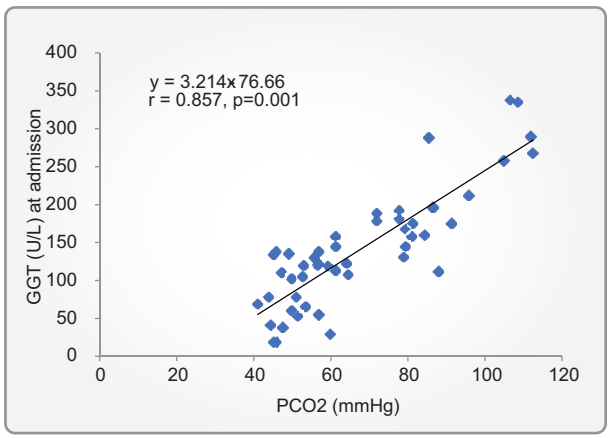

Figure 4: *Scatter diagram showing positive correlation (r= 0.857; p=0.001) between PCO_2 and GGT at admission.*

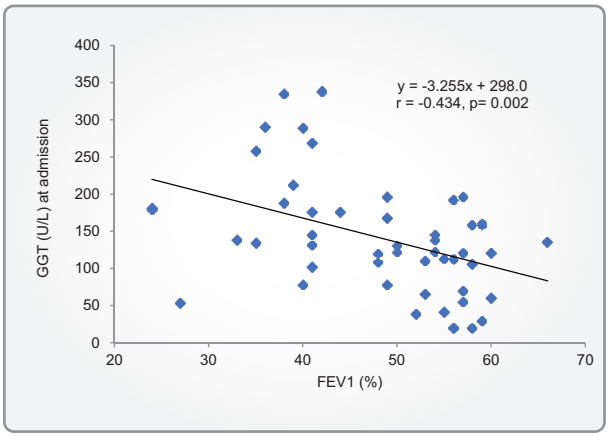

Figure 5: *Scatter diagram showing negative correlation (r= -0.434; p=0.002) between FEV_1(% predicted) and GGT at admission.*

Mean GGT at admission was found 270.5±56.2 U/L in expired group and 116.8±50.5 U/L in discharged group. The difference was statistically significant (p<0.05) between two groups (Table V).

Figure 6 presents a receiver-operator characteristic curve of GGT level for prediction of acute exacerbation of COPD.

Table VI shows the area under the receiver-operator characteristic (ROC) curve for prediction of acute exacerbation of COPD. Based on the receiver-operator characteristic (ROC) curve GGT level had area under curve 0.743. Receiver-operator characteristic (ROC) was constructed by using GGT level, which gave a cut off value e"103.5 U/L, with 74.0% sensitivity and 73.8% specificity for prediction of acute exacerbation of COPD.

Figure 7 represents a receiver-operator characteristic (ROC) curve of GGT level for prediction of referral to RCU/ICU.

The area under the receiver-operator characteristic (ROC) curve for prediction of referred to ICU is depicted in table VII. Based on the receiver-operator characteristic (ROC) curves GGT level had area under curve 0.961. Receiver-operator characteristic (ROC) was constructed by using GGT level, which gave a cut off value e"141.5 U/L, with 90.0% sensitivity and 90.0% specificity for prediction of referred to ICU.

Another Receiver-operator characteristic curve of GGT level for prediction of expired patients is presented in figure 8.

The area under the receiver-operator characteristic (ROC) curve for prediction of expired is depicted in table VIII. Based on the receiver-operator characteristic (ROC) curve GGT level had area under curve 0.981. Receiver-operator characteristic (ROC) was constructed by using GGT level, which gave a cut off value e"194.0 U/L, with 87.5% sensitivity and 95.2% specificity for prediction of expired.

Table IV

Association between GGT at admission with referral to RCU/ICU of study patients (n=50)

GGT at admission	Referred to RCU/ICU				P value
	Yes (n=22)		No (n=28)		
	n	%	N	%	
Normal (d"50 U/L)	0	0.0	5	17.8	
Abnormal (>50 U/L)	22	100.0	23	82.1	
Mean±SD	209.4	±64.9	96.0	±42.1	0.001[s]
Range (min-max)	112.0	-338.0	19.0	-158.0	

s= significant

P value reached from unpaired t-test

Table V

Association between GGT at admission with outcome of study patients (n=50)

GGT at admission	Outcome				P value
	Expired (n=7)		Discharge (n=43)		
	N	%	n	%	
Normal (d"50 U/L)	0	0.0	5	11.6	
Abnormal (>50 U/L)	7	100.0	38	88.3	
Mean±SD	270.5	±56.2	116.8	±50.5	0.001[s]
Range (min-max)	175.0	-338.0	19.0	-196.0	

s= significant

P value reached from unpaired t-test.

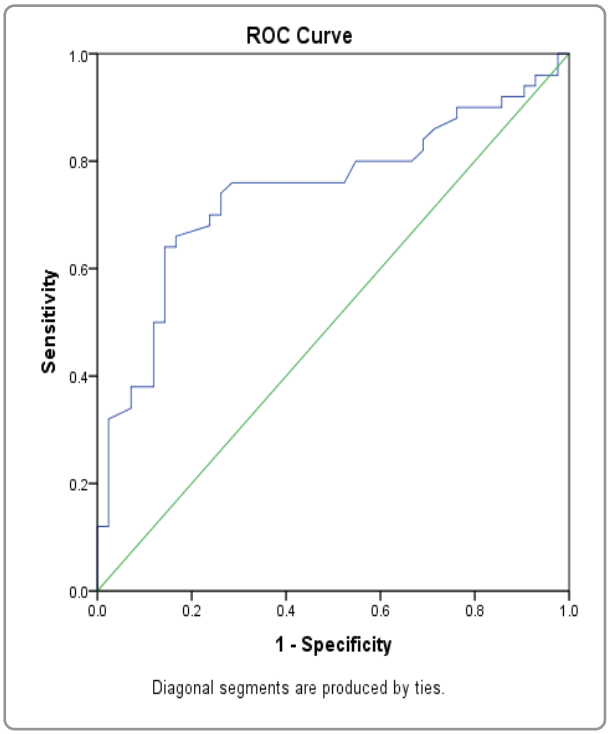

Figure 6: *Receiver-operator characteristic curves of GGT level for prediction of acute exacerbation of COPD*

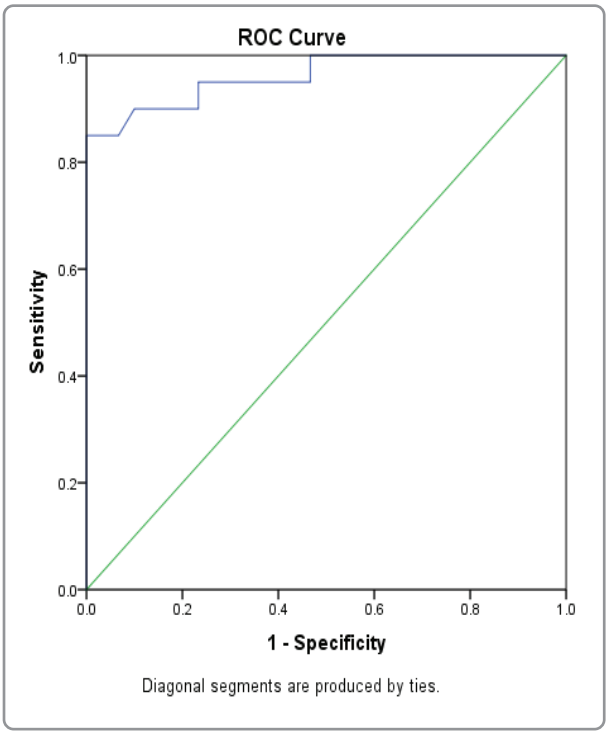

Figure 7: *Receiver-operator characteristic curves of GGT level for prediction of RCU/ICU referral*

Table VI

Receiver-operator characteristic (ROC) curve of GGT level for prediction of acute exacerbation of COPD

	Cut of value	Sensitivity	Specificity	Area under theROC curve	95% Confidence interval (CI) Lower bound	Upper bound
GGT level	≥103.5	74.0	73.8	0.743	0.640	0.847

Table VII

Receiver-operator characteristic (ROC) curve of GGT level for prediction of referred to RCU/ICU

	Cut of value	Sensitivity	Specificity	Area under theROC curve	95% Confidence interval (CI) Lower bound	Upper bound
GGT level	≥141.5	90.0	90.0	0.961	0.908	1.000

Table VIII

Receiver-operator characteristic (ROC) curve of GGT level for prediction of expired patients

	Cut of value	Sensitivity	Specificity	Area under theROC curve	95% Confidence interval (CI) Lower bound	Upper bound
GGT level	≥194.0	87.5	95.2	0.981	0.941	1.000

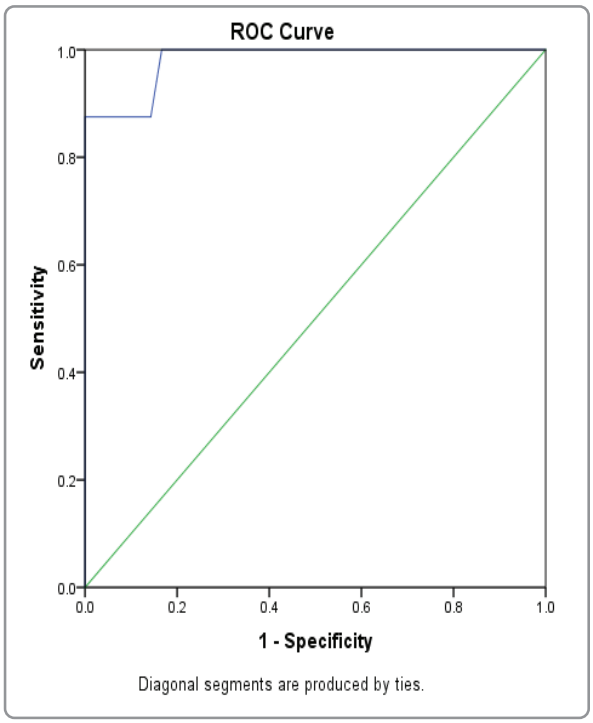

Figure 8: *Receiver-operator characteristic curves of GGT level for prediction of expired patients*

Discussion:

In this study we tried to evaluate the possibility of applying serum GGT as a biomarker in monitoring the level of oxidative stress in COPD patient. The aim of our study was to find out the link between oxidative stress and COPD and whether serum GGT might be a used as a potential marker to indicate the risk of COPD and a useful parameter to evaluate its exacerbation and outcome. We also tried to compare serum GGT level with patients' pulmonary functional status. We searched for whether there is any relationship between serum GGT level along with patient's level of dyspnea and respiratory failure on the basis of mMRC dyspnea scale and ABG analysis respectively.

In this current study, the average age of patients admitted with acute exacerbation of COPD was 64.5±6.9 years. Similar findings were seen in the study conducted by Ermis H et al.[26] where the average age was 66±10 years. Another study conducted by Sun D et al.[16] found that patients admitted with acute exacerbation of COPD had an average age of 65.4±9.8 years. Longer life expectancy, different lifestyle, peaks of air pollution, interruption of maintenance therapy, bacterial burden of the airways also have significant influence on AECOPD.

This study found that majority of the study subjects were male (98%). Almost similar findings were seen in the study carried out by Ermis H et al.[26] where the male female ratio was about 8:1; that is 88.6% patients with acute exacerbation were male. It indicates that acute exacerbation of chronic obstructive pulmonary disease itself predominates among the male that is closely resembled with Bhavesh et al.[28] study, where they found 72.67% and 27.33% patients were male and female respectively.

Across the world, smoking is the most commonly encountered risk factor of COPD. Cigarette smokers, either active or passive or past smoker, have a higher prevalence of respiratory symptoms, lung functional abnormalities, greater annual rate of decline of FEV1 and greater COPD exacerbation and mortality.[29] In our study, smoking was found to be the major risk factor associated with COPD exacerbation. 88% of the study subjects had a smoking history, which is similar with Mckeever et al.[30] study, where they found 93.9% participants had smoking history. Present study found that patients had a smoking history of about 28 pack years in average. Almost similar findings (26 pack year) were seen in the study conducted by Ermis H et al.[26] where the subjects with acute exacerbation had smoking history of 26 pack years on average. Other predominant risk factors which were found in the current study subjects were low birth weight (22% subjects), undernutrition (20%) and exposure to biomass gas (2%).

It was found that mean GGT value was 141.4±76.3 on the day of admission, it was 137±67.2 at day 3 and 85.5±45 at the day before discharge. It shows that in case of patients who could be discharged at the end the GGT values progressively reduced along with treatment and improvement of the patients.

In the current study, mean GGT at admission was found 105.0±51.6 U/L in GOLD stage 2 (moderate), 186.9±80.8 U/L in GOLD stage 3 (severe) and 137.7±73.3 U/L in GOLD stage 4 (very severe) FEV_1. The difference was statistically significant ($p<0.05$) among three groups with negative correlation ($r= -0.434$; $p=0.002$) was found between FEV_1 and GGT at admission. Bozkus F et al. shown that the mean value of gamma-GT in COPD with coexisting group is 64 and the mean value of gamma-GT in Group 2 GOLD C and D COPD is 63.5.[24] The level of gamma-GT was found to be significantly ($P < .001$) higher in the GOLD stage C and D group than in the GOLD stage A and B group. These findings correlate with the findings of our study.

Present study found that mean GGT at admission was 86.6±44.6 U/L in grade 2, 162.2±51.6 U/L in grade 3 and 240.7±106.8 U/L in grade 4 level of dyspnea according to mMRC scale. The difference was statistically significant ($p<0.05$) among three groups which showed that more severe level of dyspnea was associated with higher GGT values during admission. Similar findings were observed by Bozkus F et al.[24] also described Gamma-GT was significantly different between MMRC groups in GOLD A-B ($P < .001$).

In the current study we tried to establish a correlation between serum GGT level at admission and patients ABG analysis. negative correlation ($r= -0.815$; $p=0.001$) was observed between pH and GGT and positive correlation ($r= 0.857$; $p=0.001$) was found between PCO_2 and GGT at admission. So, it is obvious that higher serum GGT at admission was associated with type 2 respiratory failure and respiratory acidosis.

Mean GGT at admission was found 209.4±64.9 U/L among those referred to RCU/ICU group and 96.0±42.1 U/L in those without referred to RCU/ICU group. The difference was statistically significant ($p<0.05$) between two groups. Mean GGT at admission was found 270.5±56.2 U/L in expired group and 116.8±50.5 U/L in discharged group, the difference of was statistically significant ($p<0.05$). So, it can be concluded that patients who needed intensive care support and those who ultimately expired had significantly higher GGT value at admisiion. There was also a positive correlation ($r= 0.755$; $p=0.001$) between hospital stay and GGT at admission among the patients. Here it is clear that patients who were admitted with respiratory failure and higher serum GGT value at admission ultimately needed intensive care support and longer duration of hospital stay before being discharged.

A Receiver-operator characteristic (ROC) was constructed by using GGT level, which gave a cut off value e"103.5 U/L, with 74.0% sensitivity and

73.8% specificity (95% confidence interval; area under curve 0.743) for prediction of acute exacerbation of COPD. Sun D. et al.2020 in their study found that the cut off value for the prediction of acute exacerbation was 26.5 IU/L, with 69.75% sensitivity and 74.34% specificity (AUC=0.762; 95% CI, 0.701–0.823; P <0.001). The difference between the cut of value of these two studies are most probably due to difference of race and ethnicity of the study population and also due to variation of measuring kits used for detection of serum GGT level.

The cut off value of serum GGT was e"141.5 U/L for prediction of requirement of intensive care support (RCU/ICU), with sensitivity 90% and specificity also 90% (area under curve=0.961; 95% confidence interval, 0.908-1.000). It means that according to our study finding patients who had serum GGT level 141.5 U/L or more at admission had higher risk of requiring intensive care support.

The cut off value of serum GGT was e"194.0 U/L for prediction of mortality, with sensitivity 87.5% and specificity also 95.2% (area under curve=0.981; 95% confidence interval,0.941-1.000). It indicates that if serum GGT value at admission was 194 U/L or more there was high risk of mortality despite adequate treatment.

Conclusion

Serum GGT has been found to have strong correlation with patients' pulmonary functional status, level of dyspnea and also with patients ABG parameter and associated respiratory failure.

It was also evident that patients with higher GGT was associated with type 2 respiratory failure, respiratory acidosis, prolonged hospital stay, higher risk of intensive care support requirement and mortality.

In our study it was observed that serum GGT level near about more than 2 times above the reference range was associated with acute exacerbation of COPD requiring hospitalization, serum GGT value near about more than 3 times of the reference range was associated with greater RCU/ICU support requirement and GGT value near about 4 times greater than the reference range was associated with significantly higher mortality.

As a result, it can be concluded that we can predict the outcome of the patients and take urgent necessary steps to reduce the rate of intensive care support and mortality by simply measuring patients GGT level during admission and in subsequent follow up. So, serum GGT can be used as a reliable biomarker in the assessment of AECOPD patients and also to evaluate its outcome.

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REVIEW ARTICLE

Asthma of Cardiac Origin or Heart Failure: A Newer Approach to an Old Term?

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Abstract:

Chronic airway inflammation, hypersensitivity of the airways to a wide range of stimuli, and blockage of the airways are the hallmarks of asthma. It is at least somewhat curable, either naturally or with medical intervention.Edematous change of the airway mucosa lining, increase in mucoid secretion, injury to the airway epithelium, andbronchial smooth muscle spasm smaller bronchi and bronchioles can all cause obstruction of the airway.

Orthopnea, coughing, and wheezing brought on by congestive heart failure were previously known as asthma of cardiac origin or cardiac asthma.[1]The differentiation between bronchial asthma and cardiac asthma can be easily made clinically, except those who have both chronic lung illness and left heart disease.Though most patients respond poorly to diuretics, pulmonary edema, and pulmonary vascular congestion have been identified as the leading causes of cardiac asthma. When treating cardiac asthma, traditional asthma drugs like bronchodilators and corticosteroids seem to have little efficacy. Evidence points to the potential for developing innovative therapeutics as circulating inflammatory factors and tissue growth factors may also contribute to airway obstruction.

Heart failure is a disease with a high morbidity and death rate. Wheezing is one of the manifestations of heart failure that may indicate cardiac asthma. Treatment for bronchial asthma differs from that for cardiac asthma.Appropriate diagnosis and treatment may result from a thorough history and physical examination.

This review paper addressed the pathophysiological strategies for managing heart failure or asthma with a cardiac origin.

Keywords: cardiac asthma, asthma of cardiac origin, bronchial asthma, heart failure, wheezing, shortness of breath, pulmonary edema

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Asthma Definition

What is asthma?

Asthma causes respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that may vary over time including in their frequency and intensity. These symptoms are associated with variable expiratory airflow limitation, difficulty in breathing air out due to

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bronchoconstriction, airway wall thickening and increased mucus [2]

Definitions of Some Common Types of Heart Failure

Acute Heart Failure

Acute Heart Failure can be defined as the new onset or recurrence of symptoms and signs of heart failure requiring urgent or emergent therapy and resulting in seeking unscheduled care or hospitalization. Although the designation "acute" in the nomenclature suggests a sudden onset of symptoms, many patients may have a more subacute course, with gradual worsening of symptoms that ultimately reach a level of severity sufficient to seek unscheduled medical care.[3]

Chronic Heart Failure

Chronic Heart Failure refers to patients with diagnosed heart failure for a period of time (arbitrarily defined as a minimum of 3months). It follows that these patients have received some heart failure treatment.[4]

Congestive HeartFailure:

Congestive heart failure is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the heart to function as a pump to support a physiologic circulation. The syndrome of heart failure is characterized by symptoms such as breathlessness with features of circulatory congestion (fluid retention) such as jugular venous distension, rales, peripheral edema, and ascites.[5]

The presence of wheezing and coughing in addition to paroxysmal dyspnea is a characteristic manifestation of congestive heart failure (CHF), which was previously referred to as cardiac asthma. The historical definitions of cardiac asthma and asthma of cardiac origin are not dissimilar to the contemporary understanding of cardiac asthma, which attributes symptoms such as wheezing, coughing, and orthopnea to congestive heart failure rather than primary pulmonary illness.The historical definitions of cardiac asthma and asthma of cardiac origin are not dissimilar to the contemporary understanding of cardiac asthma, which attributes symptoms such as wheezing, coughing, and orthopnea to congestive heart failure rather than primary pulmonary illness. It is widely believed to be hemodynamic and a result of venous hypertension in the lungs and bronchial vessels.[6]

Prevalence of cardiac asthma

The current prevalence of HF globally is 64.34 million patients (8.52 per 1,000 inhabitants).[7]Symptoms such as dyspnea, wheezing, and coughing during the night are frequent in patients with reduced left ventricular function.While the mechanisms causing this phenomenon remain unclear, numerous pathways that may contribute to cardiac asthma have been the subject of investigation.[8]Asthma and exercise-induced bronchospasm are frequent misinterpretations for cardiac dyspnea, mainly when it manifests only during physical activity.Pulmonary edema caused by pulmonary venous hypertension rather than asthmatic bronchoconstriction is the underlying cause of cardiac dyspnea or asthma.[9]

Pulmonary Symptoms of Heart Disease

Wheezing

Orthopnea

Dyspnea in Acute Pulmonary Edema

Exercise Intolerance

Clinicians have long recognized the presence of airflow obstruction in the context of pulmonary edema; however, the precise processes underlying this phenomenon remain unknown. Reflex bronchoconstriction probably occurs in response to an increase in pulmonary or bronchial vascular pressure. Additional possible factors contributing to airway constriction comprise a geometric reduction in the airway size due to diminished lung volume, obstruction caused by intraluminal edema fluid, and bronchial mucosal swelling.[10]

The hypothesis is that a liter of outward displacement of the chest wall may occur in the supine position relative to its standing position in some situations and may result in orthopnea.[11]

Vascular and cardiac enlargement can result in the accumulation of an additional 500 mL of blood within the thorax, causing the expansion of the chest wall beyond its normal position, and it may result in dyspnea.[12]

Patients with cardiac disease, regardless of the etiology, may have a decline in exercise capacity,

which manifests as a reduction in peak oxygen consumption. While this anomaly does not have a specific impact on cardiovascular illness, its magnitude holds significant predictive value in determining which individuals are suitable candidates for heart transplantation. An unusually high ventilation-to-carbon dioxide production ratio is another characteristic of chronic heart failure.[13]

Pathophysiology

In the context of heart failure, an elevation in pressure within the pulmonary circulatory system results from the accumulation of blood in the lung vessels due to the heart's reduced pumping capacity. Lung congestion and edema result from the fluid that leaks from blood vessels into alveoli and lung tissues due to this elevated pressure.Similar to the symptoms seen in patients with asthma, the fluid irritates the airways, resulting in the induction of coughing and wheezing. These symptoms are more pronounced when lying down at night.At first, the manifestation of symptoms subsides upon the patient assuming an upright position; however, as the condition of heart failure advances, their intensity escalates.Pulmonary congestion (edema), increased coughing, profuse cold sweats, and rales are potential symptoms.[14]

Cases of "cardiac asthma" are occasionally misdiagnosed as "bronchial asthma" or other respiratory disorders, such as bronchiectasis, despite the wealth of knowledge that has been amassed over time. Differentiating respiratory causes of wheezing and coughing from secondary reasons, particularly heart failure, is paramount. Distinguishing between people with Chronic Heart Failure can present a more significant challenge due to the gradual and subtle onset of symptoms associated with this condition.

Although there are numerous potential causes for chronic cough, it is crucial not to disregard a cough that disturbs a patient's sleep and worsens when lying down, especially when accompanied by weariness and reduced activity ability.Coughs that do not exhibit a response to therapeutic interventions like respiratory inhalers or proton pump inhibitors may suggest the presence of an alternate underlying cardiac disease. A physician must, therefore keep a "strong index of suspicion.

Diagnosis

The ACC/AHA guidelines emphasize (i) careful history and physical examination, (ii) Laboratory examinations comprising of a complete blood count, renal and hepatic function tests, urine analysis, an electrocardiogram, and a chest x-ray need to be performed, (iii) two dimensional and Doppler echocardiogram (iv) thorough exclusion of thyroid and coronary artery disease in every case, and (v) additional diagnostic procedures, such as serologic studies, are administered selectively to patients who meet the criteria (based on clinical characteristics, risk factors, past medical history, and family history).[15]

To distinguish between the two, a clinical examination and other investigations may be conducted, In order to differentiate between the two, a clinical examination and other investigations may be performed:A bronchial asthma diagnosis is supported by a family history of allergies and a susceptibility to asthma attacks beginning in early childhood. A preexisting medical history of cardiovascular illness, hypertension, or diabetes characterizes cardiac asthma.

Cardinal asthma is suggested by frothy, pink sputum. Patients diagnosed with bronchial asthma may produce viscous, coated sputum.Cardiac asthma is a clinical diagnosis. In addition to pulmonary evaluation, elderly individuals with coughing, wheezing, or nocturnal dyspnea may benefit from a cardiac assessment to establish whether the underlying reason is cardiac.

Symptoms[16]

Typical

Breathlessness
Orthopnea
Paroxysmal nocturnal dyspnea
Reduced exercise tolerance
Fatigue, tiredness, increased time to recover after exercise
Ankle swelling
Less typical
Nocturnal cough
Wheezing
Bloated feeling
Loss of appetite
Confusion (especially in the elderly)
Depression

Palpitations
Dizziness
Syncope
Bendopnea

Sign
Elevationjugularvenous pressure
Hepatojugular reflux
Third heart sound (Gallop rhythm)
Laterally displaced apical impulse
Less specific
Weight gain (>2 kg/week)
Weight loss (in advanced HF)
Tissue wasting (cachexia)
Cardiac murmur
Peripheral edema (ankle, sacral, scrotal)
Pulmonary crepitations
Dull Percussion Note due to pleural effusion
Tachycardia
Cheyne Stokes respiration
Hepatomegaly
Ascites
Cold extremities
Oliguria
Narrow pulse pressure

A dramatic and rapid response to inhalers or nebulization indicates bronchial asthma.While bronchodilators may provide some relief, they are often insufficient in treating cardiac asthma. Intravenous diuretics relieve symptoms of cardiac asthma promptly.

The probability of heart failure should be initially assessed in patients who present with symptoms or signs for the first time, non-urgently, in primary care or a hospital outpatient clinic. This assessment should be based on the patient's prior clinical history, which may include diuretic use, coronary artery disease, and arterial hypertension; presenting symptoms such as orthopnea; physical examination findings including bilateral oedema, elevated jugular venous pressure, and displaced apical beat; and resting electrocardiogram (ECG).Heart Failure is highly improbable if all elements are within the normal range; alternative diagnosis should be investigated.[17].

Plasma pro-BNP should be tested, if available, in cases when at least one element is abnormal in order to identify individuals who require echocardiography (an echocardiogram is indicated if the pro-BNP level is above the exclusion threshold or if circulating pro-BNP levels cannot be assessed).[18]

Chest X-ray
When determining an alternate pulmonary explanation for a patient's symptoms and signs, a chest X-ray is likely the most beneficial. In a patient with heart failure, pulmonary venous congestion or oedema may be detected.In a patient with heart failure, pulmonary venous congestion or oedema may be diagnosed.

Electrocardiogram (ECG)
Although specificity is limited, an abnormal electrocardiogram (ECG) increases the probability of diagnosing heart failure.Certain electrocardiogram (ECG) abnormalities offer an understanding of the underlying cause (e.g., myocardial infarction), whereas other ECG findings may suggest therapeutic objectives (e.g., anticoagulation for atrial fibrillation).[19]

Echocardiography
Echocardiography is the most practical and commonly accessible diagnostic procedure utilized in patients suspected of having heart failure. It offers real-time data regarding chamber volumes and the systolic and diastolic cardiac function.

Management
Nutrition and diet: Patients with heart failure are more susceptible to weight loss as a result of appetite suppression and hypercatabolism. The nutritional and caloric requirements of these individuals are accounted for in their dietary management plans. Symptom-based salt restriction is a key component. Because salt consumption in the general population is normally high (>4 g/d), doctors should consider sodium restriction to some degree (e.g., <3 g/d).[21]

Medication
Preventing or delaying the development of symptoms-driven heart failure or death before its manifestation is important. It has been demonstrated that many antihypertensive medications [diuretics, ACEIs, angiotensin receptor blockers (ARBs), beta-blockers] are efficacious, particularly in the elderly, in patients with and without a prior myocardial infarction.[22]

Common echocardiographic abnormalities in heart failure [20]

Measurement	Abnormality	Clinical implications
LV ejection fraction	Reduced (<45–50%)	Systolic dysfunction
LV function, global and focal	Akinesis, hypokinesis, dyskinesis	Myocardial infarction/ischaemia Cardiomyopathy, myocarditis
End-diastolic diameter	Increased (55–60 mm)	Volume overload HF likely
End-systolic diameter	Increased (45 mm)	Volume overload HF likely
Fractional shortening	Reduced (25%)	Systolic dysfunction
Left atrial size	Increased (40 mm)	Increased filling pressures Mitral valve dysfunction Atrial fibrillation
Left ventricular thickness	Hypertrophy (>11–12 mm)	Hypertension, aortic stenosis, hypertrophic cardiomyopathy
Valvular structure and function	Valvular stenosis or regurgitation (especially aortic stenosis and mitral insufficiency)	May be primary cause of HF or complicating factor Assess gradients and regurgitant fraction Assess haemodynamic consequences Consider surgery
Pericardium	Effusion, haemopericardium, thickening	Consider tamponade, uraemia, malignancy, systemic disease, acute or chronic pericarditis,
Inferior vena cava	Dilated Retrograde flow	Increased right atrial pressures Right ventricular dysfunction Hepatic congestion

Intervention and device therapy

By reducing the size of the infarct during the initial phase of anST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention reduces the likelihood of developing a significant reduction in left ventricular function (LVEF) and subsequent onset of heart failure.[23]Implementing an ACEI, beta-blocker, or Mineralocorticoid Receptor Antagonist as soon as possible following myocardial infarction has been shown to decrease the rate of hospitalization for HF, particularly when the event is accompanied by LV systolic dysfunction.[24]

The rapid and dramatic response to inhalers or nebulization of asthma medications presumes bronchial asthma. In most cases, bronchodilators do not provide complete relief from cardiac asthma, although they may offer some assistance. Diuretics provide immediate clinical relief for cardiac asthma.

Treatment

The primary objectives of cardiac asthma treatment are symptom relief and improvement of cardiac contractility. Bronchodilator use is typically designed to estimate the coexistence of bronchial asthma and heart disease, for which limited evidence exists.[6]

Diuretics, nitrates, inotropic medicines, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers are examples of therapeutic approaches for cardiac asthma and acute heart failure.[14]

Indirectly, treatments that enhance the function of the left ventricle may alleviate the dyspnea associated with cardiac asthma.[25]

Conclusion

Cardiac asthma refers to the frequent manifestation of heart failure, which includes symptoms such as wheezing, coughing, and dyspnea.[6]Differentiating bronchial asthma from cardiac asthma is crucial due to different treatment approaches. Thorough physical examination and detailed history recording may differentiate cardiac asthma from bronchial asthma.While initial treatment may relieve congestion, to decrease morbidity and mortality, it is essential to initiate long-term therapy. Education of the patient, attendants, and caregiver is necessary to increase compliance.

Pulmonary congestion and edema can result from heart failure; this is often considered to be the principal etiology of cardiac asthma. Nevertheless, heart failure is recognized as a chronic inflammatory condition, and proinflammatory risk factors, such as obesity,hypertension and cigarette smoking, contribute to the development of the disease.All of these factors can potentially enhance the likelihood of developing bronchial asthma. The increased susceptibility to concurrent asthma and cardiovascular illness has caused significant complications in clinical studies investigating treatments for cardiac asthma. Pulmonary function testing, including bronchial challenge, electrocardiography or echocardiography, and serum Pro BNP level, may assist in differentiating bronchial asthma from cardiac asthma, according to some authors.[23,26]

A significant portion of individuals with cardiac asthma suffer from persistent airflow obstruction that is resistant to bronchodilators and diuretics. A high index of suspicion for cardiovascular disease should be maintained by physicians and other healthcare providers when evaluating older persons who present with persistent asthma or symptoms resembling asthma, particularly if these symptoms have only recently begun.

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CASE REPORT

Awake Pleural Decortication for Empyema Thoracis with Thickened Pleura-First Time in Bangladesh: A Case Report

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Abstract:

General anesthesia is the primary anesthetic technique used in the majority of thoracic procedures. Nonetheless, there is a growing body of documented research regarding effective non-intubated thoracic surgery cases using regional anesthetic these days. This alternative strategy technique not only avoids general anesthesia-associated risks such incomplete re-expansion, lung injury, and issues related to intubation, but it also contributes to a shorter hospital stay and lower total expenditures. Under thoracic spinal anesthesia, we were able to successfully perform non-intubated open decortication on a 62-year-old female patient with thickened pleura and multiple co-morbidities, including DM, HTN, and severe pulmonary hypertension. The patient continued to breathe on her own. The patient recovered quickly and experienced no anesthetic hazard. This is Bangladesh's first report of non-intubated thoracic surgery performed under segmental thoracic spinal anesthesia, and we anticipate other well-designed prospective studies in the near future that will support the improvement of non-intubated thoracic surgery results.

Keywords: Empyema Thoracis (ET), Decortication, Thoracic spinal anesthesia, Non-intubated

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Introduction:

Empyema thoracis (ET) is an infectious condition characterised by an accumulation of fluid in the pleural cavity that is frankly purulent[1]. Up to 50% of ET cases are caused by parapneumonic effusion; less common causes include iatrogenic pleural

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contamination from oesophageal perforation or bronchopleural fistula, superinfection following traumatic haemothorax, and extension from a subphrenic or pulmonary abscess. Regardless of the underlying cause, ET must be viewed as a serious illness that requires prompt and effective treatment[2,3].

The objectives of treating ET include draining the fluid collection(s), successfully re-expansion the lung, and sterilising the pleural cavity. Adhesions and visceral pleural thickening are the main causes of lung entrapment. A variety of therapy options, such as open window thoracostomy, video-assisted thoracoscopy (VATS), and thoracotomy, may be taken into consideration, ranging from straightforward drainage to surgical methods[4]. Although the best course of treatment is still up for debate, surgery has been shown to be more successful than conservative measures, particularly when multi-loculated collections are present, which are common findings in ET[2]. Surgery risks must be weighed against anticipated benefits, but issues in medicolegal and deontological domains come up when we look at less invasive treatments. Specifically, individuals must evaluate the fatal consequences of both general anaesthesia and one-lung breathing since they can lead to numerous life-threatening complications, including multiple organ failure, particularly in high-risk patients[4].

Thoracic surgery served as the foundation for our understanding of thoracic procedures during World War I when it was frequently used to treat bullet wounds without the use of general anaesthesia (GA)[5]. Compared to the regional anaesthesia approach, one-lung ventilation with general anaesthesia became the primary strategy for thoracic surgery with the development of the double-lumen tube. Nevertheless, this approach exposed negative consequences linked to lung injury caused by ventilators, including atelectrauma, volutrauma, and barotrauma, along with compromised heart function[6].

A successful non-intubated open decortication of empyema with thickened pleura under thoracic level spinal anaesthesia is reported here in a patient with poor respiratory function and many co-morbidities, including severe pulmonary hypertension, diabetes, and heart failure. The patient recovered quickly and without any problems despite a high risk of post-operative respiratory function decline due to various co-morbidities, including CKD, DM, and HTN with severe pulmonary hypertension. This is the first reported case in the literature of non-intubated thoracic surgery under thoracic spinal anaesthesia in Bangladesh.

Case Summary:

A 62-year-old female patient (height: 153 cm, and weight: 67 kg) was admitted with shortness of breath and cough with productive sputum. She was a known case of CKD, DM, HTN with severe Pulmonary Hypertension. The chest computed tomography (CT) indicated bilateral pleural effusion (encysted in the right) with the haziness of the lower lobe of both lungs. Pre-operative color Doppler echo showed PASP 76 mm of Hg. Then, Tablet Ambrisentan 5 mg once daily and Tablet Sildenafil 50 mg twice daily were started with other previously continued routine medications. The forced expiratory volume in one second was 57%, and the forced expiratory volume in one second to forced vital capacity ratio was 65%, indicating a significant obstructive pattern in the pulmonary function test. The patient refused to be admittedtothe hospital and went home but again came back after 2 days with severe respiratory distress and got herself admitted tothe hospital. After admission, a tube thoracostomy was done on the left side, and 2.3 litres of straw-coloured fluid came out. After 2 days of admission, the patient's respiratory distress was relieved a lot, and Spo2 92-94% was maintained with 3L of O2 via nasal prong. Then again, acolour Doppler echo was done, and PASP found 53 mm of Hg along with grade II left ventricular diastolic dysfunction; there was also trivial aortic regurgitation, tricuspid regurgitation, and moderate mitral regurgitation. After consulting with the anaesthesia and pain management team, it was decided that the patient was considered high-risk and should not be placed under general anaesthesia because of the risk of ventilator dependency. Thoracic-level spinal anaesthesia was their recommended method of administration. e informed both the patient and the patient's relatives about the anaesthesia protocol and its specific and serious hazards regarding injury involving the spinal cord due to the needle, which could result in enduring paralysis

or a combination of numbness and paralysis in either or both limbs and hazard included the occurrence of total spinal anaesthesia, necessitating the need for ventilatory support in a manner to that required during general anaesthesia. The patient acknowledged and consented to the potential hazards. After discussing it, informed written consent was obtained. After placing all necessary invasive and non-invasive monitoring systems in a sitting position, a 25-gauge Quincke spinal needle was carefully inserted through the intervertebral space between the T6 and T7 vertebrae and gradually advanced until cerebrospinal fluid became visible. The patient denied experiencing any paresthesia. Bupivacaine with a constant pressure (0.5%; 10 mg) was administered into the subarachnoid space over a period of 1 minute, after which the patient was positioned in a supine posture. The pin-prick test indicated that we successfully achieved the sensory block at the T1-T12 level.

Surgical technique:

The patient was placed in a left lateral position with a slight elevation of the trunk. A small anti-decubitus mattress was placed below the dependent hemithorax to facilitate surgery without the patient's discomfort to slightly split intercostal spaces. All the surgery team members were scrubbed before the anaesthesia procedure started to reduce the operative time as much as possible. The chest was opened through the 6th intercostal space for better visualisation of loculated fluid collections and easier exploration of costophrenic angles. After opening the chest by thoracotomy incision, the patient developed surgical pneumothorax and lung collapse, which facilitated surgery. The operational method was substantially the same as that used during the general anaesthesia surgery. However,adhesiolysis and pleural peel dissection were carried out with greater care. During the procedure, the quality of lung expansion was repeatedly tested by asking the patient to cough or inhale deeply. The pleural cavity was generously washed with normal saline at the end of the procedure. Finally, one chest drainage was placed when the complete lung re-expansion was verified. Full operation was done without switching to general anaesthesia. The skin was closed with staplers, and the total operation time from skin incision to skin closer was 70 minutes.

Post-operative management:

After three hours of observation in the surgical post-operative care unit, the patient was sent to the surgical ward. The intravenous fluid was withdrawn as soon as the patient was moved to the ward, and oral intake was initiated. The analgesia strategy thereafter included intramuscular injections of nalbuphine hydrochloride 12 hours apart and on-demand intravenous boluses of ketorolac. On the first post-operative morning, an intense respiratory rehabilitation program was initiated.

The removal of the chest drain tube was based on standard criteria, which included no air leakage after two hours after clamping the line, serous fluid loss of less than 100 millilitres per day, and no issues with the pleural area. On the fourth post-operative day, the patient was released with instructions to complete her follow-up appointments at one, three, and six months. She expressed her gratitude for the efficient analgesia provided during and after surgery.

Discussion:

Conventionally, GA with mechanical one-lung ventilation has been the primary anaesthetic option for thoracic surgery; nevertheless, patients have been exposed to a number of post-operative complications, including lung injury, inadequate re-expansion, and issues linked to intubation.

There are several potential challenges with GA combined with one-lung ventilation that might raise mortality and morbidity. Ventilation-to-perfusion mismatch, loss of surfactant, limited lung compliance, and interstitial oedema are among the inflammatory changes that can result from mechanical ventilation-induced lung injury[3]. Furthermore, mechanical one-lung ventilation creates a mismatch between the dependent lung's ventilation and perfusion, resulting in a hypoxic condition that can trigger cytokine release, tissue acidosis, alveolar oedema, and vascular congestion[4]. The justification for regional anaesthesia in thoracic surgery is that one-lung ventilation allows patients to avoid these types of problems from GA, resulting in reduced morbidity and quicker recovery.

Regional anaesthesia can be used for a variety of thoracic procedures, such as wedge resection lobectomy, pleurodesis, excision of a mediastinal mass, drainage of pleural effusion, and tracheal resection or excision[5]. It is widely accepted that, in comparison to GA, regional anaesthesia offers superior hemodynamic stability, fewer thrombotic problems, and a lower surgical stress response[6]. Patients should be carefully chosen and excluded from non-intubated thoracic surgeries if they meet any of the following criteria, which also apply to the exclusion criteria for regional anaesthesia: patients who are hemodynamically unstable; INR > 1.5 or current antiplatelet therapy; sleep apnea; unfavourable airway or spinal deformity; prior ipsilateral thoracic surgery; asthma; extreme obesity (body mass index > 35 kg/m2); pre-operative decompensated heart disease; multiple pleural adhesions over targeted hemithorax; intracranial hypertension; patient unable to cooperate with the procedure, and so forth[7,8]. Furthermore, care needs to be taken in relation to potential side effects of regional anaesthesia, which are uncommon but can include epidural hematoma, spinal cord injury, and unintentionally high anaesthetic levels.

There are several methods for achieving regional anaesthesia during non-intubated thoracic surgery, such as intrapleural analgesia, Thoracic epidural and spinal anaesthesia, paravertebral nerve block, and intercostal nerve block[9].

The anesthesiologist and the surgeon must collaborate closely, sharing information during the non-intubated thoracic surgery process. Surgical teams lacking experience and poor collaboration may face challenges while administering non-intubated anaesthesia during thoracic surgery. The total conversion rate to GA varies from less than 1% to 9%, according to data from earlier research[10]. Surgical complications, including strong adhesions, considerable mediastinal displacement, and major bleeding, are the most common causes of conversion. The non-surgical causes include tachypnea, prolonged hypoxemia, and inadequate analgesia. The anesthesiologist team should always be prepared to move quickly to oro-tracheal intubation, which is difficult for the anesthesiologist in the patient's lateral decubitus position technically, in order to facilitate early conversion to intubated GA[11,12]. As the chest tube is inserted and the surgical openings are quickly closed with a clear drape to prevent lung collapse, the anesthesiologist should help the patient breathe by providing a high flow of 100% oxygen. Introducing a bronchial blocker without repositioning the patient after inserting a single-lumen endotracheal tube under bronchoscopic supervision is advised. A skilled anesthesiologist has been found to be able to do double-lumen intubation in the lateral decubitus position[13].

Conclusion:

Segmental thoracic spinal anaesthesia with moderate sedation may be a viable approach for open thoracic surgery in patients with complicated respiratory function, as we have demonstrated. A regional anaesthesia strategy unquestionably decreased selected cohorts' duration of hospital stay, overall costs, and morbidity rates despite several biases[14]. Research on the benefits of non-intubated surgery has predominantly relied on observational or retrospective case series studies conducted in recent years. As more clinicians recognise that regional anaesthesia can serve as an alternative strategy for thoracic surgery, we anticipate a substantial increase in available data and the development of evidence-based, detailed protocols in the near future. This will enable us to improve outcomes for carefully selected patients.

Funding:

None.

Conflict of interest:

All authors have no conflict of interest.

Ethical Approval:

Ethical approval was not needed for the case report, but informed written consent was obtained from the patient and relatives.

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CASE REPORT

Accidental Balloon Dilatation of Patent Ductus Arteriosus in A Case of Critical Coarctation of Aorta: Subsequently A New Innovation for Patent Ductus Arteriosus Dependent Circulation

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Abstract:

Coarctation of the aorta is a rare form of congenital heart disease, though preductal coarctation is not very uncommon. This is a report on a 28-days-old girl who was referred to our center for evaluation. Doppler echocardiography showed severe preductalcoarctation of aorta and a tiny Patent DuctusArteriosus (PDA). Later it was confirmed by aortogram which showed critical coarctation of aorta (COA). This full-term infant with symptomatic COA was treated successfully with a Balloon angioplasty procedure. But during last inflation, wire entered through PDA to the pulmonary artery and was dilated with 8×3 Tyshak mini balloon considering balloon placement in Coarctation segment. Aortogram showed a large PDA after balloon dilatation. Immediately patient developed some features of heart failure. Patient was referred to cardiac surgeon as device closure was not possible in such a large PDA in a tiny newborn with maximum size Piccolo device. Subsequently balloon dilatation of PDA was found effective in maintaining circulation to pulmonary tree in PDA dependent cases.

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Introduction:

A combination of Coarctation of aorta (COA) and Patent DuctusArteriosus (PDA) can lead to heart failure and severe symptoms, which can be manifested by shock, and subsequently other organ failure.

Aortic coarctation indicates a narrowing at some point along the course of the aorta. Preductalcoarctation is one of the common type of Coarctation and circulation below the level of coarctation is maintained by patent ductusarteriosus (PDA) . A neonate or infant with severe coarctation of the aorta may present with symptoms of congestive heart failure, having been well days before when the ductus was still open[1,2]. Subsequently, they may develop renal failure and the feature of hypoperfusion to other organs once the ductus is closed. So, the infant becomes acutely, seriously, and even critically ill[3]. Any neonate or infant with such critical symptoms needs urgent

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intervention which includes medical management like injectionprostaglandin to keep the ductus open, surgical intervention, or balloon angioplasty[1]. Here we are reporting a case of pre-ductal coarctation of the aorta who needed balloon angioplasty and PDA ligation at 28 days of age and was cured completely. PDA was not visible in initial aortogram . Accidental crossing of wire through almost closed PDA and subsequentaccidental Ballon angioplasty resulted in a large PDA with subsequent heart failure.

Case Report:

A 28-days-old girl, weighing 2.4 kg, presented with Severe respiratory distress, and difficulty in feeding, and was referred to our center at Bangladesh Specialized Hospital (BSH), Dhaka for evaluation. Clinical examination showed, the child was ill-looking, pale, dehydrated, dyspneic, and tachypneic, with visible bilateral chest indrawing, clearly audible systolic murmur, and pulse of the lower limbs were feeble in comparison to the upper extremity.

Chest x-ray showed –cardiomegaly, with normallung fields and electrocardiography (ECG) showed right axis deviation with Right ventricular hypertrophy (RVH).

Echocardiography showed, Severe Coarctation of aorta (COA), associated with a tinyPatent DuctusArteriosus (PDA), Small Atrial Septal Defect (ASD) and severe pulmonary arterial hypertension (PAH). So patient was planned for urgent Balloon coarctoplasty. Considering the tiny PDA size, PDA device closure was not planned.

After admission,the patient was stabilized over one week, her hydration was maintained by Intravenous fluid and relevant investigations were sent. Injectable antibiotics were added to cover infection. After proper premedication and aseptic precautions, patient was taken into the cath lab on 21st march 2023 for balloon coarctoplasty.

Procedure:

Hardwires :Standard pediatric drape, Jensini catheter, Pigtail catheter, Bherman balloon angiographic catheter, Tyshak-mini balloon , Piccolo occluder, 4F long delivery system, exchange wire , PTCA all-star wire etc.

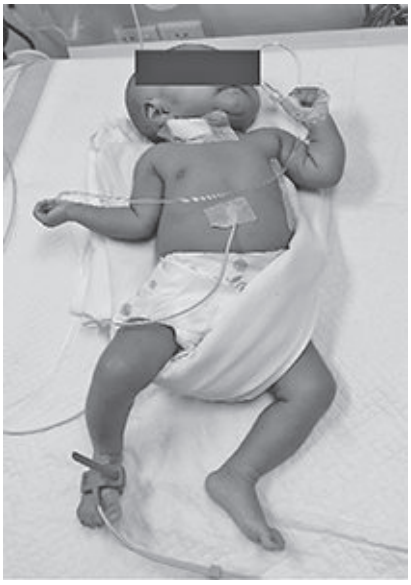

Figure-1 : *Baby T after PDA ligation:*

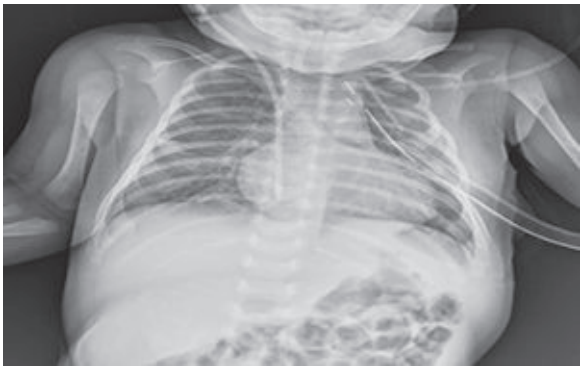

Figure-2 : *Chest X-ray after PDA ligation:*

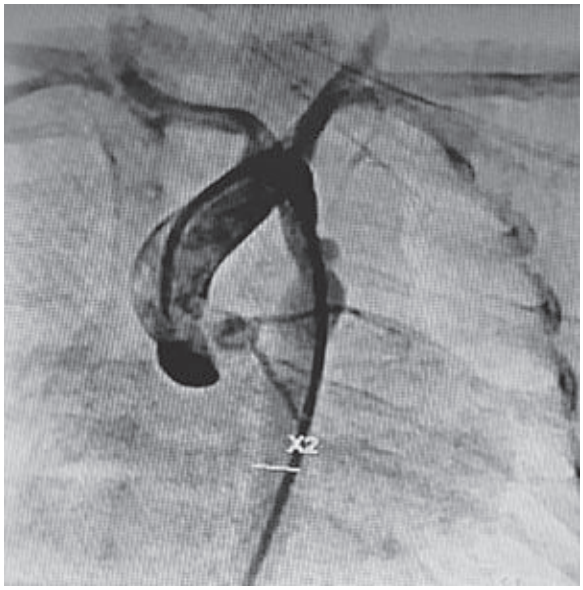

Figure-3 : *Aortogram Showing Severe Coarctation of Aorta :*

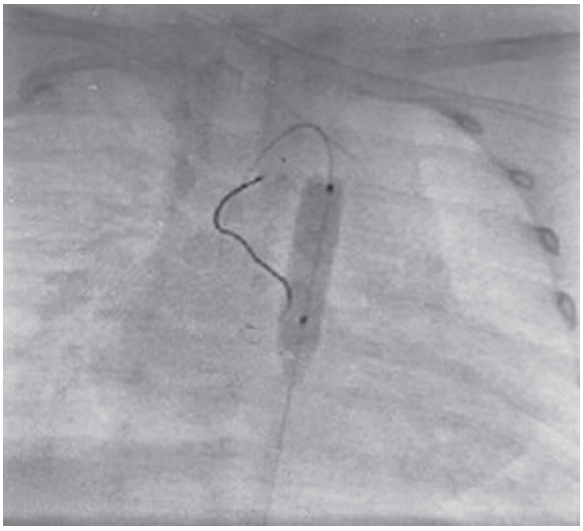

Figure-4 : *Balloon dilatation of Coarct segment with 5*20 Tyshak mini balloon :*

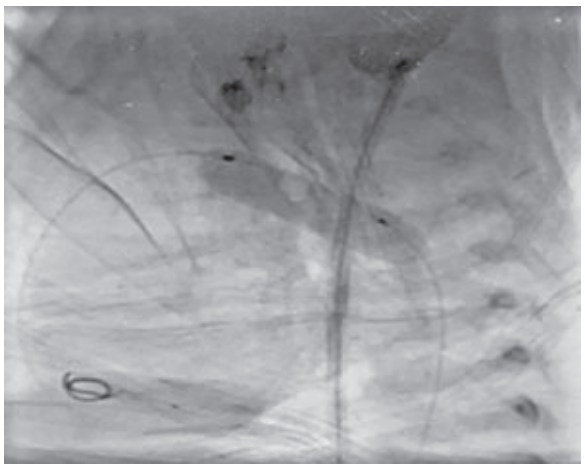

Figure-5 : *Accidental balloon dilatation of PDA by 8*30 mmTyshak mini balloon:*

Aortogram showed Critical coarctation of aorta, no PDA noticed. So, Balloon dilatation was performed with Tyshak mini 5x2 &and followed by an 8x2 balloon. Post Balloon Aortogram showed a very Large PDA out of our surprise. Second time coarctoplasty was accidentally performed through PDA. We tried to close the PDA subsequently with an 8/6 Piccolo occluder. But the PDA was larger than the device, consideringthe 2.4kg baby weight; passing a delivery sheath of 6F size through RFV/ RFA was avoided.

As the Patient developed tachypnea and respiratory distresson the procedure table,we decided to refer the case to the cardiac surgeon. Doing PDA ligation on a 2.4kg baby was difficult but the case was accepted by our surgical team. PDA ligation was performed on next day; PDA size was equal to the aorta as mentioned in surgical note.

During the postoperative period, the patient tolerated the procedure well and was on ventilator support till the next morning. Patient developed left lung collapse but recovered with Chest Physiotherapy (CPT) and gradually stepped down to CPAP then to headbox O2 supply to Room air. After Surgery improvements were also noted in the heart rate (from 150–170 beats/min to 120 beats/min), as well as in the respiratory rate (from 70 to 40 breaths/min) . There was no chest indrawing so breastfeeding was started on 2nd postoperative day. The patient was discharged on the 5th postoperative day.

Discussion:

The management of patients presenting with coarctation of aorta in neonates is revolutionized by the invention of prostaglandin E and its use to maintain and restore the patency of the ductus(1-3). Neonates presenting with preductalcoarctation have heart failure, shock, and deteriorating renal function, which could be reversed by maintaining the lower body circulation through the ductus(1-5).Any neonate or infant presented with shock within the first few weeks of life and in whom lower limb pulses are absent, it should be consider to start prostaglandin along with other resuscitative maneuvers until expert assistance is available[1,2].

Coarctation of aorta can occur as an isolated defect or in association with a patent ductusarteriosus (PDA), It can be a discrete or long segment defect associated with a variable degree of hypoplasia of the isthmus or transverse arch[1]. In the present case, coarctation was discrete and preductal in location. The indications for balloon angioplasty of thecoarctation of aorta are 1. Native or recurrent obstruction with a gradient of >20 mmHg. 2. Coarctation where there is left ventricular hypertrophy or systemic hypertension. But in neonate pre ductal significant coarctation is a medical emergency and should be treated immediately[3-5].

In neonates and infants < 1 year of age with native coarctation surgical resection and repair is recommended (1-5). Transcatheter therapy is the

treatment of choice in >1 year age with a well-developed isthmus. Balloon angioplasty is one of the modalities of transcathetertreatment[6,7]. A balloon, 2-3 times the diameter of the coarctation segment but not exceeding the diameter of the adjacent arch proximal to the narrowed segment is selected and inflated across the coarctation site[8-11].

In this case, coarctation had a pinhole opening only and the diameter was 2 mm. So, gradual dilatation of the coarctation area was performed with 5x2 & followed byup to 8x2 Tyshak miniballoon. Stent implantation in the coarctation area is another modality of treatment for older children, adolescents, and adults. Published reports of balloon angioplasty demonstrate that this procedure results in short-term effective relief of gradient in 75-90% of patients and low mortality of 0.7-02.5%[12-14]. Long-term follow-up revealed re-stenosis in 25-36% cases[15-17]. VACA (Valvuloplasty and Angioplasty for Congenital Anomalies) registry data reported suboptimal outcomes in 19% of native and 25% of recurrent lesions[18]. The study was conducted among 970 patients from 25 centers. The major drawback of angioplasty alone is the recoil of the vessel wall with recurrence of stenosis[19]. Balloon angioplasty may cause aortic wall dissection in 1-4% of patients and aneurysm formation in 4-11.5% of patients[20]. Another study reports that the immediate gradient reduction was similar in both surgery and angioplasty case[21]. But in our country, since 1998 most of the surgeons refused to do a surgical repair of coarctation on neonates and infants. So balloon angioplasty was performed as a life-saving intervention and the excellent outcome encouraged us to take it as first-choice therapy. Large PDA resulted from balloon dilatation was closed by cardiac surgeon. Trial of closure with piccolo occluder failed due to too large side.

Large PDA resulted from accidental balloon dilatation of tiny PDA considering it as coarct segment is an eye opener to think about this technique to keep ductus open in PDA dependent circulations, eg. Pulmonary atresia, Interrupted aortic arch etc[22].

Ductal stenting for maintaining pulmonary circulation in newborn with cyanotic Congenital Heart Disease (CHD) is a low risk and safe alternative to surgical aoropulmonary shunt[23]

Absolute contraindication of ductal stenting is branch pulmonary artery stenosis[24]

After PDA stenting patient need antiplatelet and/or anticoagulation therapy[22]

So balloon dilatation of PDA will be a good alternative of PDA stenting which could avoid antiplatelet and anticoagulation therapy. It can be performed in case with peripheral pulmonary stenosis as alternative option.

Conclusion:

We treated a full-term infant with symptomatic CoA successfully with a Balloon angioplasty. Large PDA wascreated by accidental balloon dilatation of PDA, considering it as aCoarct area.Learning from this mistake is to double-check balloon position in Coarctoplastyas there is a chance of crossing the wire through an almost closed PDA. Another learning is Balloon dilatation of PDA may be considered as an alternative to PDA stenting in duct-dependent circulations.

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INSTRUCTION TO AUTHORS ABOUT UNIFORM MANUSCRIPT WRITING

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