ISSN 1562 - 5044

http://chabjournal.org
Indexed & Member: Cross Ref.


# Chest & Heart Journal

Volume 42 Number 02 July 2018

A Journal
and
Official Organ
of the Chest &
Heart Association
of Bangladesh

# Chest & Heart Journal

**Volume 42, Number 02, Page 63-146** **July 2018**

## CONTENTS

# Chest & Heart Journal

**chabjournal.org**

Publication of The Chest & Heart Association of Bangladesh

Dedicated to Scientific & Professional Development of Pulmonologist & Cardiologist

**ISSN: 1562-5044**



**ONLINE**

http://chabjournal.org.
http://www.chabjournal/writer/register

**PUBLISHED BY:**

Editor in Chief
on behalf of the Chest and Heart
Association of Bangladesh

**INDEX**

Member: Cross Ref.
Indexed in: Cross Ref.

**PRINTED BY:**

Asian Colour Printing
130 DIT Extension Road
Fakirerpool, Dhaka-1000, Bangladesh
Phone: 49357726, 58313186
E-mail: asianclr@gmail.com

This publication is a dedication of The Chest & Heart Association of Bangladesh towards knowledge & professional development of Pulmonologist and Cardiologist practice in Bangladesh & the whole world. It is published biannually and accepts original article, review article and case reports. We try to accommodate any content which may help in promotion of knowledge, quality of patient care and research potential amongst concerned personnel. While every effort is always made by the Editorial Board to avoid inaccurate or misleading information appearing in the Journal, information within the individual articles are the responsibility of its author(s). The Chest and Heart Journal, its Editorial Board accept no liability whatsoever for the consequences of any such inaccurate and misleading information, opinion or statement.

**CORRESPONDENCE**

The Editor in Chief, The Chest and Heart Journal.
Association Secretariat, Administrative Block, Institute of Diseases of the Chest & Hospital.
Mohakhali, Dhaka-1212, Phone/Fax: +88-02-55067145
E-mail: chestheart@gmail.com Website: www.chestheart.org

# THE CHEST & HEART ASSOCIATION OF BANGLADESH

## EXECUTIVE COMMITTEE

| | | |
|---|---|---|
| **President** | : | Professor Mirza Mohammad Hiron |
| **Vice-President** | : | Professor Biswas Akhtar Hossain<br>Professor Bashir Ahmed<br>Dr. Md. Rafiqul Islam |
| **Secretary General** | : | Dr. Md. Abu Raihan |
| **Treasurer** | : | Professor Krishna Chandra Ganguly |
| **Joint Secretary** | : | Dr. Golam Sarwar L.H. Bhuiyan |
| **Organizing Secretary** | : | Dr. Md. Mofizur Rahman Mia |
| **Office Secretary** | : | Dr. S.M. Abdur Razzaque |
| **Members** | : | Professor Md. Rashidul Hassan<br>Professor Md. Abdur Rouf<br>Professor Md. Shahedur Rahman Khan<br>Professor S.M. Mostafa Zaman<br>Dr. Md. Khairul Anam<br>Dr. Barkat Ullah<br>Dr. Md. Zahirul Islam Shakil<br>Dr. Nihar Ranjan Saha<br>Dr. Mahmud Masum Attar<br>Dr. Abdullah Al Mujahid<br>Dr. Md. Serazul Islam |

# INSTRUCTION TO AUTHORS ABOUT UNIFORM MANUSCRIPT WRITING

The Chest and Heart Journal is published twice in a year in the months of January and July. The journal publishes original papers, reviews concerned with recent practice and case report of exceptional merits. Papers are accepted for publication with an understanding that they are subject to editorial revision. A covering letter signed by all authors must state that the data have not been published elsewhere in whole or in part and all authors agree their publication in Chest and Heart Journal. All submitted manuscripts are reviewed by the editors and rejected manuscripts will not be returned. Ethical aspects will be considered in the assessment of the paper. Three typed copies of the article and one soft copy in CD or Pen Drive processed all MS Word 6.0 should be submitted to the editor.

**Preparation of Manuscripts**

Manuscripts should be typed on one side of good quality paper, with margins of at least 25mm and using double space throughout. Each component of the manuscript should begin on a new page in the sequence of title page, abstract, text, references, tables, and legend for illustrations. The title page should include the title of the paper, name of the author(s), name of the departments) to which work should be attributed. The text should be presented in the form of Introduction, Materials and Methods, Results, and Discussion. The text should not exceed 2500 words and a word count should be supplied.

**Abstracts/Summary**

Provide on a separate page an abstract of not more than 250 words. This abstract should consist of four paragraphs, labeled Background, Methods, Results and Conclusions. They should briefly describe the problem being addressed in the study, how the study was performed, the salient results, and what the authors conclude from the results.

**Table**

Each table should be typed in on separate sheet. Table should have brief title for each, should be numbered consecutively using Roman numbers and be cited in the consecutive order, internal horizontal and vertical rules should not be used.

Results should be presented in logical sequence in the text, tables or illustration. Do not repeat in the text all data in the tables or illustrations; emphasize or summarize only important observations.

**Drug Names**

Genetic names should generally be used. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

**Illustrations**

Figure should be professionally designed symbols, lettering, and numbering should be clear and large. The back of each figure should include the sequence number and the proper orientation (e.g. “top”). Photographs and photomicrographs should be supplied as glossy black and white prints unmounted. Legend for each illustration should be submitted in separate sheets. All photographs, graphs and diagrams should be referred to as figures numbered consecutively in the text in Roman numerals.

**Discussion**

Emphasize the new and important aspects of the study and the conclusions that follow from them. The detail data or other material given in the Introduction or the Results section should not be repeated. The implications of the findings and their limitations, including implication for future research should be included in the Discussion section. The observations should be compared and related to other relevant studies, new hypothesis is appreciated, and however they should be clearly labeled as such. Recommendations may be included only when appropriate.

**References**

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legend by Roman numerals in parenthesis. Use the styles of the example below, which are based on the formats used by the US National Library of Medicine (NLM) in the Index Medicus.

Avoid using abstracts as references. References to paper accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited as "unpublished observations" with written permission from the source. Avoid using a "personal communication" unless it provides essential information not available from a public source. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication.

The references must be verified by the authors(s) against the original documents.

**1. Articles in Journal**

a) List all six authors when six or less;
Connors JP, Roper CL, Ferguson TB. Transbronchial Catheterisation of Pulmonary Abscess. Ann Thorac Surg 1975; 19 : 254-7.

b) When seven or more, list the first three and then add et al;
Karalus NC, Cursons RT, Leng RA, et al. Community acquired pneumonia: aetiology and prognostic Index evaluation. Thorax 1991; 46 : 413-12.

c) No author given;
Cancer in South Africa (editorial). S Afr Med J 1994; 84-15.

d) Organization as author
The Cardiac Society of Australia and New Zealand. Clinical exercise stress training. Safety and performance guideline. Med J Aust 1996; 164 : 282-4.

**2. Books and Other Manuscripts**

a) Personal author
Tierney LM, -McPhee SJ, Papakadis MA. Current Medical Diagnosis and Treatment. Lange Medical books/Mcgrow Hill 2000.

b) Editor(s), complier(s) as author
Baum GL, Wolinsky E, editor. Text Book of Pulmonary diseases. 5th ed. New York: Little Brown Co. 1994.

c) Organization as author and publisher
World Health Organization, Ethical Criteria for Medical Drug Promotion. Geneva: World Health Organization; 1988.

d) Chapter in a book
Macnee W. Chronic bronchitis and emphysema. Seaton A, Seaton D, editors. Crofton and Douglas's Respiratory Diseases. 5th ed. UK. The Blackwell Science; 2000; p.616-95.

e) Dissertation
Kaplan SJ. Post-hospital home health care: the elderly's access and utilization (dissertation). St. Louis (MO). Washington Univ; 1995.

**3. Other published material**

a) Newspaper article
Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996, June 21; Sect. A : 3(col. 5).

b) Dictionary and similar references
Student's medical dictionary. 26th ed. Baltimore: Williams & Wilkins; 1995. Apraxia; p.119-20.

**4. Unpublished Material**

a) In press

Leshner AI. Molecular mechanisms of cocaine addition. N Engl J Med In Press 1997.

**5. Electronic Material**

a) Journal articles in electronic format

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis Serial online I 1995 Jan-Mar I cited 1996 June 5 I; 1(1): 24 screens I

Available from: URL: http://www.cdc.gov/ncidod/E[D/eid.htm

**Nomenclature and Abbreviation**

1. Abbreviations and symbols must be standard and SI units should be used thoughtout.
2. Terms such as electrocardiogram, ultrasonogram etc. should when mentioned first, be written in full followed by accepted abbreviations (ECG, USG etc.)

**Permissions**

A written statement must accompany materials taken from other sources from both author and publisher giving permission to the Journal for reproduction. Obtain permission in writing from at least on a author of papers still in press, unpublished data, and personal communications.

**Review and Action**

Manuscripts are examined by the editorial staff and are usually sent to reviewers, but we reserve the right of final selection.

**Proof**

Two marked copies of the proofs may be sent to the principal author, which should be read carefully for error. One corrected copy must be returned to the editor within the next three days. Major alteration in the text can not be accepted.

**Editorial Mail**

Manuscripts and other communication for the editors should be addressed to

The Editor in Chief
Chest and Heart Journal
Association Secretariat, Administrative Block, Institute of Diseases of the Chest & Hospital.
Mohakhali, Dhaka-1212, Phone/Fax: 8851668

Chest Heart Journal
Vol. 42, No. 2, July 2018

## EDITORIAL

# Obstructive Sleep Apnoea: A Silent Foe

*[Chest Heart Journal 2018; 42(2) : 63-65]*
*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019580*

Obstructive sleep apnoea is an under recognized and under diagnosed medical condition, with a myriad of negative consequences on patients health and society as a whole. Symptoms include daytime sleepiness, loud snoring, and restless sleep. While the "gold standard" of diagnosis is by polysomnography, a detailed history and focused physical examination may help uncover previously undiagnosed cases. Undetected obstructive sleep apnea can lead to hypertension, heart disease, depression, and even death. Several modalities exist for treating obstructive sleep apnea, including continuous positive airway pressure, oral appliances, and several surgical procedures. However, conservative approaches, such as weight loss and alcohol and tobacco cessation, are also strongly encouraged in the patient with obstructive sleep apnea.

**Epidemiology**

It is believed that more than 85% of patients with clinically significant OSA have never been diagnosed.[1] This is thought to reflect the fact that many patients with symptoms of OSA are not aware of their heavy snoring and nocturnal arousals. It is estimated that as many as 1 of 5 adults has at least mild symptoms of obstructive sleep apnea, while 1 of 15 has moderate to severe symptoms. Most population-based studies support the existence of a twofold to threefold greater risk of OSA in men than in women. Patients aged 65 through 95 years are also at significantly increased risk of developing symptoms.

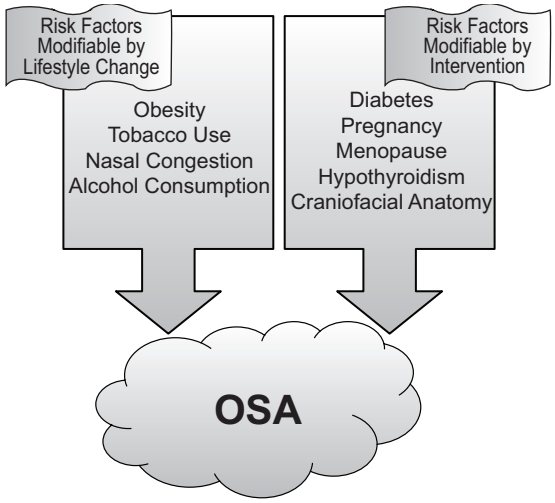
**Pathophysiology**

OSA is caused by repetitive bouts of upper airway obstruction during sleep as a result of the narrowing of respiratory passages.[3] The most common site of obstruction is the nasopharynx.[3] It is important to differentiate OSA from the less common central sleep apnea, which is caused by an imbalance in the brain's respiratory control centers during sleep. While the pathogenesis of OSA is thought to be multifactorial, anatomic defects are thought to play a major role.

Certain physical characteristics that may contribute to OSA include obesity, thickened lateral pharyngeal walls, nasal congestion, enlarged uvula, facial malformations, micrognathia, macroglossia, and tonsillar hypertrophy. Obesity contributes to airway narrowing through fatty infiltration of the tongue, soft palate, or other areas surrounding the airway.

As the patient falls asleep, muscles of the nasopharynx begin to relax and the surrounding tissue collapses, causing compromise of the airway. As oxygen levels in the body start to drop and carbon dioxide levels rise, the patient is aroused from sleep; this causes an increase in sympathetic tone and subsequent contraction of nasopharyngeal tissue, which allows alleviation of the obstruction.[1]

**Risk Factors**




Risk factors for obstructive sleep apnea (OSA).

**Clinical Manifestations**

A thorough history and physical examination will often elucidate some of the signs and symptoms of OSA. Common symptoms include snoring, awakening from sleep with a sense of choking, morning headaches, fitful sleep, decreased libido, as well as a history of hypertension, cerebrovascular disease, renal disease, diabetes, or gastroesophageal reflux disease.4.Despite being a defining feature of OSA, alleged absence of daytime somnolence is not sufficient to dismiss the diagnosis of OSA, as often somnolence may go unnoticed or be underestimated because of its chronicity. Because of the nonspecific and variable features of OSA, its diagnosis based on a clinician's subjective analysis alone is inaccurate.

**Diagnosis**

OSA can be measured by using an apnea-hypopnea index, which records the number of times per hour of sleep that a patient experiences an abnormally low respiratory rate or complete cessation of breathing. Typically, an apnea-hypopnea index of 5 or more is sufficient for a diagnosis of OSA. Polysomnography, also known as a "sleep study," is the current "gold-standard" of OSA diagnostic testing. Additional diagnostic modalities for OSA include portable sleep monitors, radiographic studies for anatomic analysis, and empiric treatment.

**Management**

Treatment of OSA depends on the severity, duration, and cause of the patient's symptoms as well as the patient's lifestyle, comorbidities, and overall health. Nonetheless, certain measures should be undertaken by nearly all persons affected by OSA. Overweight patients should be encouraged to undergo a weight-loss regimen. Studies[6]. have shown that a 10% weight loss is associated with a 26% reduction in apnea-hypopnea index scores. For severely obese patients, bariatric surgery (ie, gastric banding, gastric bypass, gastroplasty) may be considered, as studies have shown that symptoms of OSA can be relieved in up to 86% of patients undergoing such operations.

Other lifestyle changes that may help modify the signs and symptoms of OSA include cessation of alcohol and tobacco use, as well as the use of a lateral sleeping position. Furthermore, the use of benzodiazepines and other central nervous system depressants should be avoided.

First-line therapy for most patients with OSA continues to be the use of continuous positive airway pressure (CPAP). This therapy maintains adequate airway patency; it not only immediately reverses apnea and hypopnea, but it also decreases somnolence and increases quality of life, alertness, and mood. However, patient compliance levels average only 50% to 60% because of the frustrations associated with CPAP machines, including mask leaks, nasal congestion, and sleep disruption.

A commonly implemented alternative to CPAP involves the use of oral appliances designed to advance the mandible forward. Such devices decrease arousal and the apnea-hypopnea index while increasing arterial oxygen saturation. Furthermore, patients tend to have a stronger preference for oral appliances. Many clinicians, however, still consider oral appliances to be a suboptimal alternative to CPAP.

For those patients receiving little benefit from CPAP or oral appliances, surgery may be considered. The most commonly implemented surgical procedure for treatment of OSA is uvulopalatopharyngoplasty.

**Conclusion**

OSA is an important public health concern. While only 1 in 5 patients has at least mild OSA and only 1 in 15 has moderate to severe OSA, the social impacts are often much greater. Disturbed sleep patterns lead to increased levels of daytime somnolence, which can cause days of missed work and increased levels of motor vehicle and occupational accidents. Furthermore, as discussed above, OSA can both worsen existing medical conditions and influence the onset of new disease. Given that the condition is undiagnosed for 85% of patients with sleep apnea, it is important for clinicians and patients alike

to recognize and deal with the early signs and symptoms of obstructive sleep apnea.

**Prof. Dr Md. Abdur Rouf**
*Professor of Respiratory Medicine,*
*National Institute of Disease of the Chest and Hospital, Dhaka, Bangladesh*
*Mobile: 01711487002*
*E-mail: drrouf@gmail.com*

**References**

1. Kato M., Adachi T., Koshino Y., Somers V. K. Obstructive sleep apnea and cardiovascular disease. Circ J. 2009; 73(8): 1363–1370.
2. Young T., Peppard P. E., Gottlieb D. J. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002;165(9):1217–1239.
3. Morrison D. L., Launois S. H., Isono S., Feroah T. R., Whitelaw W. A., Remmers J. E. Pharyngeal narrowing and closing pressures in patients with obstructive sleep apnea. Am Rev Respir Dis. 1993;148(3):606–611.
4. Senn O., Brack T., Russi E. W., Bloch K. E. A continuous positive airway pressure trial as a novel approach to the diagnosis of the obstructive sleep apnea syndrome. Chest. 2006;129(1):67–75.
5. Peppard P. E., Young T., Palta M., et al. Longitudinal study of moderate weight change and sleep-disoriented breathing. JAMA. 2000;284(23):3015–3021.
6. Buchwald H., Avidor Y., Braunwald E., et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004; 292(14): 1724–1737. Erratum in: JAMA. 2005; 293(14):1728.

Chest Heart Journal
Vol. 42, No. 2, July 2018

*ORIGINAL ARTICLE*

# Bacteriological Profile and Their Antibiotic Sensitivity in Hospital Admitted Patients Having Acute Exacerbation of COPD

**Md. Delwar Hossain[1], AFM Nazmul Islam[2], Premananda Das[3], Mohammed Ruhul Kabir[4], Sheikh AHM Mesbahul Islam[5], Syed Abdullah Burhan Uddin[6]**

**Abstract:**

***Background:*** *The course of COPD is punctuated by episodes of "acute exacerbations" which is responsible increase in mortality and morbidity. Majority of exacerbations are infectious and bacteria are responsible for 30-50% of cases. This study was designed to know the bacteria predominantly responsible for Acute Exacerbation of COPD (AECOPD) in hospital admitted patients and their antibiogram. This may help to formulate a cost effective antibiotic strategy and reducing the emergence of drug resistance.*

***Materials and Methods:*** *This cross sectional descriptive study was carried out in Sylhet MAG Osmani Medical College Hospital, from 1st January 2016 to 31st December 2017. 86 patients with AECOPD were consecutively enrolled. The sputum and blood serology were studied and causative organisms with their antibiogram were identified by standard microbiological techniques.*

***Results:*** *The mean age of the patients was 63.94 (SD±10.54) years (range, 42 to 90 years) and 93.0% of them were male. In 38.4% of cases positive growth of organisms were detected in sputum and predominant isolated bacteria were: P. aeruginosa(11.6%), K. pneumoniae (9.3%), E. coli(7.0%), M. catarrhalis (3.5%), Acinetobacter spp (2.3%), Enterobacter (1.2%), S.pneumoniae(1.2%), S. pyogenes(1.2%), S. aureus (1.2%). Gram negative bacteria (90.9%) were more than Gram positive (9.1%) (p<0.001). Levofloxacin was the most sensitive antibiotic (75.8%), followed by gentamicin (72.7%), ceftriaxone (69.7%), imipenem (69.7%) and moxifloxacin (54.5%). Mycoplasma IgM and Chlamydia IgM antibodies were positive in blood serology of 7.0% and 10.5% cases respectively .*

***Conclusions:*** P.aeruginosa *and* K.pneumoniae *are the commonest pathogens responsible for AECOPD in hospital admitted patients. Levofloxacin is the sensitive to majority of the organisms. So, levofloxacin could be the first choice as empirical antibiotic in patients with AECOPD. However, gentamicin instead of quinolones may be used in admitted patients due to the high prevalence of tuberculosis in this region.*

***[Chest Heart Journal 2018; 42(2) : 67-75]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019581*

## Introduction

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease is a leading cause of morbidity and mortality. It exerts substantial and increasing economic and social burden worldwide.[1] In Bangladesh the

1. Registrar, Department of Neurology, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh.
2. Associate Professor, Department of Respiratory Medicine, Sylhet MAG Osmani Medical College, Sylhet.
3. ,Registrar, Dept. of Medicine, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh.
4. Assistant Professor, Department of Microbiology, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh.
5. Professor, Department of Medicine, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh.
6. Assistant Professor of Respiratory Medicine, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh.

**Correspondence to:** Dr. Md. Delwar Hossain, Registrar, Department of Neurology, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh.

**Submission on:** 15 May, 2018 **Accepted for Publication:** 10 June, 2018
Available at http.//www.chabjournal.org

prevalence of COPD is 5.9% in hospital admitted patients (≥30 years).[2]

The course of COPD is punctuated by episodes of acute deterioration in respiratory health, termed 'exacerbations'. Acute exacerbation results deterioration of lung function, health related quality of life and acceleration in disease progression.[3,4] and accounts for 50%–75% of the cost of healthcare services for COPD.[5] The mortality rate of hospital admitted AECOPD is up to 24% but it reaches to 43% in patients needing artificial ventilation.[6] Prompt antibiotic treatment shortens the duration of exacerbations and may prevent hospital admission and further lung damage.[7]

At least 50% of COPD exacerbations are responsible to pathogenic bacteria.[8] A hospital based study of acute exacerbation showed that Gram negative organisms outnumbered Gram positive organisms and *Haemophilus influenzae* and *Pseudomonas aeruginosa* were the most common in sputum culture.[9] However, in another study, microbial patterns corresponded to community-acquired pathogens (*S.pneumoniae*, *H.influenzae,* and *M.catarrhalis*) in 56% and Pseudomonas and Stenotrophomonas spp. in 44% of isolates.[10] In Bangladesh, Bari et al. found that 65% of sputum of AECOPD showed positive culture for bacteria and the common organisms were Pseudomonas and Klebsiella.[11] Infections with Pseudomonas spp, Stenotrophomonas spp, and Gram negative bacteria occur in more severe exacerbations, affecting the most debilitated patients.[12]

Prevalent flora and their antimicrobial resistance pattern may vary from region to region.[13] and the sensitivity pattern also continues to change.[14] So, the choice of the antibiotic should be based on the local bacterial resistance pattern .Knowledge of local bacteriological profile and antibiogram will help to reduce the failure cases with empirical treatment in AECOPD.

The present work is designed to find out the causative bacteria and their antibiotic sensitivity pattern in AECOPD patients in our perspective.

**.Materials and Methods:**

This cross-sectional descriptive study was conducted during the period from 1st January 2016 to 31st December 2017 in the inpatient department of Medicine, Sylhet MAG Osmani Medical College Hospital (SOMCH). A total of 86 patients were recruited as study population with the inclusion and exclusion criteria.

**Inclusion Criteria:** 1. All cases of acute exacerbation of COPD. 2. Able to produce adequate sputum containing <10 squamous epithelial cells and >25 pus cell.

Exclusion criteria: 1. Patients having bronchial asthma, bronchiectasis, interstitial lung disease (ILD), Tuberculosis, Pneumonia, Lung abscess, Malignancy or other evident diseases on chest X-ray. 2. Treatment with antibiotic in previous 7 days. 3. Spirometric finding not suggesting COPD in stable state.

**Procedure of Data Collection:**

After taking Informed written consent, following information were recorded from the study subjects : age, sex, BMI, smoking history, onset of respiratory distress, duration and stage of COPD, previous spirometry report (if available), baseline dyspnoea (MRC dyspnoea scale), exacerbation severity, exacerbations frequency in the last one year period. A spirometry was performed in all cases when patient becomes clinically stable before discharge on a computerized spirometer (Helios 401 PC based Spirometer, RMS, India). The $FEV_1$/FVC less than 0.70 (70%), after salbutamol inhalation, was considered COPD.

**Sputum collection:**

One early morning sputum was collected in a sterile container after rinsing the mouth twice with pure drinking water. Patients were instructed to collect deep coughed sputum into a sterile wide mouth container with a screw cap. At the same time, 5 ml blood was collected for serological tests. Samples were labeled for proper identification and carried immediately to the Department of Microbiology, SOMCH for microbiological and serological analysis.

**Microscopy and Culture:**

Sputum smears were prepared for Gram's stain from the area of maximal purulence and examined for presence of neutrophils on low power field (x100) and organisms in high power

field (x1000). The criteria for an acceptable sputum sample for analysis were: <10 epithelial cells and >25 leukocytes per low power field (according to a Murray -Washington and Heineman criteria).

Another documented purulent portion of sputum was used for culture. Before inoculation and incubation, the specimen was homogenized by agitation with an equal volume of 0.9% NaCl for 1 minute. The sputum samples were cultured on Blood agar (5% sheep blood) for isolation of haemolytic organisms, MacConkey's agar for isolation and differentiation of Gram negative bacilli and Chocolate agar for Hemophillus and Neisseria species.

The agar plates were kept in an incubator at 37°C and examined after 24 and 48 hours. Characteristic features of colonies' morphology on positive culture plates were observed. The cultures were assessed semi-quantitatively and was considered "positive" (proving bacterial infection) when bacterial growth occupied more than 2 quadrants (>$10^6$ CFU) of agar plate. All isolated microorganisms were identified through standard laboratory methods.

Antibiotic Sensitivity: Antibiotic sensitivity test of the isolates were performed on Mueller-Hinton agar by the disc diffusion method of Kirby-Bauer.

Serology: The qualitative immune-enzymatic determination of IgM-class antibodies against Chlamydia pneumoniae and Mycoplasma pneumoniae were done by ELISA technique by reagent from DRG International, Inc., USA. The result was interpreted as positive or negative according to manufacturer's given cut off values.

Statistical Analysis: Data were processed and were analyzed manually and by using SPSS (Statistical Package for Social Sciences) Version 22.0.

**Ethical Consideration:**

- Informed consent was taken after discussing purpose of the study in detail.
- An approval of the study protocol was obtained from the ethical committee of SOMC, Sylhet before the commencement of the study.

**Results**

From 200 (two hundred) patients with acute exacerbation of COPD 86 (Eighty six) patients were included in the study. The main causes of exclusion were: prior antibiotics ingestion, x-ray abnormality and inability to provide adequate sputum. Among the study group, 80 were males (93.0%) and 6 were females (7%), with a mean age of 63.94 (SD ± 10.54) years (range, 42 to 90 years). Most of the patients (n= 34; 39.5%) were between 61-70 years and 5 (5.8%) patients were above 80 years. 61.6% of them were current smokers.

Table-I shows the distribution of the patients according to type of exacerbation by Winnipeg criteria. Type of exacerbation by Winnipeg criteria was type 2 exacerbation (two major symptoms) in 65.1% and type 1 exacerbation (three major symptoms) in 34.9% of patients.

Figure-1 shows the distribution of the patients according to growth on sputum culture. Positive cultures were obtained in 38.4% of sputum samples and in 61.6% of cases there were no significant growth of bacteria.

Table-II shows the distribution of the patients according to bacteria isolated from the sputum cultures.

Table-III shows that Gram negative bacterial isolates were more common (90.9%) than Gram positive bacteria (9.1%). ($Ç^2$=22.091, p<0.001).

Table-IV shows the distribution of the patients according to serological characteristics. Mycoplasma IgM and Chlamydia IgM antibody were positive in 7.0% and 10.5% respectively. 2.3% cases showed both Mycoplasma IgM and Chlamydia IgM antibodies positivity.

Table-V reveals that levofloxacin was the most effective antibiotic being sensitive to majority of organisms (75.8%), followed by gentamicin (72.7%), ceftriaxone and imipenem (69.7%). Here Pseudomonas aeruginosa and Klebsiella pneumoniae, the most common isolates, were mainly (80%-87%) sensitive to levofloxacin and gentamicin followed by imipenem and ceftriaxone. E.Coli was 100% sensitive to gentamycin. Commonly prescribed amoxicillin and amoxicillin-clavulanic acid were less sensitive against frequently isolated bacteria. Acinetobacter was mostly resistant to all these antibiotics.

**Table-I**

*Distribution of the patients according to type of exacerbation by Winnipeg criteria (n=86)*

| Type of exacerbation | Frequency | Percentage |
|---|---|---|
| Type 1 (Three major symptoms) | 30 | 34.9 |
| Type 2 (Two major symptoms) | 56 | 65.1 |
| Type 3 (One major with any minor symptoms) | 0 | 0.0 |

Major symptoms: Increased sputum purulence , Increased sputum volume, Increased dyspnea and minor symptoms (a) Upper respiratory infection in the past 5 days, (b) Fever without other apparent cause, (c) Increased wheezing, (d) Increased cough, (e) Respiratory rate or Heart rate increased 20% above baseline.

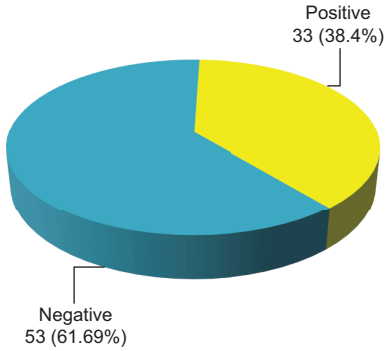



**Fig.-1:** *Distribution of the patients according to growth on sputum culture (n=86)*

**Table-II**

*Distribution of the patients according to bacteria isolated from the sputum cultures (n=86)*

| Isolated bacteria | Frequency | Percentage |
|---|---|---|
| Gram negative | | |
| *Pseudomonas aeruginosa* | 10 | 11.6 |
| *Klebsiella pneumoniae* | 8 | 9.3 |
| *Escherichia coli* | 6 | 7.0 |
| *Moraxella catarrhalis* | 3 | 3.5 |
| *Acinetobacter* | 2 | 2.3 |
| Enterobacter | 1 | 1.2 |
| Gram positive | | |
| *Streptococcus pneumoniae* | 1 | 1.2 |
| *Streptococcus pyogenes* | 1 | 1.2 |
| *Staphylococcus aureus* | 1 | 1.2 |

**Table-III**

*Distribution of the patients by status of Gram negative and Gram positive bacterial isolates (n=86)*

| Bacterial isolates | Frequency | Percentage | p-value |
|---|---|---|---|
| Gram Negative | 30 | 90.9 | |
| Gram Positive | 3 | 9.1 | p<0.001 |
| Total | 33 | 100 | |

**Table-IV**

*Distribution of the patients according to serological characteristics (n=86)*

| Serological characteristics | Frequency | Percentage |
|---|---|---|
| Mycoplasma IgM Positive | 6 | 7.0 |
| Chlamydia IgM Positive | 9 | 10.5 |
| Both Mycoplasma and Chlamydia IgM Positive | 2 | 2.3 |
| Serology negative | 69 | 80.2 |

**Table-V**

*Drug sensitivity pattern of various pathogens isolated from sputum culture (n=33)*

| Antibiotics | Sensitivity of Bacteria | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Pseudomonas (n=10) | Klebsiella (n=8) | E coli (n=6) | *Moraxella catarrhalis* (n=3) | Acinetobacter (n=2) | Enterobacter (n=1) | S. pneumoniae (n=1) | S. pyogene (n=1) | *S. aureus* (n=1) | Total |
| Amoxycillin | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 01 (2.9%) |
| Co-amoxyclav | 0 | 1 | 1 | 2 | 0 | 0 | 1 | 1 | 0 | 07 (21.2%) |
| Cefuroxime | 0 | 1 | 3 | 3 | 0 | 0 | 1 | 1 | 1 | 10 (30.3%) |
| Cefixime | 2 | 3 | 3 | 2 | 0 | 0 | 1 | 1 | 0 | 13 (39.4%) |
| Azithromycin | 6 | 4 | 2 | 1 | 0 | 1 | 1 | 1 | 1 | 17 (51.5%) |
| Moxafloxacin | 5 | 6 | 2 | 3 | 0 | 0 | 1 | 0 | 1 | 18 (54.5%) |
| Ceftriaxone | 5 | 6 | 4 | 3 | 1 | 1 | 1 | 1 | 1 | 23 (69.7%) |
| Imipenem | 6 | 6 | 3 | 3 | 1 | 0 | 1 | 1 | 1 | 23 (69.7%) |
| Gentamicin | 8 | 7 | 6 | 1 | 0 | 1 | 0 | 0 | 1 | 24 (72.7%) |
| Levofloxacin | 8 | 7 | 5 | 2 | 0 | 0 | 1 | 1 | 1 | 25 (75.8%) |

## Discussion

In our study, the age of the patients ranged from 42 to 90 years with the mean age of 63.94 (SD ± 10.54) years which was consistent with a study done by Chin et al.[15] which showed the mean age of the patients was 63.18 years (range, 40-81 years). Furqan and Paracha[16] and Shashibhushan et al.[17] reported also similar figures. This age distribution can be explained by the fact that chronic bronchitis has highest prevalence and most of patients seek medical attention at this fifth and sixth decade of life.

In this study. 93.0% of patients were male and 7.0% female, which was consistent with an international study that also showed male predominance with 92.9% males and 7.1% females.[18] Male preponderance of COPD was also reported in several other studies.[19,20,21,16] However, a Canadian study showed that out of 150 patients, 59 (39%) were males and 91 (61%) were females.[22] Males were affected more than females because they are more involved in smoking. In addition, most of females are housewives, having sheltered mode of life and less exposed to occupational dust and fumes.

In this study, sputum culture yield positive growth in 38.4% and no growth in 61.6% cases. Similar result was found by Dilektasli et al.[20] that showed no growth in 61.5% of samples. Narayanagowda et al.[23] found that 41% of AECPOD were positive for pathogenic bacteria and Cukic[24] isolated 41% pathogenic bacteria from sputum culture in AECOPD. However, Shahnawaz et al.[25] found positive sputum culture in only 13.3% of cases. Culture positivity depends on sputum nature, transportation time and the number of organisms present in the sample. It may also depend on the use of prior antibiotic by the patient.

The most frequent bacteria isolated from the sputum cultures was Pseudomonas aeruginosa (11.6%), followed by Klebsiella pneumoniae (9.3%), Escherichia coli (7.0%), Moraxella catarrhalis (3.5%), Acinetobacter spp. (2.3%) and Enterobacter (1.2%). The Gram positive bacteria isolated from the cultures were Streptococcus

pneumoniae (1.2%), Streptococcus pyogenes (1.2%), and Staphylococcus aureus (1.2%). Bari et al.[12] found almost similar picture with predominant bacteria as Pseudomonas (25%), Klebsiella (13.33%), Acinetobacter (6.66%) along with Moraxella (3.33%) and Enterobacter (1.66%) in his study. Basu et al [26] in Kolkata found predominant organisms as Klebsiella pneumoniae (33.33%), Pseudomonas aeruginosa (19.05%), Escherichia coli (9.51%) and Acinetobacter spp (9.51%). But Shahnawaz et al.[25] found Pseudomonas aeruginosa (8.35%), Staphylococcus aureus (3.33%) and Streptococcus pyogenes (1.66%). Similar results were also seen in an Indian study by Chawla et al.[27] *P. aeruginosa* was the predominant isolate (25.92%) amongst the hospitalized patients followed by *S.pneumoniae* and Acinetobacter spp (18.51% each), Klebsiella spp. and M.catarrhalis (14.80% each). Borthakur and Deb,[28] reported *Klebsiella pneumoniae* as the most commonly isolated bacteria followed by *Staphylococcus aureus*, *Pseudomonas aeruginosa* and Acinetobacter species.

In this study the prevalence of Gram negative bacteria were more common than Gram positive bacteria (90.9% compared to 9.1%) in the acute exacerbations of COPD patients ($p<0.001$). Madhavi et al.[29] also reported that Gram negative bacilli were isolated more than Gram positive cocci, which was consistent with this study. Borthakur and Deb,[30] reported that the prevalence of Gram negative isolates were 62.6%. Aleemullah et al.[31] also reported that Gram negative organisms were isolated more (62.39%), than Gram positive organisms (37.61%). However, according to the study conducted by ElFeky et al.[32] Gram positive bacteria represented 80% of isolates, while Gram negative bacteria represent the remaining 20%.

A change in the microbial pathogens is seen during infective exacerbations and infection with Gram negative bacteria including Pseudomonas spp occur more severe exacerbations, affecting the most debilitated patients.[12] The cases in our study were hospital admitted patients of AECOPD, who were mostly suffering from moderate to severe exacerbations and most of them were frequent exacerbators,hence, Gram-negative pathogens such as Pseudomonas and Klebsiella w ere more prevalent and can explain the lower numbers of Gram positive bacteria isolation, as severe COPD benefits the enterobacteriaceae and P. aeruginosa colonization.[9]

Serum IgM antibody against Mycoplasma pneumoniae was positive in 7.0%, IgM antibody against Chlamydia pneumoniae was positive in 10.5% and both antibodies were positive in 2.3% subjects. Mycoplasma pneumoniae and Chlamydia pneumoniae may be responsible for less than 10% of exacerbations reported in several studies.[10,33]

This study revealed that levofloxacin was the most effective antibiotic being sensitive to majority of organisms (75.8%), followed by gentamicin (72.7%), ceftriaxone and imipenem (69.7% each) and moxafloxacin (54.5%). Sharan et al.[34] found both levofloxacin and aminoglycosides were effective on Gram positive cocci and Gram negative bacilli combindly, whereas meropenem was most effective mainly on Gram negative organisms. Sheng-Hsiang LIN[19] in Taiwan also found that levofloxacin was 76.5 % sensitive in his study. Chawla et al.[27] in 2008 found quinolones were most effective whereas Patel et al.[35] showed piperacillin+tazobactum more effective than quiniolones. Borthakur and Deb,[30] found quinolones were less effective. Levofloxacin was resistant to 33.33% of patients having infection with Gram negative organisms. Co-amoxyclav was resistant to 34.62% and Amoxycillin was resistant to 46.15% of the patients having Gram positive organisms. Among macrolides, azithromycin was the most effective drug against Gram positive organisms having resistance of only 26.92%. These dissimilarities may be due the fact that prevalent flora and their antibiotic sensitivity pattern continues to change over time and also shows regional variation.[13,14]

**Conclusion:**

*Pseudomonas aeruginosa* and *Klebsiella pneumoniae* are the most commonly responsible for hospital admitted patients of AECOPD. Levofloxacin is the most effective antibiotic being sensitive to majority of organisms. It is followed by gentamicin, ceftriaxone and imepenem. So,

levofloxacin could be the first choice as empirical antibiotic in patients with AECOPD. However, gentamicin instead of quinolones may be used to treat acute exacerbation in hospital admitted patients due to the high prevalence of tuberculosis in this region.

**Limitations**

It was a cross-sectional, single-centered, small sample sized study and only one sputum sample was investigated from each subject which may not give actual impression of the overall disease spectrum.

Sputum study for AFB by ZN stain, culture and sensitivity were not performed for detecting Mycobacterium tuberculosis.

Some of the subjects may have reported incorrectly about their disease status and antibiotic ingestion. The duration of antibiotic free period may have an impact on culture positivity of sputum samples.

**Recommendation:**

Antibiotics should be used based on clinical judgment of individual patient as In hospital inpatient department, more than 50% of the sputum did not yield any pathogenic bacteria.

Although levofloxacin was the most sensitive antibiotic, fluroquinolones (eg. levofloxacin, moxifloxacin) can mask the diagnosis of tuberculosis and moxifloxacin should be reserved for treatment of multi-drug resistant tuberculosis in this region.

More studies like this are required at regular interval to formulate an antibiotic policy in acute exacerbation of COPD which would help in preventing mortality and morbidity of COPD.

**References:**


1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. [Cited 2016 Aug 30]. Available from: http://goldcopd.org
2. Zaman MM, Nargis N, Perucic AM, Rahman K, editors. Impact of Tobacco-related illnesses in Bangladesh. Table 9, Prevalence of eight tobacco-related diseases among patients aged 30 and above of four medical college hospitals: SEARO, WHO, New Delhi; 2007.p.30.
3. Cote CG, Dordelly LJ, Celli BR. Impact of COPD exacerbations on patient-centered outcomes. Chest.2007; 131(3): 696-704.
4. Tanabe N, Muro S, Hirai T, Oguma T, Terada K, Marumo S, et al. Impact of Exacerbations on Emphysema Progression in Chronic Obstructive Pulmonary Disease. Am J RespirCrit Care Med. 2011; 183: 1653–9.
5. Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buist A S et al. ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J. 2004; 23:932–46.
6. Johnston A K, Mannino D M. Epidemiology of COPD Exacerbations. September, 2008, Available at: http://works.bepress.com/david_mannino/216/
7. Frew AJ, Holgate ST. Respiratory disease. In: Kumar P, Clark M, editors. Clinical Medicine. Philadelphia: Elsevier Saunders; 2012. p.812-8.
8. Sethi S, Murphy TF. Bacterial infection in chronic obstructive pulmonary disease in 2000: a state-of-the-art review. Clinical Microbiology reviews.2001;14(2):336–63.
9. Boixeda R , Rabella N, Sauca G, Delgado M, Martínez-Costa X, Mauri M et al. Microbiological study of patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease (AE-COPD) and the usefulness of analytical and clinical parameters in its identification (VIRAE study). International Journal of COPD.2012;7: 327-35.
10. Soler N, Torres A, Ewig S, Gonzalez J,Celis R, El-Ebiary M et al. Bronchial Microbial Patterns in Severe COPD Exacerbations. Am J Respir Crit Care Med. 1998;157:1498–505.
11. Bari MR, Hiron MM, Zaman SM, Rahman MM, Ganguly KC. Microbes Responsible For Acute Exacerbation of COPD. Mymensingh Med J. 2010; 19(4): 576-85.

12. Sapey E, Stockley RA.COPD exacerbations. 2: aetiology.Thorax.2006; 61(3):250-8.

13. Lakshmi V. Need for national/regional guidelines and policies in India to combat antibiotic resistance. Indian J Med Microbiol. 2008; 26:105-7.

14. Brunton S, Carmichael B, Colgan R, Feeney A, Fendrick A, Quintiliani R, et al. Acute exacerbation of chronic bronchitis: a primary care consensus guideline. Am J Manag Care. 2004; 10: 689-96.

15. Chin CL, Manzel LJ, Lehman EE, Humlicek AL, Shi L, Starner TD, et al. Haemophilus influenzae from Patients with Chronic Obstructive Pulmonary Disease Exacerbation Induce More Inflammation than Colonizers. Am J Respir Critical Care Med 2005; 172: 85-91.

16. Furqan S, Paracha SAU. Frequency of Streptococcus pneumonia and Haemophilus influenza in acute exacerbation of chronic obstructive airway disease and their sensitivity to levofloxacin.JPMA. 2014;64:399-402.

17. Shashibhushan BL, Nagaraja C, Arun BJ, Nagaraj N. Bacteriological profile and antibiotic sensitivity pattern in sputum culture of chronic obstructive pulmonary disease patients. Int J Adv Med. 2016;3(3):671.

18. Reechaipichitkul W. Precipitating causes and outcomes of chronic obstructive pulmonary disease exacerbation at a tertiary care center in Northeast Thailand. Asian Biomed. 2014;8(2):229-36.

19. Lin SH, Kuo PH, Hsueh PR, Yang PC, Kuo SH. Sputum bacteriology in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease in Taiwan with an emphasis on Klebsiella pneumoniae and Pseudomonas aeruginosa. Respirology. 2007;12:81-7.

20. Dilektasli AG, Cetinoglu ED, Ozturk NAA, Coskun F, Ozkaya G, Ursavas A, et al. Bacterial etiology in acute hospitalized chronic obstructive pulmonary disease exacerbations. Eur Res J 2016; 2(2): 99-106.

21. Alamoudi OS. Bacterial infection and risk factors in outpatients with acute exacerbation of chronic obstructive pulmonary disease: A 2-year prospective study. Respirology. 2007;12:283–7.

22. Goddard RD, Mcneil SA, Slayter KL, Mclvor RA. Antimicrobials in acute exacerbations of chronic obstructive pulmonary disease-An analysis of the time to next exacerbation before and after the implementation of standing orders. Can J Infect Dis. 2003;14:254-9.

23. Narayanagowda DS, Golia S, Jaiswal J, Manasa SS. A bacteriological study of acute exacerbation of chronic obstructive pulmonary disease over a period of one year. Int J Res Med Sci. 2015;3(11):3141-6.

24. Cukic V. The Most Common Detected Bacteria in Sputum of Patients with the Acute Exacerbation of COPD.Mater Sociomed.2013; 25(4): 226-9.

25. Shahnawaz A, Saleem SM, Bhat MA, Bhat G, Dhobi GN. Bacteriological profile in acute exacerbation of chronic obstructive pulmonary disease (COPD).JK Practitioner. 2003;10:185-7.

26. Basu S, Mukherjee S, Samanta A. Epidemiological study of bacterial microbiology in acute exacerbation of chronic obstructive pulmonary disease patients of Kolkata, India. Asian journal of pharmaceutical and Clinical Research.2013; 6:112-16.

27. Chawla K, Mukhopadhay C, Majumdar M, Bairy I. Bacteriological profile and their antibiogram from cases of acute exacerbations of chronic obstructive pulmonary disease: A hospital based study. Journal of Clinical and Diagnostic Research. 2008;2:612-6

28. Borthakur AK, Deb C. Antibacterial Evaluation of Common Bacteriological Profile (Aerobic) in Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) in Tertiary Care Hospital (Silchar Medical College & Hospital). International Journal of Science and Research (IJSR). 2017; 6(3): 648-52.

29. Madhavi S, Ramarao MV, Janardhanrao R. Bacterial etiology of acute exacerbations of chronic obstructive pulmonary disease. Journal of Microbiology and Biotechnology Research. 2012; 2: 440-4.

30. Rakesh G, Kasturi T, Yuvarajan S. Bacterial agents causing acute exacerbations in Chronic Obstructive Pulmonary Disease (COPD) patients, their antibiograms to Extended Spectrum Beta-Lactamases (ESBL) production in a tertiary care hospital, India. Int J Curr Microbiol App Sci. 2013;2(11):273-82.

31. Aleemullah MF, Krishnamurthy V, Harish M, Akeel CA. Bacteriological Profile of Patients with AECOPD- Hospital Based Study. Int J Curr Microbiol App Sci. 2016; 5(4): 84-90.

32. ElFeky DF, Elmandory HM, Galal M, Hakim MA. 2016. Sputum Bacteriology in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Int J Curr Microbiol App Sci. 2016; 5(1): 289–305.

33. Miyashita N, Niki Y, Nakajima M et al. Chlamydia pneumonia infections in patients with diffuse panbronchiolitis and COPD. Chest.1998; 157: 1498–505.

34. Sharan H. Aerobic Bacteriological Study of Acute Exacerbations of Chronic Obstructive Pulmonary Disease. J Clin Diag Res. 2015; 9(8): DC10–2.

35. Patel AK, Luhadia AS, Luhadia SK. Sputum Bacteriology and Antibiotic Sensitivity Pattern of Patients Having Acute Exacerbation of COPD in India – A Preliminary Study. J Pulm Respir Med. 2015;5:238.

Chest Heart Journal
Vol. 42, No. 2, July 2018

## *ORIGINAL ARTICLE*

# Evaluation of Efficacy and Safety in between Inhaled Levosalbutamol and Inhaled Salbutamol along with Conventional therapy in Severe Asthma patients

**Md. Mahabubur Rahman[1], Md. Shahjada Tabrez[2], Mohammed Kamrul Hasan[3], Md. Abdur Rouf[4], Bashir Ahmed[4] , Bipul Kanti Biswas[5], Mahmud Rahim[5], Liaquat Ali[6], Bijoy Krishna Das[7], Lutfan Nessa[8]**

**Abstract:**

***Background:*** *Levosalbutamol causes more bronchodilatation with less side effects as compared to salbutamol in asthma patients during acute relief of asthma symptoms, symptoms relieve during maintenance treatment of asthma and protection against exercise -induced asthma. Aims: To explore the efficacy and safety of Inhaled Levosalbutamol (group A) 300 µg/day (50µg 2 puffs thrice daily) compared with Inhaled Salbutamol (group B) 600µg/day (100µg 2 puffs thrice daily) along with Conventional therapy in case of treatment of severe asthma patients. Methods: This interventional study was carried out in the Department of Respiratory Medicine in NIDCH, Mohakhali, Dhaka, during November, 2016 to October, 2017. Severe (FEV1=<50 to 30% predicted) Asthma patients with agee"12years, both sexes, non smoker, who are not known case of COPD, Bronchiectasis, GERD were enrolled in this study. A total no. of 85 patients were included in this study. Among them 43 patients were treated with Levosalbutamol inhaler and 42 patients were treated with Salbutamol inhaler along with conventional therapy for severe Asthma. Results: In this study, in case of severe asthma, in group A (Levosalbutamol inhaler 300µg/day), FEV1 was increased from 38.84 ± 5.52 to 49.53 ± 7.63 (p<.001) and in group B (Salbutamol inhaler 600µg/day), FEV1 was increased from 37.22 ± 5.13 to 43.71 ± 6.79 (p<.001), which were highly significant but group A showed significant improvement than group B (p<0.05). In group A, FVC was increased from 52.61 ± 6.96 to 63.93 ± 8.33 (p<.001) and In group B, FVC was increased from 49.24 ± 6.52 to 57.28 ±7.87 (p<.001) which were highly significant but group A showed significant improvement than group B (p<0.05). In group A, Heart rate was increased from 78.56 ± 10.56 to 86.42 ± 9.21 (p<.001) and in group B, Heart rate was increased from 77.06 ± 9.46 to 93.71 ±8.18 (p<.001) which were highly significant but group B(Salbutamol) showed more tachycardia*

1. Medical Officer, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh.
2. Medical Officer, NIDCH, Mohakhali, Dhaka, Bangladesh.
3. MD (Chest Diseases),Thesis part student, NIDCH, Mohakhali, Dhaka, Bangladesh.
4. Professor of Respiratory Medicine, NIDCH, Mohakhali, Dhaka, Bangladesh.
5. Associate Professor of Respiratory Medicine, NIDCH, Mohakhali, Dhaka, Bangladesh.
6. Professor of Biochemistry and Cell Biology, BUHS, Mirpur-1, Dhaka, Bangladesh.
7. Assistant Professor, Respiratory Medicine,AMUMC, Noakhali, Bangladesh.
8. Associate Professor, Pediatrics, AMUMC, Noakhali, Bangladesh.

**Address of correspondence:** Dr. Md. Mahabubur Rahman , Medical Officer, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh. Cell: 01732661412, e-mail: k57drmabd @gmail.com

**Correspondence to:**
**Submission on:** 18 May, 2018 **Accepted for Publication:** 15 June, 2018
Available at http.//www.chabjournal.org

*than group A( Levosalbutamol) (p<0.05). In group A, Tremor was increased from 4.20 ± 1.56 to 5.73 ± 2.07 (p<.001) and in group B, Tremor was increased from 3.80 ± 1.48 to 7.65 ± 2.63 (p<.001) which were highly significant but group B(Salbutamol) showed more tremor than group A( Levosalbutamol) (p<0.05). In group A, Serum potassium level was decreased from 4.02 ± .42 to 3.79 ± .36 (p<.001) and in group B, Serum potassium level was decreased from 4.14 ± .51 to 3.38 ± .56 (p<.001) which were highly significant but group B(Salbutamol) showed more hypokalemia than group A (Levosalbutamol) (p<0.05). Conclusion: The present study concluded that Levosalbutamol inhaler appears to be more efficacious than Salbutamol inhaler in terms of improvement in lung functions (FEV1 and FVC) while adverse events like tachycardia, tremor and hypokalemia are seen less with Levosalbutamol inhaler than Salbutamol inhaler in case of severe asthma patients.*

*Keywords: Levosalbutamol, Salbutamol, $FEV_1$, FVC , Heart rate, Tremor, Serum potassium(S. K+).*

***[Chest Heart Journal 2018; 42(2) : 76-82]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019582*

**Introduction:**

Asthma is a common and potentially serious chronic disease that imposes a substantial burden on patients, their families and the community. It causes respiratory symptoms, limitation of activity, and exacerbation that require urgent health care and may be fatal if not addressed properly. Asthma causes symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time in occurence, frequency and intensity. These symptoms are associated with variable expiratory airflow,i.e. difficulty in breathing air out of the lungs due to bronchoconstriction, airway wall thickening, and increased mucus.[1] $\beta_2$-Agonists drugs are the most commonly used bronchodilators for the treatment of asthma to relieve bronchospasm.[2,3] Bronchodilation may be the result of $\beta_2$-receptor stimulation as induced by a $\beta_2$-receptor agonist. Salbutamol is the most widely used short-acting $^2$2-agonist in the symptomatic relief of asthma.[4,5]

Racemic Salbutamol has been the mainstay of treatment for bronchial smooth muscle contraction since 1982. Salbutamol are racemic drugs containing both 'R' (Levo) and 'S' (Dextro) optical isomers. Only R-isomer fits into three-dimensional conformation of $\beta_2$-adrenoceptor Proteins.[4-6] So (R)- and RS- salbutamol have a 2:1 potency ratio for improvement in FEV1 in asthmatic patients and shows that (S)-salbutamol is clinically inactive or little active. Because the RS - salbutamol mixture contains only 50% (R)-salbutamol, it is clear that the clinical effect of salbutamol resides with the (R)-enantiomer. [7,8] Consequently, "Levosalbutamol" was approved by FDA (Food and Drug Administration) in 1999 as a purified single isomer for clinical use in asthma patients.[5] Moreover, (S)-salbutamol appears to be preferentially retained in the lungs in comparison with (R)–salbutamol.[4] So, that this slower metabolism increases the proportion of (S)–salbutamol than levosalbutamol in vivo and exposes the patient to relatively more potential adverse effects of (S)–salbutamol than levosalbutamol like hypokalemia, tremor, tachycardia.[6,8,9,10,11,12] So, the efficacy and safety of Levosalbutamol Inhaler is better than Salbutamol Inhaler in asthma patients.This study will be undertaken to test this hypothesis.

**Materials & Methods:**

This was a randomized Clinical Trial carried out in inpatient department of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period from November, 2016 to October, 2017 for one year. All patients over 12 years of both sexes suffering from asthma were taken as study population and those who fulfill the inclusion and exclusion criteria were recruited as study sample.

A total number of 96 patients were taken as study sample that means severe (FEV1=<50 to 30% predicted) asthma. A semi-structured questionnaire was followed by face to face interview on the basis of objective of study. Eligible patients were allocated randomly into

two groups. Of them 48 patients were in group A and 48 patients were in group B. Group A was treated with Levosalbutamol inhaler (300µg/day) 50 µg 2 puffs thrice daily and group B was treated with Salbutamol inhaler (600µg/day) 100 µg 2 puffs thrice daily for 4 weeks along with other with conventional therapy for asthma.

Each subject was evaluated with history and symptoms regarding the presentation. Patients age, occupation, working environment, smoking history, past medical history, current medications were asked. Patients were asked about the dyspnoea, wheezing, chest tightness, cough, sputum production, daytime symptoms, night time symptoms, triggering factor, activity level, associated diseases. They were examined and spirometry, in addition, to the other necessary baseline investigation (including CBC with ESR, Serum electrolytes, Chest X-ray P/A view, RBS, ECG, Sputum for AFB, Sputum for eosinophil count etc.) were done.

Baseline Lung function tests ($FEV_{1,}$ FVC), ECG (Heart rate), Tremor assessment, Serum potassium level ( S. K+) were obtained before the day of discharge after cessation of the fol-lowing respiratory medications: oxygen therapy, nebulization and other injectable medications.These parameters were again done during follow up after 4 weeks. Tremor assessment was observed by TRG (Tremor research group) Essential Tremor Rating Assessment Scale (TETRAS) which was the performance measures of head, upper limb and lower limb tremor.

In group A ,1 patient did not come to follow up, 2 patient need Levosalbutamol inhaler more than thrice daily and 2 patient need less than thrice daily. In group B, 2 patient did not come to follow up, 2 patient need Salbutamol inhaler more than thrice daily and 2 patient need less than thrice daily.

Finally total 85 patients were included(43 patients in group A and 42 patients in group B). All the informations were properly documented in the prescribed forms. All interviewed questionnaire were checked for completeness, accuracy and consistency to exclude missing or inconsistent data. Data were checked, cleaned and edited properly. 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 comparison was carried by Chi-square ($Ç^2$) test. 95% confidence limit was taken. A probability value (p) of less than 0.05 was considered to indicate statistical significance. All patients/legal guardians were briefed about the study. Informed and written consent were taken from all study population.

**Results:**

**Table-I**

*Distribution of patients according to Demographic profile (n= 85)*

| Parameters | Groups: Group A (n=43) (Levosalbutamol Inhaler) | Groups: Group B (n=42) (Salbutamol Inhaler) | p value* |
|---|---|---|---|
| Age | 30 ± 8.50 | 29 ± 7.58 | $>0.05^{NS}$ |
| Sex (%) | | | |
| Male | 21 (48.83) | 20 (47.61) | $>0.05^{NS}$ |
| Female | 22 (51.17) | 22 (52.39) | |

— P-value reached from chi square test and student's t test. Age was expressed as mean ± SD (Years). Figure within parentheses indicates in percentage. NS: Not significant

**Table-II**

*Mean ± SD of FEV1 by groups of severe asthma (n-85)*

| | Groups | | |
|---|---|---|---|
| | Group A (n=43) (Levosalbutamol Inhaler) | Group B (n=42) (Salbutamol Inhaler) | p value* |
| Baseline | 38.84 ± 5.52 | 37.22 ± 5.13 | .333 NS |
| After 4 weeks | 49.53 ± 7.63 (p<.001 S ) | 43.71 ± 6.79 (p<.001 S ) | .013 S |

NS: Not Significant, S: Significant; p value reached from both paired and unpaired t-test.

**Table-III**

*Mean ± SD of FVC by groups of severe asthma (n-85)*

| | Groups | | |
|---|---|---|---|
| | Group A (n=43) (Levosalbutamol Inhaler) | Group B (n=42) (Salbutamol Inhaler) | p value* |
| Baseline | 52.61 ± 6.96 | 49.24 ± 6.52 | .172 NS |
| After 4 weeks | 63.93 ± 8.33 (p<.001 S ) | 57.28 ±7.87 (p<.001 S ) | .012 S |

NS: Not Significant, S: Significant; p value reached from both paired and unpaired t-test.

**Table-IV**

*Mean ± SDof Heart rate by groups of severe asthma (n-85)*

| | Groups | | |
|---|---|---|---|
| | Group A (n=43) (Levosalbutamol Inhaler) | Group B (n=42) (Salbutamol Inhaler) | p value* |
| Baseline | 78.56 ± 10.56 | 77.06 ± 9.46 | .633 NS |
| After 4 weeks | 86.42 ± 9.21 (p<.001 S) | 93.71 ±8.18 (p<.001 S) | .010 S |

NS: Not Significant, S: Significant; p value reached from both paired and unpaired t-test.

**Table-V**

*Mean ± SD of Tremor by groups of severe asthma (n-85)*

| | Groups | | |
|---|---|---|---|
| | Group A (n=43) (Levosalbutamol Inhaler) | Group B (n=42) (Salbutamol Inhaler) | p value* |
| Baseline | 4.20 ± 1.56 | 3.80 ± 1.48 | .411 NS |
| After 4 weeks | 5.73 ± 2.07 (p<.001 S ) | 7.65 ± 2.63 (p<.001 S ) | .013 S |

NS: Not Significant,S: Significant; p value reached from both paired and unpaired t-test.

**Table-VI**

*Mean ± SDof Serum potassium level ( S. K+) by groups of severe asthma (n-85)*

| | Groups | | |
|---|---|---|---|
| | Group A (n=43) (Levosalbutamol Inhaler) | Group B (n=42) (Salbutamol Inhaler) | p value* |
| Baseline | 4.02 ± .42 | 4.14 ± .51 | .395 NS |
| After 4 weeks | 3.79 ± .36 | 3.38 ± .56 | .020 S |
| | (p<.001 S ) | (p<.001 S ) | |

NS: Not Significant,S: Significant; p value reached from both paired and unpaired t-test.

**Discussion:**

This prospective interventional study was carried out with an aim to explore the efficacy and safety of Inhaled Levosalbutamol compared with Inhaled Salbutamol along with Conventional therapy in case of treatment of severe asthma patients. The patients of either group were evaluated at base line and after 4 weeks. Lung function tests ($FEV_1$, FVC), Heart rate, Tremor assessment, Serum potassium level ( S. K+) level were done at base line and during follow up after 4 weeks. Finally 43 patients in group A and 42 patients in group B were included.

In this study among 85 cases in both Levosalbutamol and salbutamol inhaler groups majority were at or below 35 years of age. Similar study was reported by Chen et al., 2003; Schatz et al., 2006 and mentioned that younger age group are the most prevalent in asthma attack. [13,14] The distribution of the study population according to sex was shown in this study. Females (51.76%) with asthma were a bit predominant than male (48.23%). Similar result was reported by Schatz et al., 2006 and added that female is more commonly affected by asthma than male. [14]

In this study, as shown in table II, base line FEV1 was not statistically significant in both groups (p>0.05). With therapy, after 4 weeks FEV1 were increased to 49.53 ± 7.63 (p<0.05) and 43.71 ± 6.79 (p<0.05) in Levosalbutamol and salbutamol inhaler group respectively.This differences between base line and after 4 weeks were statistically significant. So, both the drugs were effective in improving FEV1 in asthma patient. Again after 4 weeks it was found that Levosalbutamol Inhaler causes more FEV1 improvement than salbutamol Inhaler because the mean differences of improvement between two groups were statistically significant (p<0.05). Nowak et al., 2006; Milgrom et al., 2001 found similar results by some other studies. [9,11] But Rathore K et al., 2012 showed in a study that significant improvement of FEV1 occurred in case of Levosalbutamol Inhaler but improvement of FEV1 in case of salbutamol Inhaler was not statistically significant. [8]

As shown in table III, Base line FVC was not statistically significant in both groups (p>0.05).With therapy,after 4 weeks FVC were increased to 63.93 ± 8.33 (p<0.05) and 57.28 ±7.87 (p<0.05) in Levosalbutamol and salbutamol inhaler group respectively. This differences between base line and after 4 weeks were statistically significant. So, both the drugs were effective in improving FVC in asthma patient. Again after 4 weeks it was found that Levosalbutamol Inhaler causes more FVC improvement than salbutamol Inhaler because the mean differences of improvement between two groups were statistically significant (p<0.05). Rathore K et al., 2012 found similar results by some other studies. [8]

As shown in table IV, Base line Heart rate was not statistically significant in both groups (p>0.05). With therapy, after 4 weeks Heart rate were increased to 86.42 ± 9.21 (p<0.05) and 93.71 ±8.18 (p<0.05) in Levosalbutamol and salbutamol inhaler group respectively.This differences between base line and after 4 weeks were statistically significant. So, both the drugs were effective in improving Heart rate in asthma patient. Again after 4 weeks it was found that Levosalbutamol Inhaler causes more Heart rate improvement than salbutamol Inhaler because mean the differences of improvement between

two groups were statistically significant ($p<0.05$). This results were consistent with Punj et al., 2009; Lotvall et al., 2001. [6,7] But Rathore K et al., 2012 showed similar result but heart rate differences between two groups were not significant.[8]

As shown in table V, Base line Tremor was not statistically significant in both groups ($p>0.05$). With therapy, after 4 weeks Tremor was increased to $5.73 \pm 2.07$ ($p<0.05$) and $7.65 \pm 2.63$ ($p<0.05$) in Levosalbutamol and salbutamol inhaler group respectively. This differences between base line and after 4 weeks were statistically significant. So, both the drugs were responsible for Tremor in asthma patient. Again after 4 weeks it was found that salbutamol Inhaler causes more Tremor than Levosalbutamol Inhaler because the mean differences of increased Tremor between two groups were statistically significant ($p<0.05$). Cazzola et al., 2012 also reported occurrence of tremor in case of using both drugs. [12]

As shown in table VI, Base line Serum potassium level ( S. K+) level was not statistically significant in both groups ($p>0.05$).With therapy, after 4 weeks Serum potassium level ( S. K+) level were were decreased to $3.79 \pm .36$ ($p<0.05$) and $3.38 \pm .56$ ($p<0.05$) in Levosalbutamol and salbutamol inhaler group respectively.This differences between base line and after 4 weeks were statistically significant. So,both the drugs were responsible for decreasing Serum potassium level(S. K+) level in asthma patient. Again after 4 weeks it was found that salbutamol Inhaler decreases more Serum potassium level(S. K+) level than Levosalbutamol Inhaler because the mean differences of decreased Serum potassium level (S. K+) level between two groups were statistically significant ($p<0.05$). Similar results were observed by Milgrom et al., 2001; Lotvall et al., 2001; Punj et al., 2009; Rathore K et al., 2012. [6,7,8,11]

## Conclusion:

There were significant improvements of $FEV_1$, FVC in Levosalbutamol inhaler while adverse events like tachycardia, tremor and hypokalemia are seen less with Levosalbutamol inhaler than Salbutamol inhaler in case of severe asthma patients. So treatment with Levosalbutamol inhaler is a better bronchodilator in terms of efficacy and safety than Salbutamol inhaler in patients with severe asthma along with Conventional therapy for symptomatic relief.

**Acknowledgement:**

Author Contribution: Dr. Md. Mahabubur Rahman had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Dr. Md. Mahabubur Rahman contributed to study conception and design, data collection, analysis and interpretation of data, drafting of the manuscript and critical revisions of the article.

Prof. Dr. Md. Abdur Rouf, Prof. Dr. Bashir Ahmed, Prof. Dr. Liaquat Ali, Associate Prof. Dr. Bipul Kanti Biswas, Associate Prof. Dr. Mahmud Rahim, Dr. Shahjada Tabrez , Dr. Mohammed Kamrul Hasan contributed to concept and design of the study, interpretation of data, critical revisions and editing of the manuscript.

**Conflict of Interest:** The authors of this paper have declared that there is no conflict of interest to any of the authors.

Funding Agency: This study has been performed without any funding from outside else.

## References:

1. GINA,2018, A Pocket Guide for asthma management & prevention.
2. Ezeamuzie CI, Mary A..Differential effects of salbutamol and salmetrol on human eosinophil responses. J. Pharmacol. 1998; Exp. Ther. 284: 25-31.
3. Carl JC, Myers TR, Kirchner HL, Kercsmar CM. Comparison of racemic albuterol and levalbuterol for treatment of acute asthma. J Pediatr. 2003;143:731-6.
4. Dhand R,Goode M, Reid R, Fink JB, Fahey PJ, Tobin MJ. Preferential pulmonary retention of (S)-albuterol after inhalation of racemic albuterol. Am J Respir Crit Care Med. 1999; 160(4):1136–41.
5. Punj A, Prakash A, Bhasin A. Levosalbutamol vs racemic salbutamol in the treatment of acute exacerbation of

asthma. Indian J Pediatr. 2009;76(11): 1131-1135.

6. Penn RB, Frielle T, McCullough FR, Aberg G, Benovic J. Comparison of R-, S- and RS-albuterol interaction with human ²1-and ²2 adrenergic receptors. Clin Rev Allergy Immunol. 1996;14: 37-45.
7. Lotvall J, Palmqvist M, Arvidsson P, Maloney A, Ventresca GP, Ward J. The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients. J. Allergy Clin. Immunol. 2001;108:726-731.
8. Rathore K, Sharma TK, Aseri ML, Mathur SK, Gupta RC, Vardey SK, et al. Comparative study of pulmonary functions after administration of albuterol and levalbuterol in patients with moderate to severe bronchial asthma. International Journal of Medicine and Medical Sciences. 2012; 4(2): 39 – 44.
9. Nowak RM, Emerman CL, Schaefer K, Disantosterfano RL, Vaickus L, Roach JM. Levalbuterol compared with racemic albuterol in the treatment of acute asthma: results of a pilot study. Am J Emerg Med. 2004; 22 : 29-36.
10. Nelson HS, Bensch G, Pleskow WW, Di Santostefano R, DeGraw S, Reasner DS. Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. J Allergy Clin Immunol. 1998; 102: 943-952.
11. Milgrom H, Skoner DP, Benscn G, Kim KT, Claus R, Rudolf BA. Low-dose Levalbuterol in children with asthma safety and efficacy in comparison with placebo and racemic albuterol. J Allergy Clin Immunol. 2001;108: 938-45.
12. M. Cazzola, M.G. Matera Tremor and ²2 adrenergic agents: Is it a real clinical problem? Pulmonary Pharmacology & Therapeutics. 2012, 25 (4): 4.
13. Chen, Y., P. Stewart, et al. Sex difference in hospitalization due to asthma in relation to age.¼ Journal of clinical epidemiology. 2003;56(2):180-187.
14. Schatz M, Clark S, Camargo CA Jr. Sex differences in the presentation and course of asthma hospitalizations. Chest. J. 2006; 129(1):50-55.

Chest Heart Journal
Vol. 42, No. 2, July 2018

## ORIGINAL ARTICLE

# Role of C-reactive protein (CRP) and interleukin-6 (IL-6) level as predictors of multiple organ Failure in polytrauma patients.

**Siddiqui O[1], Nur-E-Elahi M [2], Taher A[3], Imdad S[4], Akter T[5]**

**Abstract:**

***Background:*** *The initial pathophysiological events immediately after the 'trauma' event has been found to play key role for future development of multiple organ failure (MOF).*

***Objective:*** *This study was aimed to assess the role of C-reactive protein (CRP) and interleukin-6 (IL-6) as predictors of Multiple Organ Failure (MOF).*

***Methodology:*** *This prospective study concluded 283 Polytrauma patients as sample who were treated in Department of Casualty of Sir Salimullah Medical College Mitford Hospital, Dhaka from January 2013 to January, 2018. Patients arriving within 24 hours of trauma, age ranging from 16-65 years, surviving more than 48 hours and with Injury Severity Score ee 18 ('Polytrauma") were included. We excluded all patients with injury to CNS.*

***Result:*** *A statistically significant difference was noted in average CRP levels between patients with and without MOF on all days. IL-6 concentration also followed decreasing trend being highest initially.*

***Conclusion:*** *The most important parameters of MOF development are serum IL-6 concentration on the first day of hospitalization and the number of positive SIRS criteria on the fourth day of hospitalization.*

***Key words:*** *Polytrauma, Multiple Organ Failure (MOF), CRP, IL-6*

***[Chest Heart Journal 2018; 42(2) : 83-87]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019583*

## Introduction:

With the advent of time though improvement of therapeutic concepts has decreased trauma related fatalities[1] still 'Organ Dysfunction' remains a frequent and severe complication during clinical course and the sole cause of high mortality. Survival rate of 'Polytrauma' patients has improved but the frequency of development of organ dysfunction remains static.[2,3]

To formulate a prudent combat strategy against the stress response of Polytrauma it requires to identify patients with a high risk for

1. Omar Siddiqui, Junior Consultant, DGHS (OSD), BSMMU (Deputation), Bangladesh.
2. Md. Nur-E-Elahi, Assistant Professor, Department of Hepatobiliary, Pancreatic & Liver Transplant Surgery, BSMMU, Bangladesh.
3. Md. Abu Taher, Associate Professor, Department of Colorectal Surgery, BSMMU, Bangladesh.
4. Sadia Imdad, Junior Consultant, Department of Surgery, Shaheed Suhrawardi Medical College Hospital, Bangladesh.
5. Tasnuva Akter, HMO, Department of Gyn & OBS, SSMCMH, Bangladesh.

**Correspondence to:** Dr. Omar Siddiqui, Junior Consultant (Surgery), DGHS (OSD), Bangabandhu Sheikh Mujib Medical University (Deputed), Bangladesh. Contact No. : +880-1705322990, E-mail: omar24th@yahoo.com

**Submission on:** 10 May, 2018 **Accepted for Publication:** 20 June, 2018
Available at http.//www.chabjournal.org

posttraumatic complications within very short interval after the assault. Polytrauma to date possess a great challenge for evaluation of clinical state and prognosis as many clinical parameters such as blood pressure, pH or heart rate failed to assess the posttraumatic situation.[4]

A tight correlation been noted between cytokine plasma level, development of MOF and mortality rate.[5] Thus immune monitoring can be our answer to help in the selection of patients at risk for posttraumatic complications.

The aim of this study was to assess the kinetics of C-reactive protein (CRP) and interleukin-6 (IL-6) as predictors of MOF in Polytrauma cases.

**Methodology:**

This prospective study concluded 297 Polytrauma patients as sample who were treated in Department of Casualty of Sir Salimullah Medical College Mitford Hospital, Dhaka from January 2012 to January, 2016. Patients arriving within 24 hours of trauma, age ranging from 16-65 years, surviving more than 48 hours and with Injury Severity Score e" 18 ('Polytrauma') were included. We excluded all patients with injury to CNS. Development of MOF in the first 24 hour and lethal outcome in the first 48 hours made us to exclude 14 patients. The remaining 283 cases were followed up for next 10 days. Markers and mediators of inflammation (CRP & IL-6) were first assessed within 24 hours of injury and then consecutively on every day till the tenth day. Concentration of CRP was standardized with a normal value being < 9 mg/ml and reference range for IL-6 was 0–8 pg/mL.

The SAPS II has 17 variables, 12 of which assess physiology, age and type of treatment and 3 of which identify the presence of chronic diseases such as AIDS, metastatic cancer or hematologic malignancy. For the 12 physiologic variables, the poorest values in the first 24 hours upon admission (those with the highest number of points) were taken into account.

We determined the Injury Severity Score (ISS) from the formula (ISS = Abbreviated Injury Score $[AIS]^2 + AIS^2 + AIS^2$) where $AIS^2$ represents squared single highest scores from 3 regions of the body in the first 24 hours. We also applied the combined MOF/MODS score that defines organ damage according to the presence of 1 or more variables.[1,6,7] Respiratory failure was deemed present when mechanical ventilation was necessary for at least 72 hours, when $PaO_2/FiO_2 < 37.3$ kPa positive end-expiratory pressure (PEEP) was over 8 cm $H_2O$ and when there was radiographically confirmed acute respiratory distress syndrome(ARDS) or a respiratory rate d" 5/min or e" 49/min. Hepatic failure was defined as bilirubinemia over 51 ìmol/L for at least 48 hours. Renal insufficiency was defined as serum creatinine over 177 ìmol/L for at least 48 hours. Heart failure was defined as cardiac index $< 3.0 \times min^{-1} \times m^{-2}$, obligatory application of inotropic therapy, heart rate d" 54/min, present ventricular tachycardia and/or fibrillation and mean arterial pressure d" 49 mm Hg or pH d" 7.24. Hematologic insufficiency was defined as a platelet count < 20000 or a white blood cell count $< 1 \times 10^{-9}$/L. We analyzed these parameters in all patients included in our study, and the worst results in the first 24 hours were taken into account when we qualified for the existence of organ insufficiency. The presence of at least 1 of the mentioned criteria during hospitalization defined existing organ damage. MOF duration was not significant because it represents an "all-or-nothing" event.

For statistical analysis help from a statistician was sought. $\div^2$, Student's *t* test and the Mann–Whitney *U* test were used as deemed appropriate for intergroup comparisons. A logistic regression coefficient was used to investigate the correlation between the number of SIRS criteria per hospital days and the development of MOF. Values of $p < 0.05$ or $p < 0.01$ were considered significant. Each variable was assessed individually with univariate analysis as a resulting variable for MOF. Parameters that were found to be statistically significant predictors with univariate analysis were then included in a multivariate model.

**Results:**

The MOF patients' average age was 32.1 (standard deviation [SD] 1.9) years. Most patients had blunt injuries (192 patients, 67.84%), whereas 55 (19.43.9%) had open wounds. Most patients had triple (50.7%), double (27.3%) or single (19.7%) organ insufficiency. Only 8.7 % of patients had 4 or more insufficient organs. The male: female ratio was 4.05:1, which is common for traumatic injuries. The average ISS score was 21.79 ± 0.6 (SD), and the average SAPS II score was 41.12 ± 1.5(SD).

**Table-I**

*Demographic variables & General Data*

| Variable | MOF | No MOF | All Patients | *p* value |
|---|---|---|---|---|
| Patients | 41 | 242 | 283 | >0.05 |
| Age (Mean ± SD) | 32.1 ± 1.9 | 31.1±.9 | 35±3.9 | |
| Sex (M : F) | 5.1:1 | 3.9:1 | 4.05:1 | |
| GCS | 7.5 ± 1.9 | 10.1 ± 0.3 | 10 ± 0.4 | >0.05 |
| ISS(Mean ± SD) | 27.9 ± 2.4 | 23.2 ± 1.1 | 21.79 ± 0.6 | <0.01 |
| Sepsis | 15(36.56%) | 192(79.34%) | 207(73.15%) | <0.05 |
| SAPS II (Mean ± SD) | 23.8 ± 1.7 | 51.2 ± 2.3 | 41.12 ± 1.5 | <0.01 |
| Hospital Stay(Mean ± SD) Days | 31.15 ± 3.1 | 23.56 ± 4.3 | 24.65 ± 2.7 | <0.05 |
| Mortality (%) | 29(70.73) | 24(9.91) | 53(18.73) | <0.01 |

Table-I Shows the patients' distribution according to MOF presence in relation to age, sex, duration of hospitalization, frequency of sepsis, ISS and SAPS II scores and mortality. A highly statistically significant difference was noted in survival between groups of patients with and without MOF.

Early MOF appearing in the first 72 hours after the injury, was present in 22 patients (53.6%), whereas 20 patients (48.78%) had late MOF appearing 72 hours after the injury. (Fig. 1)

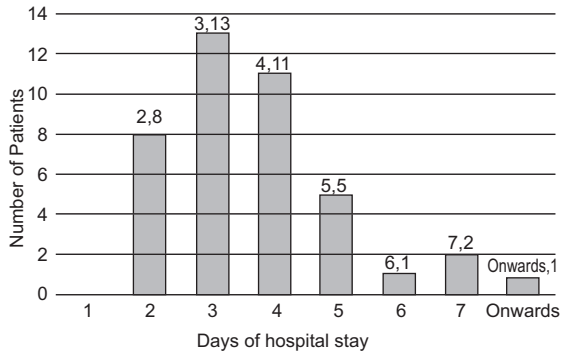



**Fig.-1:** *Onset of MOF after injury in Polytrauma patients.*

The number of SIRS variables was significantly different between the patient groups with and without MOF on day 5 of hospitalization, as shown in Fig. 2. Further, a significant correlation was found between SIRS determinants and the appearance and progression of MOF in the first 5 of 7 observed days.

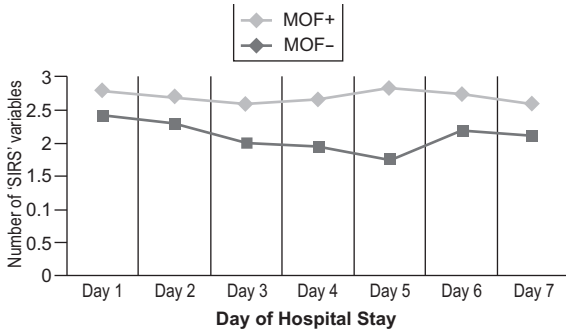



**Fig-2:** *Number of positive SIRS variable per hospital days in Polytrauma patients with or without MOF.*

Average CRP (mg/L) and IL-6 (pg/mL) on the first, second, third, seventh and tenth day after the injury are shown in Fig. 3 & 4. During the entire follow-up period, a statistically significant difference in average CRP level was noted between patients with and without MOF. Concentrations of IL-6 significantly varied on all days of hospitalization.

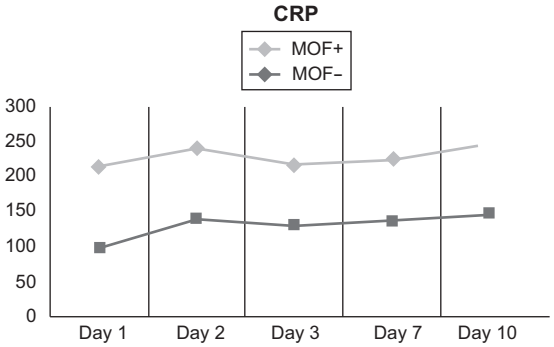



**Fig-3:** *Average CRP (mg/L) with or without MOF following Polytrauma (Mann-Whitney U Test) White Star indicates p < 0.05*

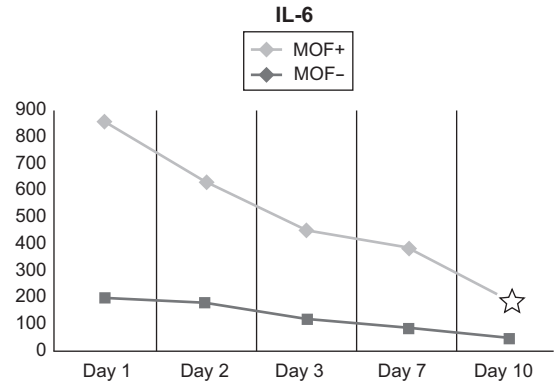



**Fig-4:** *Average IL-6 (pg /mL) with or without MOF following Polytrauma (Mann-Whitney U Test)*

*White Star indicates p < 0.05*

**Discussion:**

The high average ISS score in our group of patients reflects the inclusion of only Polytrauma patients in our study. MOF rate among these patients been found quite high in many studies. Most studies consider the period within 72 hours of admission to be the upper limit for diagnosis of early MOF. MOF appearing after 72 hours is diagnosed as late. In our study, out of 41 patients with MOF, 53.6% had the early form. These data only refer the onset of failure of the first damaged organ or system.

The mortality rate follows the increase in the number of affected organs. It varies from 11% in patients with single organ system failure to 62% in patients with failure of 2 systems, as reported by some authors.[8, 9] Insufficiency of 3 or more organs almost always results in a lethal outcome.[10]

Apart from the order in which failures appear, their combination is also important. In a study of 1171 patients, lethal outcome after combined cardiac-respiratory failure occurred in 66.7% patients, after respiratory-hepatic failure, it occurred in 53.9%, and after hepatic-respiratory insufficiency, it occurred in 33.3%.[5-13] In our study, 89% of patients with MOF had signs of respiratory failure, 28% had signs of renal failure and 32% had signs of cardiovascular decompensation, which is accompanied by an especially high mortality rate. Hepatic failure was also present in a significant number (34%), but it usually appeared later and resolved more quickly.

In 81% of patients in our study, respiratory insufficiency appeared first, which is consistent with the findings of other authors.[7,8,11] A smaller number of patients had renal failure (11%), cardiovascular insufficiency (5%) and cerebrovascular insufficiency (2%) as the first manifestation of MOF. Most of our patients had failure of 3 (50.7%), 2 (27.3%) or 1 (19.7%) organ system, and only 8.7% had 4 or more insufficient organs. The most frequent combination of organ failure in our patients was respiratory-renal failure and respiratory-hepatic failure. In patients with 3 or more affected organs, the most frequent combination was respiratory-renal-cardiovascular insufficiency, followed by respiratory-renal-hepatic failure.

The mortality rate in patients with MOF was high (70.73%). The average ISS value in our study was higher than reported by other authors in studies with similar mortality rates. In patients with failure of 2 organs, several studies reported a mortality rate of 42%,[10] while another study reported a mortality rate of 35%.[11] The mortality rate in patients with 2 insufficient organs was higher in our study (83%) than that reported by other authors. However, all patients with single organ failure survived. Our lack of in depth knowledge and strategy to combat MOF in such cases might be the reason behind these dissimilarity.

All our patients with MOF had significantly higher CRP levels, compared with patients without MOF, indicating that CRP levels are a good early marker of morbidity in intensive care unit patients.

The plasma IL-6 level may be a marker of cytokine cascade and may reflect a complex inflammatory host response and the severity of disease (or injury).[12] The ratio of IL-6 to IL-10 may be a predictive factor in SIRS.[13] Some authors always include cytokine status when distributing injured patients according to severity of the injury and expected outcome.[13-15] According to these models, cytokine concentrations are classified in 4 groups with adequate prognostic significance (number of points).[16] Almost one-half of the patients in our study (45%) belonged to the third (IL-6 > 250 pg/

L) and fourth (IL-6 > 500 pg/L) group, suggesting a bad prognosis. There are reports that IL-6 level on days 2 and 4 were significantly higher in MOF patients than in those without MOF.[17]

Some authors describe significant IL-6 increase on the first or even second day; however, most state that the window closes after 3 days, indicating that IL-6 levels have no prognostic value after that point.[15-17]

**Conclusion:**

IL-6 kinetics in the first days of hospitalization may suggest the development of MOF, even before clear clinical symptoms develop. The kinetics of CRP concentration differ significantly between groups, depending on MOF development, especially from the second to the seventh day of hospitalization.

**References:**


1. Regel G, Grotz M, Weltner T, Sturm JA, Tscherne H. Pattern of organ failure following severe trauma. World J Surg. 1996;20:422–429. doi: 10.1007/s002689900067. [PubMed] [Cross Ref]
2. Sauaia A, Moore FA, Moore EE, Norris JM, Lezotte DC, Hamman RF. Multiple organ failure can be predicted as early as 12 hours after injury. J Trauma. 1998;45:291–301. doi: 10.1097/00005373-199808000-00014. [PubMed] [Cross Ref]
3. Sauaia A, Moore FA, Moore EE, Lezotte DC. Early risk factors for postinjury multiple organ failure. World J Surg. 1996;20:392–400. doi: 10.1007/s002689900062. [PubMed] [Cross Ref]
4. Waydhas C, Nast-Kolb D, Trupka A, Zettl R, Kick M, Wiesholler J, et al. Posttraumatic inflammatory response, secondary operations, and late multiple organ failure. J Trauma.1996;40:624–630. doi: 10.1097/00005373-199604000-00018. [PubMed] [Cross Ref]
5. Keel M, Trentz O. Pathophysiology of polytrauma.*Injury* 2005;36:691-709.
6. Sauaia A, Moore FA, Moore EE, et al. Multiple organ failure can be predicted as early as 12 hours after injury. J Trauma1998;45:291-303.
7. Waydhas C, Nast-Kolb D, Trupka A, et al. Posttraumatic inflammatory response, secondary operations, and late multiple organ failure. J Trauma1996;40:624-31.
8. Moore FA, Sauaia A, Moore EE, et al. Postinjury multiple organ failure: a bimodal phenomenon. *J Trauma*1996;40:501-12.
9. Sauaia A, Moore FA, Moore EE, et al. Early risk factors for postinjury multiple organ failure. *World J Surg*1996;20:392-400.
10. Rixen D, Siegel JH, Friedman HP. "Sepsis/SIRS," physiologis slassification, severity stratification, relation to cytokine elaboration and outcome prediction in posttrauma critical illness. *J Trauma* 1996; 41:581-98.
11. Zimmerman JE, Knaus WA, Sun X, et al. Severity stratification and outcome prediction for multisystem organ failure and dysfunction. *World J Surg*1996;20:401-5.
12. Patrick DA, Moore FA, Moore EE, et al. The inflammatory profile of interleukin-6, interleukin-8 and soluble cell adhesion molecule-1 in post-injury multiple organ failure. *Am J Surg*1997;172:425-31.
13. Suffredini AF. Current procpets for the treatment of clinical sepsis. *Crit Care Med*1994;22:12-8.
14. Bernard GR. Sepsis trials: intersection of investigation, regulation, funding, and practice. *Am J Respir Crit Care Med*1995;152:4-10.
15. Borden EC, Chin P. Interleukin-6: a cytokine with potential diagnostic and therapeutic roles. *J Lab Clin Med*1994;123:824-9.
16. Bone RC. Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: what we know and do not know about cytokine regulation. *Crit Care Med*1996;24:163-72.
17. Spindler-Vesel A, Wraber B, Vovk I, et al. Intestinal permeability and cytokine inflammatory response in multiply injured patients. *J Interferon Cytokine Res* 2006; 26:771-6.

Chest Heart Journal
Vol. 42, No. 2, July 2018

## *ORIGINAL ARTICLE*

# Burden of Laparoscopic Port Site Mycobacterium Tuberculosis Infection in Bangladesh

**Md.Ahashan Habib[1], Syeda Farhana Naznin[2], Md. Aminul Islam Joarder[3], Md.Abdullah Al Mujahid[4], Md.Abu Raihan[5], Md. Ashraful Islam[6], Md. Mofizur Rahman Mia[7], Bijoy Krishna Das[8]**

**Abstract:**

***Background:*** *Port site infection is a previling, chronic nagging treatment refractory complication of laparoscopic surgery .It neutralizing the advantage of minimally invasive surgery and increase morbidity, treatment cost of the patients,leading to loss of confidence on operating surgeon. Source of port site infection with non-tuberculas and tuberculas mycobacterium are also being reported from different parts of the world.*

***Objective:*** *This study is carried out to see the prevalence of port site Mycobacterium Tuberculosis infection in Bangladesh perspective.*

***Result:*** *The present study pertains to 150 patients from Dhaka city Bangladesh who underwent laparoscopic surgery in BSMMU hospital .Total 8 (5.33%) patients shows port site infection ,among these 6 (4%) had underwent laparoscopic cholecystectomy . In the present study all the port site infections were diagnosed to be due to mycobacterium tuberculosis .The main source of M tuberculosis is exogenous and is due to the reused laparoscopic instruments which was sterilized with 2% gluteraldehyde .*

***Conclusion:*** *It has been reported that Mycobacterium Tuberculosis have become resistant to sterilization with gluteraldehyde. Thus proper sterilization of the laparoscopic instruments is of utmost importance in preventing infectious complications and ideally autoclaving should be used for this purpose.*

***Key words****: Port site, Laparoscopic surgery,Sterilization,Mycobacterium Tuberculosis.*

***[Chest Heart Journal 2018; 42(2) : 88-91]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019584*

## Introduction:

The aim of laparoscopic surgery was to enhance the cosmetic ,outlook of surgical field, lessen the post operative pain and duration of hospital stay so as to bring about reduction in magnitude of convalescence .Though it is a key hole surgery

1. Medical Officer, 250 Beded, TB Hospital, Shyamoli, Dhaka, Bangladesh.
2. Medical Officer, 250 Beded, TB Hospital, Shyamoli, Dhaka, Bangladesh.
3. Associate Professor, Department Surgery, BSMMU, Dhaka, Bangladesh.
4. Junior Consultant (Respiratory Medicine) , 250 Beded, TB Hospital, Shyamoli, Dhaka, Bangladesh.
5. Deputy Director & Project Director & Associate Professor (Respiratory Medicine), 250 Beded, TB Hospital, Shyamoli, Dhaka, Bangladesh.
6. Medical Officer, Department Surgery, BSMMU, Dhaka, Bangladesh.
7. Associate Professor of Thorasic Surgery, National Institute of Diseases of the Chest & Hospital, Mohakhali, Dhaka, Bangladesh.
8. Assistant Professor of Respiratory Medicine, Abdul Malek Ukil Medical College, Noakhali, Bangladesh.

**Correspondence to:** Dr. Md. Ahashan Habib, Medical Officer, 250 Beded, TB Hospital, Shyamoli, Dhaka, Bangladesh. Mobile: 01712-503159, E-mail: rupsa27@gmail.com

**Submission on:** 13 May, 2018 **Accepted for Publication:** 21 June, 2018

Available at http.//www.chabjournal.org

but when these small wound get coursed with infections with a dragging and indolent course, the entire purpose of decreasing morbidity goes in to vain.In Bangladesh tuberculosis is one of the major health problem, among which 1/5$^{th}$ are extra pulmonary. It has been noted that port site TB in usually due to improper sterilization of the laparoscopic instruments ,but few case report publish which has attributed port site TB to an endogenous source[1].Port site TB has been reported following laparoscopic cholecystectomy[2,3], appendectomy[4], urological surgery[5].Review of literature shows that the problem of port site infection is a global one and not restricted to developing countries only ,no doubt the incidence in developed countries is far less in copmparison to developing nations[6].In the present study 150 cases of laparoscopic surgeries, 8 cases are being reported with port site infection by mycobacterium tuberculosis.

**Materials and methods:**

The present study includes 150 patients who underwent laparoscopic surgeries for various indications in a BSMMU hospital in Dhaka city.This study was conducted for a period of 24 months march 2014 to February 2016.All those patients who underwent laparoscopic surgery during this period were included in the study and those patients ,who were converted to open procedure were excluded from the study . In all the patients the pre-operative skin preparation done by on table shaving method and use providone iodine wash.The patients were admitted in the morning of the day of surgery and one pre-operative dose of ceftriaxone 1 gm at the time of induction and two subsequent postoperative dose of the same were given 12 hourly and then it convert in to oral cefixime preparation for total 7 days. All surgeries were done under general anesthesia. Pneumo-peritonium was created through open method in supra or infra umbilical transverse incision. Through the incision 10mm primary trocar was introduced in to peritoneal cavity.The time duration from first incision to end of the procedure was calculated.All the specimens of gall bladder ,appendix,and ovarian cyst were extracted through the umbilical port,and used endobag in ovarian cyst and appendix extraction.All laparoscopic instruments were sterilized by 2% gluteraldehyde solution with a contact time of 20 minutes .Before surgery all the instruments were washed with normal saline.Gluteraldehyde solution was replaced after every 15 days.

All patients were monitored for superficial and deep port site infections .Port site infections were included those occurring within 30 days of an operation[7].Wounds were assed clinically on 3$^{rd}$ post operative day and after 7days of operation .In case of infection had occurred , pus was sent for culture and sensitivity ,dressing and cleaning of wounds were done regularly and a course of empirical antibiotic was started till the culture sensitivity report was received .The infected wounds were re examined once weekly for four weeks or more ,depending on the response of antibiotic ,if no response was seen ,pus/discharge was sent for AFB staining. In case of AFB positive ,pus was sent for culture in L J media to rule out mycobacterium tuberculosis.In case of sinuses in addition to above, excision of the sinuses tract were done and sent for histopathological examination.

**Result:**

Out of 150 laparoscopic surgeries ,142 were of laparoscopic cholecystectomy, 2 of laparoscopic appendectomy,and 6 of laparoscopic ovarian cystectomy .Only 8(5.3%) of patients developed port site infections ,of which 6 undergone laparoscopic cholecystcetomy and 1 underwent appendicectomy and another 1 underwent ovarian cystectomy .Superficial infection was seen 6 cases (75%) and deep infection seen in 2(25%) patients .All patients present with pus discharge,erythrema ,induration with mild tenderness but no fever .Nodule and discharging sinus were only seen in deep infections.The sinuses involved the muscle plane and did not involve the peritoneum.The infections did not respond to second or third generation cephalosporins.

The umbilical port through which all specimens were extracted ,shows infection in 5(62.5%) cases thus being the most frequent.The infection involving in epigastric port 2(25%) patients and both lateral port in 1(12.5%) patient.The operative findings in cases of port site infection

in laparoscopic cholecystectomies, appendectomies and ovarian cystectomies ,including acute cholecystitis in 2(25%),chronic cholecystitis with thick walled gall bladder in 4(50%) patients and acute appendicitis in 1(12.5%) and ovarian cyst in 1(12.5%) patient .In all patients with port site infection or without port site infection the operative time varied from 45-50minutes,except ovarian cystectomies where it was 50 -65 minutes .

Pus for culture was taken from both superficial and deep infection wounds .Culture and sensitivity done were negative for both gram positive and negative bacteria .AFB staining of the same pus was positive for acid fast bacilli.In culture done on LJ media , mycobacterium tuberculosis was isolated from all 8 cases of port site infections. Histopathology of the excised sinuses revealed typical granulomas formed of central caseation necrosis surrounded by epitheloid cells and lymphocytes.Langhans giant cells were also found.All the patients with port site infection recovered within 2-3 months of starting of first line anti TB drugs ,but the treatment was continued for six months.

**Table-1**

*Demography*

| Age (Year) | Male | Female |
|---|---|---|
| 20-40 | 22 | 50 |
| 41-60 | 19 | 32 |
| > 60 | 11 | 16 |

Demography shows that, young age group & female sex predominant.

**Table-2**

*Type of laparoscopic surgery (N=150)*

| Laparoscopic surgery | Male | Female | Numbers |
|---|---|---|---|
| Cholecystectomy | 51 | 91 | 142 |
| Ovarian cystectomy | 0 | 6 | 6 |
| Appendicectomy | 1 | 1 | 2 |
| Total | 52 | 98 | 150 |

Laparoscapic Cholecystectomy & female sex predominant.

**Table-3**

*Port site Mycobacterium Tuberculosis infection rate*

| Port | Frequency | Percentage |
|---|---|---|
| Umbilical port | 5 | 62.5% |
| Epigastric port | 2 | 25% |
| Lateral port | 1 | 12.5% |

Umbilical port site infection is predominant.

**Table-4**

| Procedure | N | Port site infection (%) | P Value |
|---|---|---|---|
| Laparoscopic Cholecystectomy | 142 | 6 (4.22%) | > 0.05 NS |
| Ovarian Cystectomy | 6 | 1 (16.66%) | > 0.05 NS |
| Appendectomy | 2 | 1 (50%) | > 0.05 NS |

P Value > 0.05 non significant.

**Discussion:**

On review of literature the incidence of port site infection has been seen to be variable,it has been reported as low as 2.3% from Israel[8] as high as 9.2% in cairo[9].In the present study it was recorded as 5.3% which is similar to the one reported by Waqar J Alam 5.7%(8)Den Hoed PT5.3%[10] ,slightly higher percentage has been reported by Shindholimath VV 6.3%[11]. The CDC classification of SSI categories these wound in two sub types superficial and deep. The superficial one include those involve skin and subcutaneous tissue ,where as deep one pertain to fascia, muscle and organ or space infection[12].In the present study the wounds predominantly belonged to the superficial category (75%).The percentage of deep infections extending in to muscle plane was (25%), which was similar the one reported by Waqar A Jan et al 2008[8].Overall it has been noted that port site infections are mostly restricted to superficial skin infection.The causative agents of these port site infections are mostly mycobacteria and it having been most reported in developing countries[9]. It is interesting to note that in the present study M tuberculosis was encountered in all port site infections.M tuberculosis has been reported to cause port site infection by Ramesh et al [13]. Nader A Elhamid et al 2012 in their study,report NTM in 4 cases out of 75.

The way of such type of port site tuberculosis infection generally occurs,

1). From an exogenous source, 2). From an endogenous source(secondary tuberculosis) 3). From a haematogenous source.

The most common practice of laparoscopic instruments "sterilization" in our country has been to immerse instruments in 2% glutaraldehyde for 20 min. Although sterilization is defined as "the complete elimination of all forms of microbial life". It is now widely agreed that 2% gluteraldedhde achieves high level of disinfection and not sterilization.

This has been further reinforced by Griffiths et al ,who have highlighted the failure of a 20 min instruments soak in 2% glutareldehyde to sterilize laparoscopic instruments[14].Another study, mycobacterium TB was present in one of five scopes after 45 min exposure.In present study the umbilical port showed infection in maximum case (62.5%) which is in conformity with the finding of Sasmal et al[15] , it is suggested by some authors that the port used for extraction of specimens is the most commonly involved port in infection because of spillage.Therefore the cause of infection seems to be exogenous and most probably the contaminated instruments. Time taken for all the surgeries in the present study was almost same hence this factors is not regarded to be involved in causing the infection in the present case.

**References:**


1. Cunnigaiper ND, Venkatraman S port site tuberculosis :Endogenous infection?Sung Infect(Larchmrt)2010;11:77-8.
2. Tauro LF, Satish RB ,Matris JJ,Divakar HS.port site tuberculosis :a rare complication following laparoscopic cholecystectomy .Indian J Surg.2005;67: 104-5.
3. Ramesh H, Prakash K,Lekha V, Jacob G,Venugopal A,Venugopal B,port site tuberculosis after laparoscopy:Report of eight case.Surg Endosc.2003;17:930-2.
4. Bhandrakar DS,Bhagwat S,Punjani R,por-site infection with mycobacterium chelonei following laparoscopic appendicectomy. Indian J Gastroenterol.2001;20:247-8.
5. Rahul Gupta,Arati Mahajan , Chaman Gupta.post per-cutaneous nephrolithotripsy nephrostomy site tuberculosis :a report of 6 cases . Urol Ann.2012;4(1):41-4.
6. William E G Thomas.Basic surgical skills and anastomoses .In Normans S William etal.fditors.Baily &Love's short practice of surgery.24th ed.London:Arnold 2004. pp118-32.
7. Horan TC ,Gaynes RP,Martone WJ,et al.CDC definitions of nosocomial surgical site infections,1992:A modification of CDC definitions of surgical wound infections, Infect control Hosp Epidemiol 1992; 13 : 606-8.
8. Waqar Aj,Sabir Ali I,et al.The frequency of port site infection following laparoscopic cholecystectomies.JPMI 2008;22:66-70.
9. Nader Abd-Elhamid ,Khaled Kasim, Anahtar Kelimeler.port site Non-tuberculous Mycobacterial Infection after Laparoscopic cholecystectomy:A case series.TAF Prev Med Bull 3013;12:481-484.
10. Den Hoed PT , Boelhourwer RU,Veen HF,et al.Infections and bacteriological data after laparoscopic and open gallbladder surgery.J Hosp Infect 1998;39:27-37.
11. Sharma AK,Sharma S,Sharma R,port site infection In laparoscopic surgeries.Indian Med Gazette 2013;224-29.
12. Centers of Disease Control and prevention.The National Healthcare Safety Network(NHSN) Manual:Patient safety component Atlanta ,GA:Division of Healthcare Quality Promotion.National Center for Emerging and Zoonotic Infection Disease Available from: URL : http:// www.cdc.gov/nhsn/acute-care-hospital/ index.html.2015.
13. Ramesh H,Prakash K,Lekha V,et al.port site tuberculosis after laparoscopy:report of eight cases .Surg Endosc 2003;17:930-32.
14. Griffith PA,Babb JR,Bradley CR,Fraise AP.Glutaraldehyde-resistant Mycobacterium chelonae from endoscope washer disinfectors.J Appl Microbial. 1997; 82:519-26.
15. Sasmal PK,Mishra TS,Rath S,et al.port site infection in laparoscopic surgery :A review of its management.WJCC 2015;3-18.

Chest Heart Journal
Vol. 42, No. 2, July 2018

## ORIGINAL ARTICLE

# Comparative Study between Sweet and Ivor Lewis Operation

**Mosharraf Hossain[1], Shiren sultana[2], Md Mofizur Rahman Mia[3], Manabendra Biswas[4], Zahidul Islam[5], Mohammad Lutfor Rahman[6].**

**Abstract**

*Importance Sweet esophagectomy is performed widely in China, while the Ivor-Lewis procedure, with potential benefit of an extended lymphadenectomy, is limitedly conducted owing to concern for a higher risk for morbidity. Thus, the role of the Ivor-Lewis procedure for thoracic esophageal cancer needs further investigation.*

***Objective:*** *To determine whether Ivor-Lewis esophagectomy is associated with increased postoperative complications compared with the Sweet procedure.*

*A randomized clinical trial was conducted from January 2015 to December 2016 at National Institute of Diseases of The Chest and Hospital and outside. 100 patients with resectable squamous cell carcinoma in the middle and lower third of the thoracic esophagus. Intent-to-treat analysis was performed.*

*Interventions Patients were randomly assigned to receive either the Ivor-Lewis (n=50) or Sweet (n=50) esophagectomy.*

*Main Outcomes and Measures the primary outcome of this clinical trial was operative morbidity (any surgical or nonsurgical complications). Secondary outcomes included oncologic efficacy (number of lymph nodes resected and positive lymph nodes), postoperative mortality (30-days and in-hospital mortality), and patient discharge.*

***Results:*** *resection without macroscopical residual (R0/R1) was achieved in 49 of 50 patients in each group. Although there was no significant difference between the 2 groups regarding the incidence of each single complication, a significantly higher morbidity rate was found in the Sweet group (21 of 50 [44%]) than in the Ivor-Lewis group (15 of 50 [30%]) (P =.04). More patients in the Sweet group (3 of 50 [6%]) received reoperations than in the Ivor-Lewis group (1 of 50 [2%]) (P=.04). The median hospital stay was 18 days in the Sweet group vs 16 days in the Ivor-Lewis group (P =.002). Postoperative mortality rates in the Ivor-Lewis (1 of 50) and Sweet (2 of 50) groups were 2% and 4%, respectively (P=.25). More lymph nodes were removed during Ivor-Lewis esophagectomy than during the Sweet procedure (22 vs 18, P <.001).*

***Conclusions and Relevance:*** *Early results of this study demonstrate that the Ivor-Lewis procedure can be performed with lower rates of postoperative complications and more lymph node retrieval. Ivor-Lewis and Sweet esophagectomies are both safe procedures with low operative mortalities.*

***[Chest Heart Journal 2018; 42(2) : 92-99]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019585*

1. Associate Professor, Thoracic Surgery, NIDCH, Dhaka, Bangladesh.
2. Ex Associate Professor, Gynae & Obs. Monnu Medical College, Manikganj, Dhaka, Bangladesh.
3. Associate Professor, Thoracic Surgery, NIDCH, Dhaka, Bangladesh.
4. Associate Professor, Thoracic Surgery, NIDCH, Dhaka, Bangladesh.
5. Registrar, Thoracic Surgery, NIDCH, Dhaka, Bangladesh.
6. Medical Officer, Thoracic Surgery, NIDCH, Dhaka, Bangladesh.

**Correspondence to:** Dr. Mosharraf Hossain, Associate Professor, Thoracic Surgery, NIDCH, Dhaka, Bangladesh.

**Submission on:** 5 May, 2018 **Accepted for Publication:** 25 June, 2018

Available at http.//www.chabjournal.org

**Introduction:**

Esophageal cancer is one of the most common lethal malignant diseases worldwide [1]. Surgery offers the best curative option; however, the optimal surgical technique is still under debate with regard to the surgical approaches and extent of lymphadenectomy. Controversy in the West exists between an extended transthoracic approach and a limited transhiatal esophagectomy[2,3] , In China, Sweet esophagectomy is widely performed through a single left-sided thoracic incision[4-6]. although it is criticized for inadequate lymphadenectomy in the upper mediastinum. However, the right-sided Ivor-Lewis procedure, while offering better visualization of the thoracic esophagus and thus facilitating an extended lymph node dissection, is performed less often because it is considered to be associated with more postoperative complications.[5]

Only a few retrospective studies to date have compared left- and right-sided thoracic esophagectomies and with controversial clinical outcomes regarding short-term complications and long-term survival[7-11] . In an attempt to answer this question, we undertook a randomized clinical trial to compare Ivor-Lewis esophagectomy with Sweet esophagectomy in patients with esophageal squamous cell carcinoma in the middle and lower third of the thoracic esophagus, assessing short-term outcomes of perioperative morbidity, mortality, and oncologic efficacy.

**Methods:**

**Study Design**

This study was a randomized multi-centre trial. Outcomes were assessed on the day of patient discharge. All patients enrolled provided written informed consent.

**Participants**

Oncological evaluation included upper gastrointestinal endoscopy with histologic examination, upper gastrointestinal barium swallow, computerized tomography of the chest and upper abdomen, and ultrasonography of the cervical region. Eligible patients included those with resectable disease (cT1-T3, N0-N1, and M0), no evidence of distant metastases (including the absence of histologically confirmed tumor-positive cervical or positive celiac lymph nodes), and histologically confirmed squamous cell carcinoma or high-grade dysplasia in the middle and lower thirds of the thoracic esophagus (inferior to carina and 3 cm superior to cardia). Exclusion criteria included age older than 75 years, presence of enlarged lymph nodes in the upper mediastinum 5<mm) history of other malignant disease, previous gastric or esophageal surgery, neoadjuvant chemotherapy or radiotherapy, severe major organ dysfunction.

Randomization

Eligible patients were randomly assigned to undergo either the Ivor-Lewis or Sweet procedures. Randomization, by the sealed envelope method, took place on the morning of the planned resection. Sealed envelopes were prepared and provided by the Department of Biostatistics.

**Surgery**

Surgery was performed by consultant thoracic surgeons. The surgical technique of both procedures has been described elsewhere[12,13]

Briefly, in the Sweet procedure, patients were placed in a right lateral decubitus position at an angle of 80°. A thoracic incision was performed through the sixth or seventh intercostal space. The diaphragm was incised to access and expose the abdominal cavity. The esophagus was mobilized and a gastric tube, about 4 cm in width, was placed along the greater curvature. The tumor was then resected with at least 5 cm of proximal clearance. Finally, an end-to-side esophagogastric anastomosis was fashioned with a circular staple at the sub- or supra-aortic level. Anastomosis with manual suture on the left side of the neck was performed in selected cases. A feeding tube was inserted in the jejunum and nasogastric tube positioned in the gastric tube.

In the Ivor-Lewis procedure, the patient was placed initially supine. Through an upper midline abdominal incision, gastric tubulization was completed and feeding jejunostomy performed. Then, the patient was positioned in the left lateral decubitus, and a right thoracotomy with a muscle-sparing incision was made in the fourth intercostal space. After ligating and dissecting

the azygos vein, the esophagus was resected. Then, the gastric tube was delivered into the thorax and a circular stapled end-to-side esophagogastric anastomosis was fashioned in the upper mediastinum. A nasogastric tube was also positioned in the gastric tube to prevent vomiting and acute gastric tube distension. It should be noted that thoracic duct ligation was routinely conducted in the Ivor-Lewis procedure but not in the Sweet procedure.

**Lymphadenectomy**

During the Sweet procedure, standard lymphadenectomy was performed, removing all lymph nodes in the middle and lower periesophageal portion, subcarinal region, lower posterior mediastinum, perigastric region, and those along the left gastric and splenic arteries. However, common hepatic and celiac nodes were not routinely removed owing to limited exposure through the left thoracic incision and rare metastases according to the map of lymph nodes metastases in our previous study for esophageal squamous cell carcinoma.[14] During the Ivor-Lewis procedure, total lymphadenectomy was performed including lymph nodes along the bilateral recurrent nerves and those resected during standard lymphadenectomy. All lymph nodes resected were labeled for pathologic examination according to anatomical sites.

**Postoperative Treatment**

Patients in both groups received similar postoperative care. Patients were extubated at the end of the procedure if physiologically stable, then admitted to the post-operative ward , and finally discharged the next day to a general surgical ward. In the first 3 days after surgery, patient-controlled epidural analgesia was the main postoperative pain-control system. On postoperative day (POD) 1, patients were encouraged to move out of bed, and enteral nutrition was commenced via feeding tube. Contrast swallow, not routinely but optionally, was performed on POD 5 or 6. Patients were given sips of clear liquids on POD 7, soft solid foods on POD 8, and discharged routinely on POD 9 or 10.

Data of postoperative complications were collected prospectively, and data regarding tumor size, histologic type, tumor penetration, lymph node metastases, and TNM stage were obtained from the pathologic records.

**Outcomes**

The primary outcome of this study was operative morbidity. Secondary outcomes included oncologic efficacy and postoperative mortality.

Postoperative complications included anastomotic leak (identified clinically or radiographically); respiratory complications (defined as clinical manifestation of pneumonia or bronchopneumonia confirmed by computed tomographic scan); cardiovascular complications (defined as persistent arrhythmia requiring medical treatment); chylothorax (defined as the appearance of milky fluid from thoracic drains after onset of enteral nutrition); wound infections; and other complications (delayed gastric emptying, pleural effusion, recurrent nerve injury). Postoperative mortality was defined as death from any cause.

**Statistical Analysis**

We used power analysis and sample-size software for sample-size calculation. Previous data indicated a 15% difference in 3-year survival between the Sweet (35%) and Ivor-Lewis (50%) procedures[11,15-17] .With an estimation of 10% loss of follow-up. To reduce the proportion of loss of follow-up, we included 50 patients for each group. The ÷2 or Fisher exact tests were used to compare categorical data and the t test or Mann-Whitney U test for continuous data. All analyses were performed with the statistical package SPSS (SPSS 16.0(P 05< was considered statistically significant.

**Results**

Characteristics of the Patients

From January 2015 to December 2016. 100 eligible patients were randomly assigned to receive either the Ivor-Lewis (n =50) or Sweet (n =50) esophagectomy at National Institute of Diseases of The Chest and Hospital and outside. Baseline demographics and clinicopathologic characteristics, including age, sex, comorbidities (hypertension, diabetes mellitus, and heart disease), and tumor site, of the 2 groups were comparable.

**Table-I**
*Basic patients Characteristics and clinical data*

| Characteristic | Group No.(%) | | P Value |
|---|---|---|---|
| | Sweet(n-50) | Ivor-Lewis(n-50) | |
| Age, Median(range) | 60(39-74) | 60(38-74) | .56 |
| Sex | | | |
| Male | 41(82) | 39(78) | .25 |
| Female | 9(18) | 11(22) | |
| Comorbidity, No(%) | | | |
| Hypertension | 9(18) | 13(26) | .76 |
| Heart disease | 2(4) | 1(2) | .45 |
| DM | 3(6) | 4(8) | .45 |
| Total | 14(28) | 18(36) | .49 |
| Tumor site | | | |
| middle | 28(56) | 32(64) | .13 |
| lower | 22(44) | 18(36) | |
| Histology | | | |
| High grade Dysplasia | 2(4) | 1(2) | |
| Squamous cell carcinoma | 47(94) | 48(96) | .30 |
| Small cell carcinoma | 1(2) | 1(2) | |

Table-1 shows Basic patients Characteristics and clinical data

**Table-II**
*Histological parameters*

| Parameter | Group No.(%) | | P Value |
|---|---|---|---|
| | Sweet (n-50) | Ivor-Lewis (n-50) | |
| Tumor Staging | | | |
| Tis | 3(6) | 1(2) | |
| T1a | 2(4) | 3(6) | .40 |
| T1b | 8(16) | 8(16) | |
| T2 | 10(20) | 15(30) | |
| T3 | 24(48) | 22(44) | |
| T4 | 3(6) | 1(2) | |
| Nodal Status | | | |
| N0 | 27(54) | 28(56) | |
| N1 | 21(42) | 20(40) | .93 |
| N2 | 1(2) | 2(4) | |
| N3 | 1(2) | 0 | |
| TNM Staging | | | |
| 0 | 2(4)) | 1(2) | |
| I | 7(14) | 9(18) | .64 |
| IIA | 18(36) | 18(36) | |
| IIB | 6(12) | 8(16) | |
| IIIA | 14(28) | 11(22) | |
| IIIB | 2(4) | 2(4) | |
| IV | 1(2) | 1(2) | |

Table 2 shows Histological parameters

**Table-III**

*Post-operative outcomes*

| Outcome | Group No.(%) | | P Value |
|---|---|---|---|
| | Sweet (n-50) | Ivor-Lewis (n-50) | |
| Operative time, mean(SD), min | 174(35) | 202(38) | <.001 |
| Hospital Stay, Median(Range) | 18(10-90) | 16(10-60) | .002 |
| Post-operative complication | | | |
| Pulmonary infection | 5(10) | 4(8) | .56 |
| Cardiac complication | 7(14) | 5(10) | .49 |
| Pleural Effusion | 3(6) | 2(4) | .71 |
| Chylothorax | 2(4) | 1(2) | .20 |
| Anastomotic leakage | 2(4) | 1(2) | .10 |

Table-3 shows Post-operative outcomes

**Table-IV**

*Number of Lymph Node resected.*

| Region | Group No.(%) | | P Value |
|---|---|---|---|
| | Sweet (n-50) | Ivor-Lewis (n-50) | |
| Mediastinum | | | |
| Upper | 0(0-10) | 1(0-15) | |
| Middle | 2(0-16) | 3(0-16) | <.001 |
| Lower | 1(0-15) | 1(0-10) | |
| Middle/Lower | 5(0-16) | 4(0-15) | |
| Celiac | 0(0-10) | 1(0-14) | <.001 |

Table 4 shows Number of Lymph Node resected.

**Morbidity and Mortality**

Postoperative mortality did not differ significantly between the 2 cohorts (2 of 50 [4.0%] in the Sweet vs 1 of 50 [2%] in the Ivor-Lewis group. In the Sweet group, 2 patients died of respiratory failure secondary to pulmonary infections. In the Ivor-Lewis group, only 1 patient died of cerebrovascular accident.

Although operating time was significantly longer in the Ivor-Lewis than in the Sweet groups (mean [SD], $202^{38}$ minutes vs $174^{35}$ minutes, respectively; (P<001) the hospital stay was significantly shorter for patients who underwent the Ivor-Lewis esophagectomy (median, 18 days in the Sweet group vs 16 days in the Ivor-Lewis group; P = .002). The incidences of anastomotic leakage, chylothorax, and pulmonary infections were numerically, but not significantly, higher in the Sweet group. There was no significant difference with regard to other postoperative complications. However, a significantly higher morbidity rate was found in patients who underwent Sweet esophagectomy (21 of 50 [42%]) than those who underwent Ivor-Lewis esophagectomy {15 of 50(30%)}.

**Lymphadenectomy**

Because we lacked the data on circumferential involvement, the percentage of R0 resection was unavailable. Resection without macroscopical residual (R0/R1) was achieved in 49 of 50 patients (98%). A significantly higher number of lymph nodes was retrieved in the Ivor-Lewis group (median, 22; range, 8-56) compared with the Sweet group (median, 18; range, 3-51; P <.001). We further classified lymph node groups according to dissection area. The Ivor-Lewis

procedure showed superiority in the dissection of lymph nodes both in the upper mediastinum and areas around the common hepatic and celiac arteries, whereas the number of lymph nodes retrieved in the middle/lower esophagus and perigastric regions was similar between the 2 groups (Table 4). Consequently, more patients in the upper mediastinum had positive lymph nodes following the Ivor-Lewis procedure (06 of 50 (12.0%) than the Sweet procedure 2 of 50 (4%) (P<.001) Three cases in the Ivor-Lewis group had positive celiac nodes, although there was no significant difference in this area (Table-4).

**Discussion:**

Esophagectomy is among the surgical procedures with the highest incidence of complications[19,20]. Although Ivor-Lewis esophagectomy is advocated by the Chinese Anti-Cancer Association,[18] a left posterolateral approach with limited lymphadenectomy remains a priority in China given the debate on the extent of lymphadenectomy necessary and, more importantly, concern about the Ivor-Lewis esophagectomy being associated with higher postoperative complications. However, our study has demonstrated that patients in the Ivor-Lewis group experienced a lower incidence of in-hospital morbidity and shorter hospital stay compared with those in the Sweet group, although operative time was somewhat longer. Importantly, our trial showed significantly better lymph node resection in the Ivor-Lewis procedure than in the Sweet esophagectomy.

The overall incidence of patients having at least 1 postoperative complication was 35% in our trial. Although the incidence of each complication did not differ significantly between the 2 groups, more patients in the Sweet group did experience postoperative complications than in the Ivor-Lewis group. This higher incidence of morbidity in the Sweet group was associated with a higher rate of reoperations and longer hospital stay.

A variety of factors, including advanced age, preexisting poor pulmonary function, poor performance status, smoking status, and, notably, surgical approach, were believed to be related to respiratory problems.[21] In our trial, no patient in the Sweet group underwent surgery through the combined thoracoabdominal approach, in consideration of potentially increased postoperative pain with costal cartilage incision. This may explain our lower incidence of pulmonary complications than that in published reports.[22] Although the incidence was comparable between the 2 groups in our trial, we prefer the Ivor-Lewis procedure because of more lymph nodes being resected. During the Sweet procedure, division of the diaphragm and 1-lung anesthesia throughout the operation may also contribute to pulmonary problems. Of note, no Ivor-Lewis group patient died of pulmonary complication, whereas death was due to pulmonary complication in 2 following Sweet esophagectomy.

Anastomotic leakage is an important issue in the management of surgical complications because it can be fatal. The rate of leakage in our series was lower than that in many other series using a similar intrathoracic stapling technique[17,22,23]. High surgeon volume may be an important factor for this lower incidence.[24,25]Although there was no significant difference, more patients in the Sweet group experienced anastomotic leakage. We note that the Ivor-Lewis procedure was our preferred approach and more widely performed during the period of this study. The Sweet approach was our major surgical approach prior to 2006, during which time our chief surgeons performed at least 50 Sweet esophagectomies. Hence, the comparison is valid. Importantly, no death in this trial was related to anastomotic leakage. Early identification, clear thoracic and mediastinal drainage, and sometimes reoperation for drainage seem to be of most importance in the avoidance of additional severe complications.

Cardiovascular events and other minor complications, including wound infection, pleural effusion, and delayed gastric emptying, were also comparable between the 2 groups. Although the incidence of persistent recurrent nerve injuries can be biased because none received laryngoscopy in the postoperative period, strict criteria of patient selection contributed to this low incidence. Only patients without enlarged lymph nodes in the upper mediastinum <5 mm in diameter were enrolled so that the possibility of recurrent nerve injury was reduced during upper mediastinal lymphadenectomy.

Although the distribution of TNM stages was similar between the 2 groups, stage migration may still be a consideration owing to inadequate lymphadenectomy during the Sweet procedure. Lymph nodes in 2 regions were always omitted during Sweet esophagectomy: those along bilateral recurrent nerves in the upper mediastinum due to anatomical limitation by the aortic arch and lymph nodes along the common hepatic and celiac arteries in the upper abdomen because we chose a single left-sided thoracic approach for the Sweet procedure, which resulted in poor exposure in these regions. Although abdominal lymphatic involvement was rare, involvement in the upper mediastinum was common.14 In this study, 06 of 50 (12.0%) patients in the Ivor-Lewis group showed positive lymph nodes along bilateral recurrent nerves. This implies that the more extensive lymph node resection of the former procedure was needed to remove more potential positive lymph nodes, thus offering better tumor staging. With regard to the current question on the extent of lymphadenectomy, future follow-up of this trial may clarify the long-term benefits of the extended lymphadenectomy using the Ivor-Lewis procedure.

One limitation of this study was that we did not evaluate postoperative functional status and therefore cannot comment in detail on quality of life following surgery. Moreover, pulmonary complications may be reduced if a left thoracoabdominal approach is performed with the diaphragm incised at its periphery, thus preserving its innervation. However, because of what is widely done in China and considering potentially increased wound complication and postoperative pain, we chose the left-sided thoracic approach with the diaphragm incised vertically in this study.

**Conclusions:**

Our data provide evidence for the superiority of the Ivor-Lewis esophagectomy over the Sweet procedure with regard to short-term outcomes such as lymph node retrieval and overall morbidity for patients with squamous cell cancer in the middle and lower third of the thoracic esophagus. Further follow-up may elucidate whether the Ivor-Lewis procedure also has an advantage in disease control and long-term survival.

**References:**

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;90(2): 61-69.
2. Omloo JM, Lagarde SM, Hulscher JB, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg. 2007; 992-1000(6)246.
3. Hulscher JB, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002; 1662-1669(21)347.
4. Liu JF, Wang QZ, Ping YM, Zhang YD. Complications after esophagectomy for cancer: 53-year experience with 20,796 patients. World J Surg. 2008;32(3):395-400.
5. Chen SB, Weng HR, Wang G, et al. Surgical treatment for early esophageal squamous cell carcinoma. Asian Pac J Cancer Prev. 2013;6:3825-3830.
6. Song PI, Liang H, Fan JH, Wei WQ, Wang GQ, Qiao YL. Long-term survival after esophagectomy for early esophageal squamous cell carcinoma in Linxian, China. J Surg Oncol. 2011;104(2):176-180.
7. Launois B, Paul JL, Lygidakis NJ, et al. Results of the surgical treatment of carcinoma of the esophagus. Surg Gynecol Obstet. 1983;156(6):753-7601.
8. Yu Y, Wang Z, Liu XY, Zhu XF, Chen QF. Therapeutic efficacy comparison of two surgical procedures to treat middle thoracic esophageal carcinoma. World J Surg. 2010;34(2):272-276.
9. Fu SJ, Fang WT, Mao T, Chen WH. Comparison of surgical outcomes after different surgical approach for middle or lower thoracic esophageal squamous cancer [in Chinese]. Zhonghua Wei Chang Wai Ke Za Zhi. 2012;15(4):373-376.
10. Suttie SA, Li AG, Quinn M, Park KG. The impact of operative approach on outcome of surgery for gastro-oesophageal tumours. World J Surg Oncol. 2007;5:95.
11. Luo KJ, Fu JH, Hu Y, et al. Efficacy of surgical resection of left and right

transthoracic approaches for middle thoracic esophageal squamous cell carcinoma [in Chinese]. Ai Zheng. 2009;28(12):1260-1264.

12. Fujita H, Sueyoshi S, Tanaka T, et al. Optimal lymphadenectomy for squamous cell carcinoma in the thoracic esophagus: comparing the short- and long-term outcome among the four types of lymphadenectomy. World J Surg. 2003;27(5):571-579.
13. Li B, Guo Q, Yang H, et al. Left thoracoabdominal approach in surgical treatment of adenocarcinoma of the esophagogastric junction in the Northern Henan Province of China. Dig Surg. 2011;28:2-8.
14. Li B, Chen H, Xiang J, et al. Pattern of lymphatic spread in thoracic esophageal squamous cell carcinoma: a single-institution experience. J Thorac Cardiovasc Surg. 2012;144(4):778-785.
15. Page RD, Khalil JF, Whyte RI, Kaplan DK, Donnelly RJ. Esophagogastrectomy via left thoracophrenotomy. Ann Thorac Surg. 1990;49(5):763-766.
16. Stilidi I, Davydov M, Bokhyan V, Suleymanov E. Subtotal esophagectomy with extended 2-field lymph node dissection for thoracic esophageal cancer. Eur J Cardiothorac Surg. 2003;23(3):415-420.
17. Chen G, Wang Z, Liu XY, Liu FY. Recurrence pattern of squamous cell carcinoma in the middle thoracic esophagus after modified Ivor-Lewis esophagectomy. World J Surg. 2007;31(5):1107-1114.
18. Mao YS, He J, Xue Q, et al. Nationwide speaking tour of standardized diagnosis and treatment for esophageal cancer [in Chinese]. Zhonghua Wei Chang Wai Ke Za Zhi. 2013;16(9):801-804.
19. Lerut T, Nafteux P, Moons J, et al. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. Ann Surg. 2004;240(6):962-972.
20. Biere SS, van Berge Henegouwen MI, Maas KW, et al. Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial. Lancet. 2012;379:1887-1892.
21. Ferguson MK, Celauro AD, Prachand V. Prediction of major pulmonary complications after esophagectomy. Ann Thorac Surg. 2011;91(5):1494-1500.
22. Gillies RS, Simpkin A, Sgromo B, Marshall RE, Maynard ND. Left thoracoabdominal esophagectomy: results from a single specialist center. Dis Esophagus. 2011; 24(3):138-144.
23. Ott K, Bader FG, Lordick F, Feith M, Bartels H, Siewert JR. Surgical factors influence the outcome after Ivor-Lewis esophagectomy with intrathoracic anastomosis for adenocarcinoma of the esophagogastric junction: a consecutive series of 240 patients at an experienced center. Ann Surg Oncol. 2009;16(4): 1017-1025.
24. Derogar M, Sadr-Azodi O, Johar A, Lagergren P, Lagergren J. Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study. J Clin Oncol. 2013;31(5):551-557.
25. Lai FC, Chen L, Tu YR, Lin M, Li X. Prevention of chylothorax complicating extensive esophageal resection by mass ligation of thoracic duct: a random control study. Ann Thorac Surg. 2011;91(6): 1770-1774.

Chest Heart Journal
Vol. 42, No. 2, July 2018

## ORIGINAL ARTICLE

# Effect of Therapeutic Exercise of Upper Extremity in COPD patients

**Pervin S [1], Amin MR[2], Kabir J[3], Rahman A[4], Khan MH[5] , Islam MS[6] , Jahan R[7], Habib RB[8], Happy BD[9]**

**Abstract:**

***Background and Objective:*** *Chronic obstructive pulmonary disease is one of the major causes of mortality and morbidity in the world. This study aim to determine the effects of home based upper extremity exercises in patients with Chronic Obstructive Pulmonary Diseases.*

***Methods:*** *Experimental study was performed with 30 COPD Patients, they were selected based on the inclusion and exclusion criteria and randomly assigned to 2 groups. All the participants were explained about the study in which Chest expansion measurement was assessed by using inch tape at 3 levels, dyspnea level was graded by using Modified Borg scale, Wellbeing and activity of daily life score was assessed by using CAT questionnaire and those was performed as a pre-test and same tests were repeated as post-test after the training session for a period of 4 weeks. Group A participants were taught to perform the exercise and asked to do at home for 5 days a week for total duration of 4 weeks. Group B - Control group was treated with thoracic mobility exercise, repetition -3sets/10rep and frequency -7days per week.*

***Results:*** *Group A: chest expansion measurements at all 3 levels were improved in post-test compared to pre- test and Group A is higher when compared with Group B. Dyspnea score were reduced in Group A compared to Group B and wellbeing, activity of daily living score improved in both groups, Group A was higher compared to Group B ($P < 0.05$, statistically significant).*

***Conclusion:*** *This study proven that home based upper extremity exercise are effective in improving chest expansion, reduced dyspnea and improved quality of wellbeing and activity of daily living.*

***Keywords:*** *Chronic obstructive pulmonary disease (COPD), Dyspnea, Therapeutic exercise.*

***[Chest Heart Journal 2018; 42(2) : 100-106]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019586*

1. Assistant Professor, Department of Physical Medicine & Rehabilitation, NIDCH, Dhaka, Bangladesh.
2. Associate Professor and Head, Department of Physical Medicine & Rehabilitation, NIDCH, Dhaka, Bangladesh.
3. Medical Officer. Gynae & Obs Department, Dhaka Medical College Hospital, Dhaka, Bangladesh.
4. Associate Consultant, Anesthesia Department, Imperial Hospital, Chittagong, Bangladesh.
5. Assistant Professor, Physical Medicine & Rehabilitation Department, NITOR, Dhaka, Bangladesh.
6. Assistant professor & RP, NIDCH, Dhaka, Bangladesh.
7. Professor, Respiratory Medicine, NIDCH, Dhaka, Bangladesh.
8. Epidemiologist, Junior Consultant, Pediatrics, DGHS, Dhaka, Bangladesh.
9. Medical Officer, Physical Medicine & Rehabilitation Department, NINS, Dhaka, Bangladesh.

**Correspondence to:** Dr. Sanjida Pervin, Assistant Professor, Department of Physical Medicine & Rehabilitation, NIDCH, Dhaka, Bangladesh. Mobile: +8801911620771.Email: sanjida.pervin26@gmail.com.

**Submission on:** 7 May, 2018 **Accepted for Publication:** 18 June, 2018
Available at http.//www.chabjournal.org

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) represents an important public health challenge that is both preventable and treatable. Many people's suffer from this disease for years, and die prematurely from it or its complications. COPD is a lung disease characterized by chronic airflow limitation of the airways, which can be prevented but cannot be cured. COPD mainly caused by cigarette smoking; air pollution is also considered a risk factor in many developing countries which contributes the disease to both gender whereas COPD is more commonly observed in long term smokers of middle age. The disease symptoms add on the co-morbidities with the age and also due to smoking[1]. COPD is a major cause of mortality and morbidity in the world[2] and it is currently the 4$^{th}$ leading cause of death in world[3]. Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of population[4]. Individual with COPD are illustrated with various other problems like nutritional deficits, cardiovascular disease, diabetes, osteoporosis. Whereas disease progresses with major changes including airway obstruction, increased dyspnea, hyperinflation, reduced lung functions[5], and peripheral muscle weakness[6] is more predominant which leads to fatigue of the patient when performing their daily activities. Increased chest wall resistance and stiffness causes respiratory muscles tightness and further contributes to mechanical disadvantage of respiratory muscles[7]. Major complaints of COPD are dyspnoea and fatigue especially while doing their routine activities with the use of their upper limbs like combing hair[8]. Dyspnoea during these activities may be due to the irregular and superficial breathing pattern forced by the mechanical effects of arm during arm elevation. Physical activity level is lowered especially when patients use the upper limbs without any support, as well some upper limb muscles such as the sternocleidomastoid and upper trapezius diminish their participation in ventilation as they are recruited to help with the postural support of the arms[1]. Hereby it alters the mechanics of rib cage and abdominal compartments. Generally, accessory muscles are inactive during inspiration at rest in healthy individuals and they act vigorously during physical activity in COPD, ultimately during activities with upper limb, accessory muscles become ineffective in respiration as they perform their major action to sustain the shoulder girdle in position as a consequence, the respiratory work is shifted to the diaphragm which is already at a mechanical disadvantage in patients with COPD[9]. Usage of upper limbs play a major role in daily activities, normal subjects usually perform such activities without noticing the energy lost, but patients with COPD report tiredness when performing them[1]. There is evidence that physical activity is decreased in COPD patients[10]. This leads to a downward spiral of inactivity which predisposes patients to reduce quality of life, increased rates of hospitalization and mortality[11-13]. Disease creates a burden for the sufferers and for the society as the natural history of the disease is progression to disability and death from respiratory failure at a relatively early age[14]. Both upper and lower extremity muscle are impaired in individual with COPD, muscle weakness does not affect all the muscles. As some studies report that quadriceps is more affected than upper limb muscles due to under usage of lower limb among COPD. Whereas strength of upper limb muscles such as pectoralis major, latissimusdorsi, biceps and middle deltoids is also impaired restricting the movement of upper extremity which further limits the thoracic expansion among the COPD[1]. For these reasons upper extremity resistance training is required to enhance the functional performance of upper limbs in daily care. Upper extremity resistance training is also the part of pulmonary rehabilitation. The basic need for this study is to provide the ease of treatment for the patients with COPD; it is difficult for the patients to travel on regular basis to the hospital for exercises, for that reason the patients were taught a simple exercise that enhances their performance in activity of daily living. Hence purpose of this study is to provide a home based upper extremity exercises for the patients with COPD.

## Methods:

Experimental study was performed with 30 Subjects randomly assigned to 2 groups. Group

A (Experimental group) and Group B (Control Group). Study was performed at National Institute of Diseases of the Chest & Hospital, Dhaka. All the participants were explained about the study by providing information sheet and Informed consent signed by all the participants prior to initiation of the study. Both male and female Subjects with Mild to Moderate COPD based on GOLD classification, Age group between 30-65 years, Ex-smoker and those with dyspnoea are included. Subjects are excluded if they are known to have Restrictive lung disease, recent thoracic surgery, unstable vital signs, unstable hypertension, Musculoskeletal and neurological disease involving upper limb and thorax. Both the group participants underwent assessment, As a pretest they are assessed for Chest expansion at 3 levels – axillary level, 4th intercostals level and xiphisternal level using inch tape and dyspnoea grade was noted using Borg scale and their wellbeing and activity of daily life score assessed using CAT questionnaire. All these tests were repeated for post test following the treatment period for 4 weeks. Group A- 15 participants were asked to perform Upper extremity exercises at home. All the participants were taught to perform the exercise in OPD and exercise protocol was clearly explained and they were given an exercise regimen chart, and recording chart to follow the frequency of the exercise in which they are asked to record the date whenever the exercise is performed. Participant was asked to come to OPD once in a week along with the recording chart which was verified. Upper extremity exercise includes.

*Shoulder front raise with weight*

Patient was asked to hold 1 liter water bottle in hands in erect standing posture. Then asked to raise the hands in front of thighs with palms in a neutral position, without bending elbows with co-ordinate breathing exercise. (ie, inspiration during lifting up the hand and expiration during lowering the hand down) and then lower the weights.

*Shoulder lateral raise with weight*

Patient was asked to hold 1 liter water bottle in hands in erect standing posture. Then asked to raise the hands in front of thighs with the top of each weight pointed away, and then lift arms up by sides without bending elbows with co-ordinate breathing exercise.(i.e., inspiration during lifting up the hand and expiration during lowering the hand down), then lower the arms.

*External rotators with weight*

Patient should be positioned in supine lying by holding 1 liter water bottle with the shoulder abducted to $90^0$ and the elbow bent to $90^0$, so the hand points to the roof, patient should rotate the shoulder joint externally so that the hand moves backwards and the palm faces the roof along with co-ordinate breathing exercise.

*Internal rotators with weight*

Patient should be positioned in supine lying by holding1 liter water bottle with the shoulder abducted to $90^0$ and the elbow bent to $90^0$, so the hand points to the roof. Patient should rotate the shoulder joint internally so that the hand moves forwards and the palm faces the floor along with coordinate breathing exercise.

*Shoulder shrugging exercise*

Patient should stand upright, arms should be fully extended to the waist, feet shoulder width apart and head looking forwards, shrug the shoulders up as high as possible, and patient should pause at top of the movement and then relax back down along with co-ordinate breathing exercise.

**Treatment Protocol**

- Resistance\weight - 1 liter water bottle.
- Frequency-5days per week for a period of 4 weeks.
- 1 session per day.
- 8 to 10 repetitions \ 3 sets.
- Intensity - Borg scale, Rate of perceived exertion of 12-14.
- Total duration for upper extremity exercise is 30 minutes per day same for all the exercises.

*Group B*

Group B - Control group was treated with thoracic mobility exercise with a repetition of 3sets/10rep and frequency-7days per week.

*Thoracic mobility exercises*

Position of the subject: Sitting.

Procedure: the patient should exhale while bending forward to touch the floor with arms crossed at the feet then the patient should extend up while taking a deep inspiration and lift the arm up with a frequency of 7days per week and 3 sets of 10 repetitions.

Position of the patient: standing.

Procedure: The patient should stand with his knees straight, the patient instructed to exhale while bending forward to touch the floor with arms; then the patient should extend up by lifting his hands simultaneously taking a deep inspiration. 10 repetitions/ set – 3 sets with a frequency of 7 days per week. Both the groups will be advised to continue their normal activity and follow their inhalers and medications prescribed by the chest physicians

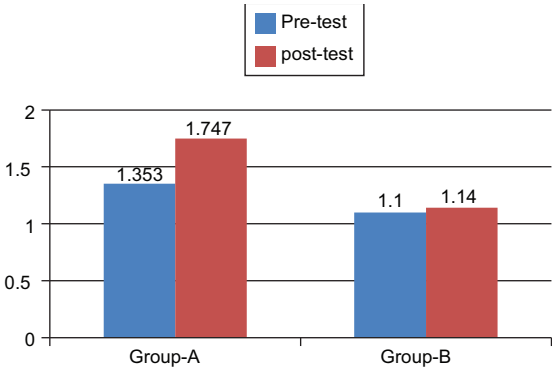



**Fig.-1:** *Comparison of pre test and post test values of Chest expansion measurements at Axillary level for Group A& Group B.*

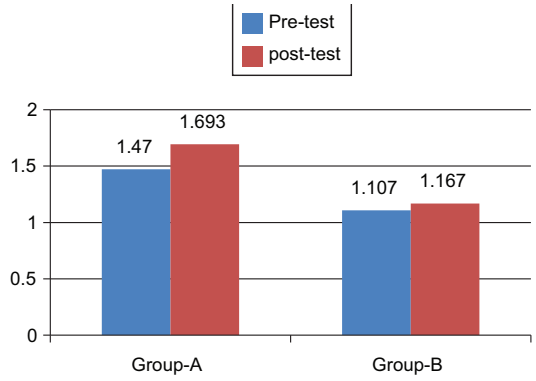



**Fig.-2:** *Comparison of pre test and post test values of Chest expansion measurements at 4th Intercostal level for Group A& Group B.*

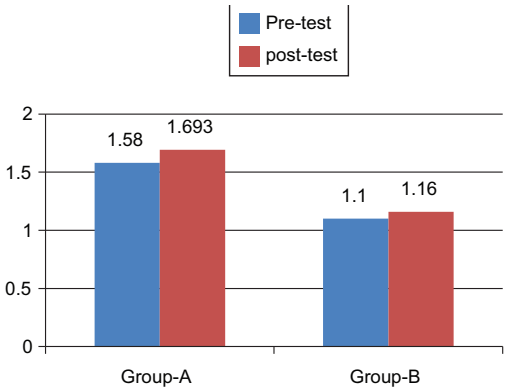



**Fig.-3:** *Comparison of pre test and post test values of Chest expansion measurements at Xiphi sternal level for Group A & Group B.*

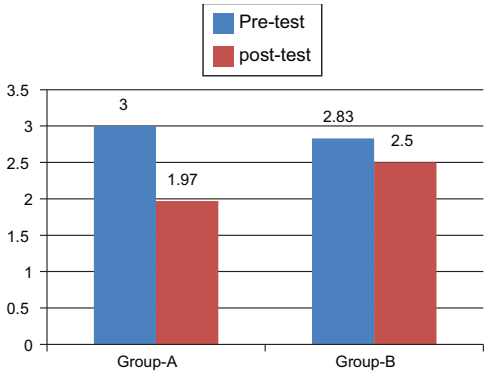



**Fig.-4:** *Comparison of pre test and post test values for Modified Borg scale between Group A and Group B.*

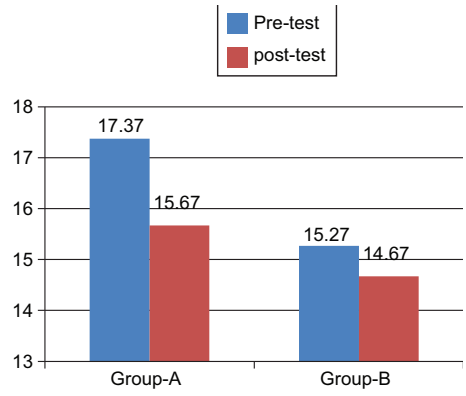



**Fig.-5:** *Comparison of pretest and post test values of CAT questionnaire between Group A & Group B.*

| Test | Group-A | | | | Group-B | | | |
|---|---|---|---|---|---|---|---|---|
| | Mean | | Standard deviation | | Mean | | Standard deviation | |
| | Pre | Post | Pre | Post | Pre | Post | Pre | Post |
| Modified Borg Scale | 3.00 | 1.97 | 1.195 | 1.157 | 2.83 | 2.50 | 1.358 | 1.296 |
| CAT questionnaire | 17.33 | 15.67 | 3.885 | 3.395 | 15.27 | 14.67 | 3.173 | 3.222 |

In this unpaired t test df 28 at 5% level of significance, in the table critical value is 1.70. Test statistics (2.55) is greater than critical value (1.70). So, $P < 0.05$

Table1: Comparison of pre test and post test values between Group A and Group B for Modified Borg scale and CAT questionnaire.

**Results**

The collected data was used for statistical analysis, Paired 't' test was used to compare the data of pre and post within the groups for chest expansion measurement. Wilcoxon rank test was used to compare the data of pre and post within the groups for Borg's scale and CAT questionnaire. Independent 't' test was used to compare the data between the groups for chest expansion measurement. Mann whiteny U test was used to compare the data between the groups for Borg scale and CAT questionnaire. Graph 1 shows the difference in pre test and post test values between Group A and Group B for chest expansion measurement at axillary level. Group A difference in pre and post values are greater than Group B. Graph 2 shows the difference between Group A and Group B in pre test and post test values at 4th Intercostal level and similar difference was seen in xiphisternal level shown in Graph 3. Graph 2 & 3 shows higher difference between pre and post test values of Group A. Graph 4 given that Dyspnea score rated with Modified Borg scale was comparatively lower in post test than pre test which shows that dyspnea is reduced well in group A than Group B also seen in Table 1. Graph 5 shows the wellbeing and activity of daily living score which improved in post test in both groups. Whereas score is higher in group A compared to group B, shown in Table 1($P < 0.05$).

**Discussion**

COPD is the commonest heterogeneous pulmonary condition and it is the major cause of morbidity and mortality among the pulmonary patients. This disease is usually characterised by dyspnea, and a small proportion of excessive secretions particularly during exacerbation[15]. COPD patients also develop peripheral muscle dysfunction that further contributes to exercise intolerance. These impairments limit the independence of the patient in daily life and simple activities of daily care becomes difficult and it affects the health related quality of life[16]. COPD patients poorly tolerate activities involving upper limb compared to lower limb. Upper limb movements are associated with ventilatory strategies thereby it increases metabolic demand it has been observed that at arm elevation at rest significantly decreased vital capacity and functional residual capacity[17]. But during upper limb activities arm fatigue is reported as a common limiting symptom. Supported upper limb activity increases the functional residual capacity due to the passive stretch of thoracic muscles imposed on the rib cage when the arms are raised with weights it strengthens the upper limb muscles[1] and concluded that supported arm activity improves the endurance and quality of life[17]. Stefaniacostie et al stated that unsupported upper extremity exercise results in ventilator constraints, concluded that more studies are recommended to prove the benefits of supported arm exercise and unsupported upper extremity exercise, whereas unsupported arm exercise may determine progressive restriction of the activities performed with the arm, where the diaphragm is functionally compromised[18]. Thereby our study performed with supported arm exercises along with co-ordinated breathing exercise that reduces the rate of dyspnoea and improves the ability to perform the arm activities without restriction. Sarah Bernard et al described the effects of Aerobic and strength training in patients with COPD and concluded that the combination of strength training in

aerobic training showed significant improvement in patients with COPD[19]. Unsupported arm exercise poses a unique challenge for patients with COPD, because upper limb muscles acts as accessory muscle for respiration. During arm activities the participation of accessory muscles in ventilation decreases and shifts the respiratory work to diaphragm due to which activities with upper limb in daily living becomes difficult. Further it causes thoracoabdominaldyssynchrony. It has been proved that upper limb exercise training improves work capacity and endurance and reduces oxygen consumption during workload[20]. Ganesan et al reviewed the effects of upper extremity exercises in COPD and reported that arm strength training should be included in pulmonary rehabilitation protocol and it showed that unsupported arm training improved arm endurance capacity in majority of people with COPD. And arm training positively influenced peak arm exercise capacity, metabolic and ventilatory demands and also improved activities of daily living[21]. For these reason this study focuses on upper extremity exercises which helps and encourages thoracic movements and expands the thoracic cage and also strengthens the upper limb muscles which eases the way to perform daily activities by reducing the rate of dyspnoea increasing the chest expansion and improving the wellbeing and activity of daily living.

**Conclusion:**

From the results, this study concludes that home based upper extremity exercise are effective in improving chest expansion, reduced dyspnea and improved quality of wellbeing and activity of daily living. Thereby this study recommends the need to involve the upper limb exercises as a part of rehabilitation program. Pulmonary Rehabilitation is appropriate for patients with COPD and it should be considered part of integrated patient management.

**References:**

1. Tania Janaudis-Ferreira. Strategies for exercise assessment and training in patients with chronic obstructive pulmonary disease. Umea University Medical Dissertations, New Series No 1360.2010: 1- 68.
2. Andre Nyberg. Assessing the effect of high repetitive single limb exercise on exercise capacity and quality of life in patients with chronic obstructive pulmonary disease (COPD): study protocol for randomized controlled trial. Trial.2012; 13:114.
3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859): 2095-128.
4. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLOS Med 2006; 3(11): e442.
5. Annemarie L Lee, Anne E Holland. Time to adapt exercise training regimens in pulmonary rehabilitation – a review of the literature.International journal of COPD.2014; 9: 1275-1288.
6. C.J. Clarke, L.M. Cochrane, E. Mackay, B. Paton. Skeletal muscle strength and endurance in patients with mild COPD and the effects of weight training.EurRespir J. 2000; 15: 92-97.
7. Carla Malaguti, Rafaella R Rondelli, Leandra M de Souza, Marcia Domingues, Simone Dal Corso. Reliability of chest wall mobility and its correlation with pulmonary function in patients with chronic obstructive pulmonary disease.Respiratory Care. 2009; 54(12): 1703-1711.
8. Marcelo Velloso, Sergio Garcia Stella, Sonia Cendon, Antonio Carlos Silva, Jose R. Jardim. Metabolic and ventilator parameters of four activities of daily living accomplished with arms in COPD patients. Chest.2003; 123: 1047-1053.
9. Dirceu Costa, Karina Maria Cancelliero, Daniela IKE, Thais Lima Laranjeira, Camila Bianca FalascoPantoni, Audrey Borghi Silva. Strategy for respiratory exercise pattern associated with upper limb movements in COPD patients. CLINICS. 2011; 66(2): 299-305.
10. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics

of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005; 171(9): 972-7.

11. Watz H, Pitta F, Rochester CL, et al. An Official European Respiratory Society statement on physical activity in COPD. Eur Respir J 2014; 44(6): 1521-37.
12. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax 2006; 61(9): 772-8.
13. Yohannes AM, Baldwin RC, Connolly M. Mortality predictors in disabling chronic obstructive pulmonary disease in old age. Age ageing 2002; 31(2): 137-40.
14. Kenji Shibuya, Colin D Mathers, Alan D Lopez. Chronic Obstructive Pulmonary Disease (COPD): Consistent Estimates of Incidence, Prevalence, and Mortality by WHO Region. Global Programme on Evidence for Health Policy.World Health Organization.2001; 1-28.
15. Jane Cross. Chest physiotherapy during an acute exacerbation of chronic obstructive pulmonary disease. Chronic respiratory disease. 2012; 9(2): 73-75.
16. Tania Janaudis Ferreira, Kylie Hill, Roger S Goldstein, Priscila Robles Ribeiro, Marla K. Beauchamp, Thomas E Dolmage, et al. Resistance arm training in patients with COPD. A randomized controlled trial.Chest. 2011; 139(1): 151-158.
17. Thomas E Dolmage, Luigi Maestro, Monica A Avendano, Roger S Goldstein. The Ventilatory response to arm elevation of patients with chronic obstructive pulmonary disease.Chest. 1993; 104(4): 1097-1100.
18. Stefaniacosti, Mauro Di Bari, Paolo Pillastrini, Roberto D'Amico, Ernesto Crisfulli, CinziaArletti, et al. Short-term Efficacy of upper extremity exercise training in patients with chronic airway obstruction: A systematic review. Physical Therapy. 2009; 89(5): 443-455.
19. Sarah Bernard, Francois Whittom, Pierre Leblanc, Jean Jobin, Roger Belleau, Chantal Berube, et al. Aerobic and strength training in patients with chronic obstructive pulmonary disease.Am J RespirCrit Care Med. 1999; 159: 896-901.
20. Subin, VaishaliRao, V. Prem, Sahoo. Effect of upper limb, lower limb and combined training on health related quality of life in COPD.Lung India. 2010; 27(1): 4-7.
21. GanesanKathiresan, Senthil Kumar Jeyaraman, JayachandranJaganathan. Effect of upper extremity exercise in people with COPD. J Thorac Dis. 2010; 2: 223- 236.

Chest Heart Journal
Vol. 42, No. 2, July 2018

*ORIGINAL ARTICLE*

# Outcome of Mechanical Ventilation in Criticaly ILL Patients

**Md. Sayedul Islam[1], Nihar Ranjan Saha[2], Subrata Gain[3], Sanjoy Kumar Kar[4], Snehashis Nag[5]**

**Abstract:**

***Method:*** *This is a prospective study carried out during the period of Nov" 2006 to Nov 2007 in a modernized private hospital, Dhaka. The patients were admitted to ICU after primary assessment that they may need organ support or life support and all the patients fulfilled the complete code of ICU. Patients who were weaned and extubated and subsequently shifted to ward were considered good outcome and adverse who cannot be extubated, if they died, or sought discharge against medical advice.*

***Result:*** *Total number of patient admitted were 844 during this period. Male and female ratio was 16:9 and the mean age for the ventilated patients was 52±SD (10.25). Among them, 370 (43.68%) patients needed artificial respiration by mechanical ventilation in the course of their management. Among the ventilated patients 199(52.45%) has successful weaning, 5(1.35) needed tracheostomy, 171 (46.25%) expired. The rate of survival from ventilator support is statistically significant, P value is < .05.*

***Conclusion:*** *Mechanical ventilation is a very effective measure in the course of management of critically ill patients when there is definite indication. This single centred study must be justified with other large scale study from different worldwide.*

***[Chest Heart Journal 2018; 42(2) : 107-112]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019587*

## Introduction:

The concept of artificial respiration was recognized in the 16th century by Vesalius and it is the 20th century that mechanical ventilation became a widely used therapeutic modality1. Over the past decade, there has been an explosion of new ventilatory techniques that present a bewildering array of alternatives for the treatment of patients with respiratory failure.

Respiratory support for respiratory failure can be given through lung in intubated or tracheostomised patient as positive pressure ventilation .This support can also be given through the devices not primarily applied to the lung, such as extra corporeal membrane oxygenation (ECMO)2,3, extracorporeal carbon dioxide removal (ECCO2R)4 or intravascular blood gas exchanger (IVOX)5

The main objectives of mechanical ventilation are to support pulmonary gas exchange, to increase lung volume & to decrease the WOB. All these necessities can be obtained by setting up different mode of ventilator & by adjustment of different parameters appropriate for a particular clinical setting.

This is a long process consisting of endotracheal intubation, appropriate use of sedative or

1,2. Associate Professor Respiratory Medicine, NIDCH, Bangladesh.

3,4,5 Regitrar, Respiratory Medicine. NIDCH, Bangladesh.

**Correspondence to:** Dr. Md. Sayedul Islam, Associate Professor Respiratory Medicine, NIDCH, Bangladesh. Cell: 01552390582, E mail: drsayedul@ gmail.com

**Submission on:** 11 May, 2018 **Accepted for Publication:** 17 June, 2018

Available at http.//www.chabjournal.org

paralyzing agents, ventilator setting, monitoring & an artistic process of weaning. All these events pass through the risk of complication & many adverse situations.

Mechanical ventilation is not a curative measure for the disease entity but it is the life support during which primary disease should be treated vigorously. It is the gold standard support for the respiratory failure patients6. As the process is not without hazards it should not be used until there is clean cut indication.

Objectives of the study:

To show the effectiveness of this supportive system.

To change the attitude towards its use.

To improve the overall awareness

**Study procedure:**

This prospective study carried out during the period of Nov" 2006 to Nov 2007 in a modernized private hospital, Dhaka. The patients were admitted to ICU after primary assessment that they may need organ support or life support and all the patients fulfilled the complete code of ICU

**Indications for mechanical ventilation:**

Severe dyspnoea using accessory muscle of respiration & features of exhaustion.

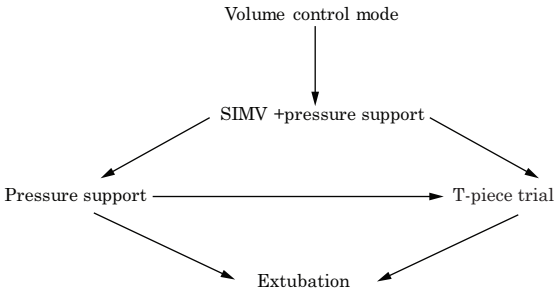
Life threatening hypoxemia (Pao2 < 50).

Severe acidosis PH < 7.25.

Respiratory arrest.

Increase Pco2 with change of mental status.

For all the patients having definite indication of mechanical ventilation a written consent was taken from the close relative after proper counseling. The patients were sedated properly, pain killer and paralytic agents were used as necessary. Intubation was done very carefully with maintaining all precaution. Then it was connected to the mechanical ventilation with appropriate setting. When the patients were improving, support is at baseline, then the process of weaning started following the below mentioned protocol




**Results:**

This pie chart below shows that total 844 patients were admitted to the ICU during that period. Among them 370(43.68%) patients needed mechanical ventilation. This indicates that a significant bulk of patients needed mechanical ventilation and mechanical ventilation is a main supporting system in the ICU which will by time to treat the primary disease.

Total patients distribution:

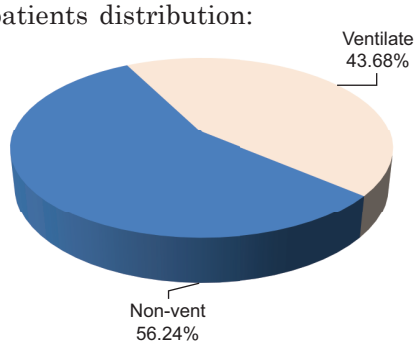



**Fig.-1:** *Patients with mechanical ventilation versus without ventilation*

**Demographic profile;**

Among the 370 patients ventilated patients 236 (64%) were male and 134(36%) were female. The number of male patien is significantly higher than the female. Pvalue is >.05. This indicates that male patients are more hospitalized than female getting priority in the treatment in our culture and also valueable in socio-economic perspective.

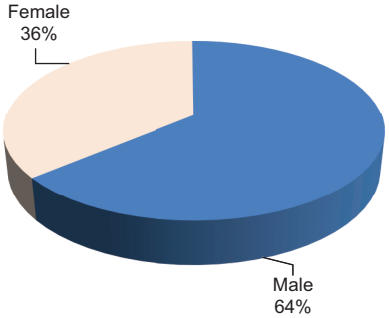



**Fig.-2:** *Demographic profile; Sex distribution of study population*

Age distribution of the patients shows that majority of patients were>60 years(48.64%) and mean age were 52±(SD 10.34). This distribution is shown in the Bar graph.

Mean Age = 52± SD(10.34)

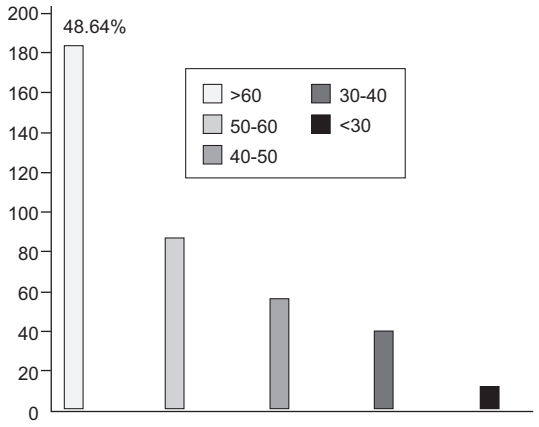



**Fig.-3:** *Demographic profile; Age distribution of study population*

**Distribution of disease profile requiring ventilation**

This pie chart below shows that 37.17% patients were CVD complicated with respiratory failure, 11.65% patients were CKD complicated with respiratory failure, next bulk of patients were septisemia 11.23%. and respiratory failure due to pulmonary disease were 9.15. As this was an general ICU, CVD patients with poor GCS were more in number admitted through emergency department. Septicemia and ARDS patients requiring organ support are also required ventilation 11.23%.

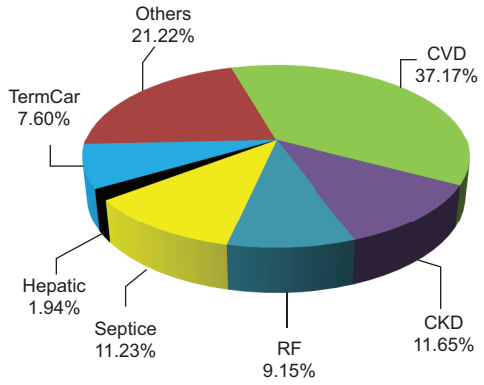



**Fig.-4:** *Distribution of patients according to disease profile*

This bar graph below shows the out come of ventilated patients and nonventilated patients in ICU. Out of 370 ventilated patients 199(52.45%) improved and 171( 46.25%) patients died. Non ventilated patients 298(87.6% ) improves and 52 ( 15.2% ) died. In the ventilated patients 52% improved with discharge from hospital and 46% expired. The difference between improvement and death was not statistically significant ( P value>.05% ). This means that improvement and death rate in ventilated patients is nearer to equal. Total 134(15.85%) out of 844 patients left the ICU either signing DAMA or DNR

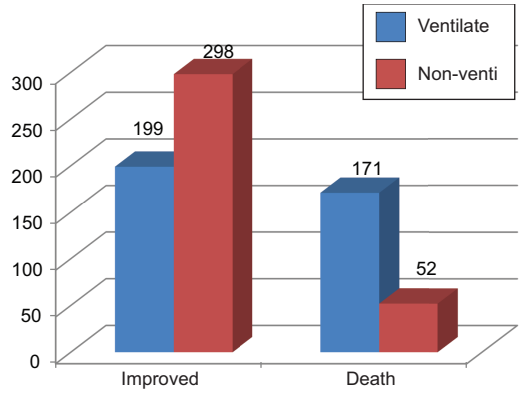



**Fig.-5:** *Outcome of ventilated patients in ICU*

This bar chart below shows the disease wise outcome of ventilated patients. It shows that in patients with respiratory disease required ventilation has highest outcome (97.22%). Among the respiratory disease respiratory failure due to acute exacerbation of COPD and Asthma predominant. ARDS , diffuse parenchymal lung disease having MOF shows moderate outcome. Next to respiratory disease CKD was with good outcome (61.36%)

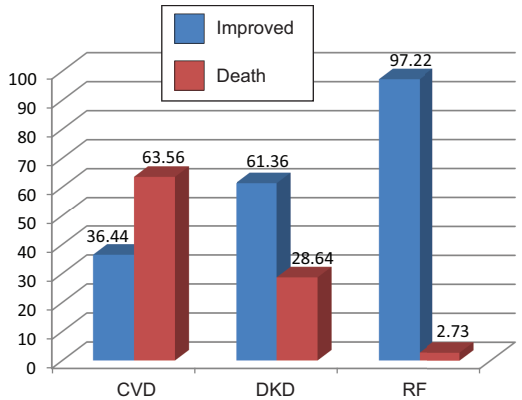



**Fig.-6:** *Disease wise outcome of ventilated patients*

**Outcome of ventilation in respiratory diseases:**

This bar graph below shows the outcome of ventilation in lung disease which was better than any other disease causing respiratory failure. Data showed 97.33% of patients were successfully extubated and discharge home in stable condition and death occured only in 2.77%. This is statistically significant P value<.01. a few 6.2 % of patients needed tracheostomy for prolong intubation but majority of them successfully weaned from mechanical ventilation.

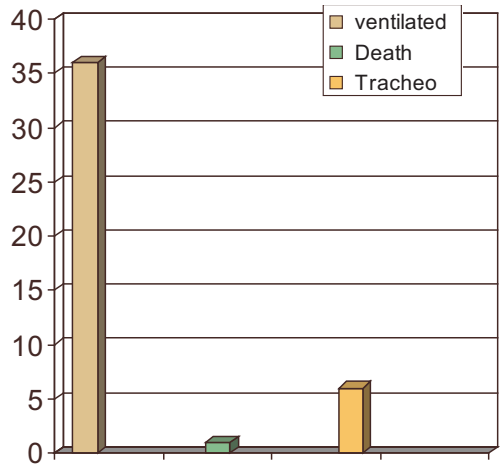



**Fig.-7:** *Outcome of ventilation in respiratory diseases.*

**Discussion:**

This prospective study done in the department of ICU in a specialized private hospital in Dhaka, Bangladesh to see the overall outcome of ventilation support, to see the negative prediction for the outcome and to alleviate the fear of mechanical ventilation. It was observed from the study that male patients(64%) are more than female(36%). This may be due to the fact that male are socially more important than female in contest of our society and more adhere to even in costly treatment. It was also observed that most of the patients were elderly and most of the patients have multiple diseases that are age related co-morbid illness.

In the year November 2016 to November 2017 total 844 patients were admitted to the ICU Among them 370 patients received mechanical ventilation , with an average of 8 ventilation day for each patient. For those who were mechanically ventilated199(52.45%) patients survive to ICU and hospital discharge 171 patients expired and Hospital mortality rate was 46.25%.

Note worthy, ventilation was used in370(43.68%) patients who were deemed irrecoverable as confirmed by very poor vitals and unstable hemodynamic parameter;

And fulfilling the criteria of intubation. Out of which 171(46.25%) died in the average 8 days of intubation. Mortality rate would have been modest in our study.if there had been joudicious admission criteria as seen in studies which excluded patients deemed irrecoverable from the selection criteria

Out of 370 patients on mechanical ventilation AKI on CKD(11.65%), sepsis (11.25%) and neurological causes (37.17%) accounting for nearly 90% of total cases in need of invasive mechanical ventilation. Only 9.15% patients had a respiratory pathology. Cases with respiratory cause and other causes like poisoning or unknown causes were associated with relatively less mortality 2.77%; whereas sepsis, neurological, renal, hepatic causes and malignancy were associated with ~*75% mortality. Absence of significant dysfunction in other organ system and the potentially reversible nature of bronchospasm may explain their better survival. This is contrary to other studies where most of the admissions were due to pneumonia and chronic obstructive pulmonary disease[7]. This finding also differs from other studies performed in rural India where poisoning and envenomation were leading causes of high mortality[8].

Factors like age and comorbidities are also independently associated with hospital mortality. Patients enrolled in the study were a decade older than other Indian studies (52±SD10.25 vs 43±SD12.43 years). In fact, in some studies, patients enrolled were much younger[9]. The finding in this study correlates with studies in which increasing age is independently associated with hospital mortality[10,11,12]. Male cases accounted for more than half of the patients in the present study; however, various studies have shown that the gender was not independently associated with

hospital mortality. In the present study, comorbidities like CKD, cardiac diseases like CAD, diabetes and hypertension were found to be significantly associated with mortality and these findings were in line with other published studies[13].

In addition, elevated serum urea and creatinine levels were observed in the study indicating altered kidney functions in patients on IMV. It is noteworthy that most of the cases placed on IMV had acute kidney injury. Also CKD was the commonest comorbidity reported. In these patients, early dialysis could have led to improved outcome. This is also another invasive management which most patients decline to avail. ABG had an important role in determining acid base status in patients on IMV. Metabolic acidosis is a finding in sepsis, renal failure, shock and diabetes. In our study decreased partial pressure of oxygen and low bicarbonate levels along with low pH suggested metabolic acidosis. Findings were in line with other studies which show that abnormal kidney function and acid–base imbalance indicated poor prognosis[13,14].

There should be effective 'team communication which is a simple and the easiest way to help improve outcomes in an open ICU[15-15]. In addition, the most important aspect in developing countries is, timely screening of patients in the outpatient department and need for an early referral to a tertiary care facility should be considered a priority to improve outcome of ventilation patient.

**Conclusion:**

Increasing number of critically ill elderly patients are admitting to ICU & getting ventilation support. Outcome is affected to some extend by age which is also reflected by APACHE II score. Success rate is significant & increasing day by day due to development of newer ventilation strategy. So the rational use is recommended. It is the gold standard therapy for RF when needed.

**Reference:**


1. Arthur S. Slutsky History of Mechanical Ventilation. From Vesalius to Ventilator-induced Lung Injury. AJRCCM. 2015; 191:10
2. Toomasian JM, Schreiner RJ, Meyer DE, Schmidt ME, Hagan SE, et al. A polymethyl pentene fiber gas exchanger for long-term extracorporeal life support. ASAIO J.2005; 51: 390-397.
3. Chung M, Shiloh AL, Carlese A. Monitoring of the adult patient on venoarterial extracorporeal membrane oxygenation. Sci World J. 2014: 1-10.
4. Gattinoni L, Agostoni A, Pesenti A et al. Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO2. Lancet. 1980; 2:292–294
5. Gasche Y[1], Romand JA, Prêtre R, Suter. PM IVOX in ARDS: Respiratory effects and serious complications Eur Respir J. 1994 ;7(4):821-3.
6. P J .Papadakoe, B Lachman. Mechanical ventilation: clinical application and pathophysiology. In chapter four, text book of Critical care medicine. Sounder publication 2008; 262-1
7. R.P. Gonzalez, G.R. Cummings, H.A. Phelan, M.S. Mulekar, C.B. Rodning. Does increased emergency medical services pre-hospital time affect patient mortality in rural motor vehicle crashes? A statewide analysis. Am J Surg,2009;197: 30
8. B. Karthikeyan, T. Kadhiravan, S. Deepanjali, R.P. Swaminathan. Case-mix, care processes, and outcomes in medically-III patients receiving mechanical ventilation in a low-resource setting from Southern India: a prospective clinical case series. PLoS ONE.2015;10 (8) : 1-16
9. C.S. Vora, N.D. Karnik, V. Gupta, M.Y. Nadkar, J.V. Shetye. Clinical profile of patients requiring prolonged mechanical ventilation and their outcome in a tertiary care medical ICU. J Assoc Physicians India,2015: 63; 14-19
10. O.W. Luhr, K. Antonsen, M. Karlson, the ARF Study Group, *et al.* Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and

Iceland. Am J Respir Crit Care Med,1999: 159; 1849-1861

11. C.E. Behrendt Acute respiratory failure in the United States. Chest,2000: 118; 1100-1105
12. T. Steiner, G. Mendoza, M. De Georgia, *et al.* Prognosis of stroke patients requiring mechanical ventilation in a neurological critical care unit.Stroke,1997: 28; 711-715
13. L.C. Azevedo, M. Park, J.I. Salluh, A. Rea-Neto, V.C. Souza-Dantas, P. Varaschin, *et al.* Clinical outcomes of patients requiring ventilatory support in Brazilian intensive care units: a multicenter, prospective, cohort study. Crit Care,2013: 17 (2); R63
14. A.A. Jeffrey, P.M. Warren, D.C. Flenley. Acute hypercapnic respiratory failure in patients with chronic obstructive lung disease; risk factors and use of guidelines for management. Thorax 1992: 47 ;34
15. U.G. Ludwigs, S. Baehrendtz, M. Wanecek, *et al.* Mechanical ventilation in medical and neurological disease: 11 years of experience. J Intern Med 1991; 229: 117-124
16. P.J. Pronovost, D.C. Angus, T. Dorman, K.A. Robinson, T.T. Dremsizov, T.L. Young Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. JAMA 2002: 288; 2151-2162

Chest Heart Journal
Vol. 42, No. 2, July 2018

## *ORIGINAL ARTICLE*

# Blood eosinophils and inhaled corticosteroid/long acting $\beta_2$ agonist efficacy on Quality of life and COPD exacerbation rate in Stable Chronic Obstructive Pulmonary Diseases

**Md. Shahjada Tabrez[1], Md. Mahabubur Rahman[2], Mahboba Akther[3], Mohammed Kamrul Hasan[4], Md. Ali Hossain[5],Bashir Ahmed[5], Md. Abdur Rouf[5], Bipul Kanti Biswas[6], Liaquat Ali[7], Kazi Saifuddin Bennoor[8]**

**Abstract:**

***Background:*** *COPD patients with increased airway eosinophilic inflammation show a favorable response to inhaled corticosteroids (ICS) in combination with a long-acting bronchodilator(LABA). Thus, this study investigated the effect of 3-months treatment with Inhaled Corticosteroid/long-acting beta2-agonist (LABA) in stable COPD patients with high blood eosinophils with an improvement in quality of life and reduction of COPD exacerbation rate.*

***Methods:*** *It was a interventional study conducted at the outpatient department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka from which 80 stable COPD patients were selected. Baseline blood eosinophils level was measured of all patients and randomly assigned to 12-weeks treatment withSalmeterol/fluticasone proprionate inhaler (ICS/LABA) 25/250 mgin group A and Salmeterol 25mg in group B. Subjects began 3-month ICS/LABA treatment after washout period. Subjective measurement of symptoms by COPD assessment test (CAT) score were done in initial visit and during follow up at $4^{th}$ ,$8^{th}$ and $12^{th}$ week. Among all , 29 patients in group A and 28 patients in group B came up to final follow-up.*

***Results:*** *In this study, Mean COPD Assessment Test (CAT) score change between two group in first visit was 1.53 ($p<0.01$), at second visit 1.45 ($p<0.05$) and at final visit was 2.06 ($p<0.05$). Differences were statistically significant.CAT score decreases in consecutive 3 follow up than baseline record in both group.CAT score with baseline records between group A and group B showed statistically significant differences ($p=<0.05$).Thus, patients with eosinophilia, ICS-based therapy was associated with significant improvements in CAT scores and lower incidence of acute exacerbation (3.45% vs 7.14% ) compared with bronchodilator (BD) therapy alone.*

1. Medical Officer, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh.
2 . Medical Officer, NIDCH), Mohakhali,Dhaka, Bangladesh.
3. MD Phase B Resident (Neonatology), BSMMU, Shahbag, Dhaka, Bangladesh.
4. MD (Chest Diseases) Final Part Student, NIDCH, Mohakhali, Dhaka, Bangladesh.
5. Professor of Respiratory Medicine, NIDCH, Mohakhali, Dhaka, Bangladesh.
6. Associate Professor, Respiratory Medicine, NIDCH,Mohakhali, Dhaka, Bangladesh.
7. Professor of Biochemistry and Cell Biology, BUHS, Mirpur, Dhaka, Bangladesh.
8. Assistant Professor of Respiratory Medicine, NIDCH, Mohakhali, Dhaka, Bangladesh.

**Correspondence to:** Dr. Md. Shahjada Tabrez, Medical Officer, MU-7, National Institute of Diseases of the Chest & Hospital (NIDCH), Mohakhali, Dhaka, Bangladesh. Cell: 01915478978, e-mail: dr_shahjada@yahoo.com

**Submission on:** 10 May, 2018 **Accepted for Publication:** 28 June, 2018
Available at http.//www.chabjournal.org

***Conclusions:*** *High blood eosinophils are associated with improved lung function after 3-months ICS/LABA treatment in COPD patients. So, in combination with age and baseline lung function parameters, blood eosinophils may be a possible biomarker for identification of COPD patients with favorable response to ICS/ LABA treatment.*

***Key words:*** *COPD, Eosinophil, Inhaled corticosteroid, COPD Assessment Test (CAT) score.*

***[Chest Heart Journal 2018; 42(2) : 113-119]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019588*

**Introduction:**

COPD is a progressive inflammatory disorder that is characterized by persistent airflow limitation[1]. It affects approximately 10% of adults over 40 years of age and is the fourth leading cause of death worldwide[2]. Although most COPD guidelines advocate the use of inhaled corticosteroids (ICS) for only those with frequent exacerbations, in real clinical practice, they are widely used especially in combination with a long-acting beta2- agonist (LABA)[3]. Because only a small fraction of COPD patients are responsive to ICS-based therapy[4], identifying characteristics associated with ICS-responsiveness is crucial for clinicians to make therapeutic decisions. Although neutrophils are thought to play a prominent role in the pathogenesis of COPD[5], Christenson et al[6] recently reported that eosinophilia and T helper type 2 (Th2) inflammation might also play a significant role in a subset of patients with COPD and that approximately 20% of smokers with COPD have a Th2-high signature. This result is consistent with previous findings that airway eosinophilic inflammation is not uncommon, but is present in approximately 20%–40% of COPD patients[5]. Inhaled corticosteroids (ICS) are an important treatment for COPD[1]. Exacerbations, defined as acute worsening of symptoms necessitating treatment with antibiotics and/or systemic corticosteroids or hospitalization, are a key determinant of COPD morbidity, mortality and healthcare costs[7]. Compared with placebo, ICS such as fluticasone propionate (FP) and budesonide reduce exacerbations by up to 20% as monotherapy, and up to 30% in combination with a long-acting $\beta_2$-agonist (LABA)[8]. National and international guidelines on the management of COPD[1] recommend that patients with COPD at risk of exacerbations receive ICS/LABA maintenance therapy. A predictive marker for ICS/LABAeffectiveness in preventing COPD exacerbations could aid clinical decision-making by identifying patients likely to gain the most beneût from ICS-based treatment. Blood eosinophil count may provide such a marker. Studies have demonstrated associations between airway eosinophilia and exacerbations of chronic bronchitisand COPD[9]. Exacerbations are heterogeneous, presenting as one of four distinct phenotypes, and airway eosinophilia in the stable state was found to be predictive of subsequent exacerbation phenotype[10]. The use of systemic corticosteroids in patients experiencing acute exacerbations of COPD has shown greater beneût in patients with a blood eosinophil level of ≥2% versus those with <2%[11]. There is also evidence for an association between airway eosinophilia with response to systemic corticosteroids for quality of life[11]. A recent retrospective analysis of data from two parallel 1-year studies of once-daily ICS/LABA, ûuticasone furoate (FF)/vilanterol (VI) in patients with moderate-to-very severe COPD showed a greater reduction of moderate and severe exacerbations in patients with a blood eosinophil level ≥2% vs <2% when treated with ICS/LABA compared with LABA alone[12].Thus this study is designedto investigate the potential of blood eosinophil level as a marker for the efûcacy of ICS/LABA on quality of life and prevention of exacerbations in stable COPD patients. The relationship between dyspnea and quality of life in COPD has previously been indicated in a few studies[13]. Perceived dyspnea was shown to have a greater impact on health-related quality of life than spirometric or functional measurements in these patients[14]. In an international study, the most frequently reported symptom was dyspnea (78%)and the most frequent complaint reported by patients with COPD was daily activity limitation[15]. Hajiro, et al.[13] showed that dyspnea is one of the main determinations of disease specific health related quality of life, and has moderate to strong correlations with impairments in the health related quality of life in patients with COPD. On the other hand, quality of life measurements did not correlate well with the severity of airflow limitation[16].

Furthermore, factors such as dyspnea, depression, anxiety and exercise tolerance were found to be more correlated with health status than the widely used spirometric values[16]. The CAT was developed as a short validated COPD-specific questionnaire for assessing the impact of COPD on health status. It provides a reliable measure of overall COPD severity from the patient's perspective, independent of language[17]. It is not a diagnostic tool; its role is to supplement information obtained from lung function measurement and assessment of exacerbation risk[17]. The relative frequency of severe exacerbations within these patients was shown to be higher in patients with higher CAT scores. We observed that the increase of exacerbation frequency was parallel to the increase of CAT scores. Additionally, CAT scores were the same in males and females, and were not influenced by age[18].

**Methods:**

This was an interventional study. COPD Patients attending outpatients department(OPD), National Institute of disease of the chest and Hospital during the study period from November, 2016 to October, 2017 for the treatment and follow up, were the study population and those fulfilling the inclusion and exclusion criteria were enrolled as study sample by purposive sampling. Patients of more than 40 years of age with history of smoking, post bronchodilator FEV1/forced vital capacity (FVC)<70%, pre-treatment blood eosinophil count >5% and absence of feature of acute exacerbation for last one month were included whereas patients having any cardiac diseases or long term oxygen therapy were excluded. 80 stable COPD patients were selected and randomly assigned to 12-weeks treatment with Salmeterol/fluticasone proprionate inhaler (ICS/LABA) 25/250 mg in group A(n=40) and Salmeterol 25 mg in group B(n=40). They were evaluated by taking history, examined thoroughly and Spirometry was done to confirm the diagnosis, in addition to the other necessary baseline investigation (including Chest X-ray PA view, CBC with ESR, Serum bilirubin, Serum creatinine, sputum for AFB, Electrocardiography etc.). Baseline peripheral blood eosinophil count, Spirometry along with other clinical data were obtained after cessation of the fol-lowing respiratory medications: an ICS for 2 weeks, an inhaled LABA, or long-acting muscarinic antagonist for 2 days, an inhaled short-acting $\beta_2$-agonist or inhaled short-acting antich-olinergic for 12 hours. After 2 weeks of washout period, all patients with baseline eosinophil count >5% were allocated to 'Group-A' and 'Group-B' by simple randomization. Each subject were treated with fixed-dose combination of ICS and LABA (25¼g salmeterol/ 250¼g fluticasone) along with conventional therapy for COPD twice daily for the following 3 months in group A and only with conventional therapy for COPD for the following 3 months in group B.All patients were assessed at monthly for 3 months by CAT score and compared with the baseline values to see the outcomes. De-worming was done by albendazole for every patient.Total 23 patients had lost to follow up. All the information were properly documented in the prescribed forms. Data were processed manually and analyzed with the help of SPSS (Statistical package for social sciences) Version 21.0.

*Eosinophilia :* Eosinophils constitutes up to 5% total leukocyte count in blood. So, differential count of blood eosinophil more than 5% regarded as higher eosinophil count or eosinophilia[18].

**Results:**

**Table-I**

*Comparison between the effect of salmeterol/fluticasone proprionate and salmeterol on CAT score at the end of the first visit(4th week). (N=57; n1=29, n2=28)*

| CAT score | Group AMean(±SD) | Group BMean(±SD) | P-value |
|---|---|---|---|
| Initial | 16.26(±1.32) | 16.08 (±1.14) | $>0.05^{NS}$ |
| First visit | 14.42(±1.08) | 15.77(±1.03) | $<0.05^{S}$ |
| P-value | $<0.001^{S}$ | $>0.05^{NS}$ | |

P-value reached from unpaired and paired t test.
Group A = Salmeterol/fluticasone proprionate 25/250µg; Group B = Salmeterol 25¼g
S: Significant NS: Not significant
*CAT Score Decrease means improvement of symptoms.
The mean difference of CAT score of initial and 1st follow up record in Group A shows statistically significant difference (p <0.01).

**Table-II**

*Comparison between the effect of salmeterol/fluticasone proprionate and salmeterol on CAT score at the end of the second visit (8th week). (N=57; n1=29, n2=28)*

| CAT score | Group AMean(±SD) | Group BMean(±SD) | p-value |
|---|---|---|---|
| Initial | 16.26(±1.32) | 16.08(±1.14) | >0.05$^{NS}$ |
| Second visit | 13.99(±1.07) | 15.26(±1.01) | <0.01$^{S}$ |
| P-value | <0.001$^{S}$ | >0.05$^{NS}$ | |

P-value reached from unpaired and paired t test.
The mean difference of CAT score of initial and 2nd follow up record of both Group A and B shows statistically significant difference (p <0.001).

**Table-III**

*Comparison between the effect of salmeterol/fluticasone proprionate and salmeterol on CAT score at the end of the third visit (12th week). (N=57; n1=29, n2=28)*

| CAT score | Group AMean(±SD) | Group BMean(±SD) | P-value |
|---|---|---|---|
| Initial | 16.26(±1.32) | 16.08 (±1.24) | >0.05$^{NS}$ |
| Third visit | 13.28(±1.36) | 15.16(±1.06) | <0.001$^{S}$ |
| p-value | <0.001$^{S}$ | >0.05$^{NS}$ | |

P-value reached from unpaired and paired t test.
The mean difference of CAT score of initial and 3rd follow up record of both Group A and B shows statistically significant difference (p = <0.001$^{S}$)

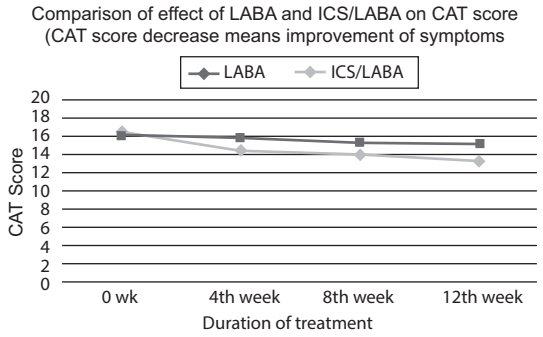



**Fig.-I:** *Comparison between the effect of salmeterol/fluticasone proprionate and salmeterol on CAT score.*

**Table-IV:** *Effect of drugs on risk measurement among groups during study period (N=57; n1=29, n2=28).*

| Group | Exacerbation occured | Exacerbation not occurred | EER | CER | RR | NNT |
|---|---|---|---|---|---|---|
| Group A | 1(a) | 28 (b) | 0.03 | 0.07 | 0.42 | 25 |
| Group B | 2 (c) | 26 (d) | | | | |

EER : Experimental event rate; a/a+b
CER: Control event rate; c/c+d
RR: Relative Risk ; EER/CER
NNT: Number of patients needed to be treat ; 1/CER-EER

## Discussion

In this study, all patients of COPD were selected with blood eosinophilia (>5%). Pre-treatment blood eosinophil count in group A was 5.93±2.16 and group B was 5.84±1.86 which correlates with the study of in which they aimed to investigate the potential of blood eosinophil level as a marker for the preventive efûcacy of ICS/LABA in COPD patients[19].In this study the mean age of the group A patients was 58.70 ±8.56 years and group B patients was 57.25±10.03 years. The mean age difference was not statistically significant.A similar study[20] showed mean age of patients in both groups were 64.3±18.1 years. The mean age of the present study was lower can be explained, as the average life expectancy is comparatively low in our set up as compared to the Western world[21].Among group A patients, highest percentage were male (93.1%) and 6.9% female. Similarly in group B patients, highest percentage were male (96.4%) and only 3.6% were female. No statistically significant sex difference was found between the two groups of patients which correlated with the study[22], in which overall male were 97% and only 3% were female.In the present study, COPD Assessment Test (CAT) score change in 1st visit decreased 1.84(±0.67) in group A and decreased 0.31(±0.02) in group B that was statistically significant ($p<0.01$). Mean CAT score change in 2nd visit decreased 2.27 (±0.53) in group A and decreased 0.82 (±0.07) in group B that was statistically significant ($p<0.05$). Mean CAT change in 3rd visit decreased 2.98 (±0.38) in group A and decreased 0.92 (±0.13) in group B that was statistically significant($p<0.05$) . Findings of this study consistent with the result of the study[22], in which their data extend these findings by demonstrating that high blood eosinophils were associated with treatment response (defined as an increase in FEV1 and decrease in CAT score from baseline) following ICS and LABA treatment in COPD for 3 months.Few previous studies have evaluated the use of eosinophil cell counts as a biomarker of ICS responses in patients with COPD. Leigh et al.2006[23]observed an association of sputumeosinophilia(>3% in induced samples) with significant improvements indyspnea following treatment with inhaled corticosteroid. Similar findings were reported for prednisone[24].A post hoc analysis of data from the Foster 48-week trial to reduce exacerbations in COPD to examine the role of blood eosinophil levels on treatment responses and observed that in the highest eosinophil count group, treatment with fluticasone plus LABA resulted in significantly better improvements of quality of life, measured by decremental CAT score(P-values <0.001)[25]. Cheng et al. 2017 used data from a previous prospective randomized study and classified patients into higher and lower eosinophil count groups[26]. The authors observed that patients with high plasma eosinophilia have a significantly greater pulmonary response, a reduced risk of acute exacerbations and improved CAT scores when treated with a combination of ICS- and bronchodilator-based therapy, compared with bronchodilator therapy alone. ($P<0.05$).Lee et al.2016 also evaluated the effectiveness and safety of high- or medium-dose ICS when combined with salmeterol for patients with different blood eosinophil counts in COPD and found similar results as this study reveals[26]. DiSantostefano et al.2013 also found that blood eosinophil level was the primary driver of treatment response, with a greater treatment effect observed in patients with blood eosinophil levels >2.4% when treated with ICS/LABA versus LABA alone[27].

## Conclusions:

This study concludes that ICS with conventional therapy significantly improves lung functions as revealed by FEV1 and quality of life as revealed by CAT score in patients with COPD with higher blood eosinophils. ICS with conventional therapy significantly reduce frequency of exacerbation with improvement of clinical outcomes as compared to conventional therapy.

## Acknowledgement:

Author Contributions: Dr. Md. Shahjada Tabrez had full access to all data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Dr. Md. Shahjada Tabrez contributed to study conception and design, data collection, analysis and interpretation of data, drafting of the manuscript and critical revisions of the article.

Professor Md. Ali Hossain, Dr. Md. Mahabubur Rahman, Dr. Mahboba Akther, Dr. KaziSaifuddinBennoorcontributed to concept and design of the study and critical revisions of the manuscript.

**Conflict of Interest:** The authors of this paper have declared that there is no conflict of interest to any of the authors.

Funding Agency: This study has been performed without any funding from outside else.

**References:**

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease; 2015.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–2128.
3. Price D, West D, Brusselle G, et al. Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. Int J Chron Obstruct Pulmon Dis. 2014;9:889–904.
4. Miravitlles M, Soler-Cataluna JJ, Calle M, Soriano JB. Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. Eur Respir J. 2013;41(6):1252–1256.
5. Barnes PJ. Mediators of chronic obstructive pulmonary disease. Pharmacol Rev. 2004;56(4):515–548.
6. Christenson SA, Steiling K, van den Berge M, et al. Asthma-COPD overlap. Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;191(7): 758–766.
7. Anzueto A. Impact of exacerbations on COPD. Eur Respir Rev 2010;19:113–18.
8. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and ûuticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003;361:449–56.
9. Siva R, Green RH, Brightling CE, et al. Eosinophilic airway inûammation and exacerbations of COPD: a randomised controlled trial. Eur Respir J 2007;29: 906–13.
10. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of COPD: identiûcation of biological clusters and their biomarkers. Am J Respir Crit Care Med 2011;184: 662–71.
11. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med 2012;186:48–55.
12. Pascoe S, Locantore N, Dransûeld MT, et al. Blood eosinophil counts, exacerbations, and response to the addition of inhaled ûuticasone furoate to vilanterol in patientwith chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med 2015;3:435–42.
13. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Oga T, Izumi T. A comparison of the level of dyspnea vs disease severity in indicating the health-related quality of life of patients with COPD. Chest 1999;116:1632-7
14. Von Leupoldt A, Hahn E, Taube K, Schubert-Heukeshoven S, Magnussen H, Dahme B. Effects of 3-week outpatient pulmonary rehabilitation on exercise capacity, dyspnea, and quality of life in COPD. Lung 2008;186:387-91.
15. Miravitlles M, Anzueto A, Legnani D, Forstmeier L, Fargel M. Patient's perception of exacerbations of COPD—the PERCEIVE study. Respir Med 2007;101: 453-60.
16. Mahler DA, Mackowiak JI. Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with COPD. Chest 1995;107: 1585-9.

17. Jones PW, Brusselle G, Dal Negro RW, Ferrer M, Kardos P, Levy ML, et al. Properties of the COPD assessment test in a cross-sectional European study. Eur Respir J 2011;38:29-35.

18. Blumenreich MS. The White Blood Cell and Differential Count. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths, Chapter 1990;153:724-727.

19. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD.Thorax, 2016;71:118–125.

20. Cheng S-L, Wang HH, Lin C-H. Effect of allergic phenotype on treatment response to inhaled bronchodilators with or without inhaled corticosteroids in patients with COPD. International Journal of Chronic Obstructive Pulmonary Disease, 2017; 12:2231-2238.

21. Iqbal F, Hussain S, Hassan M. Hypertension, diabetes mellitus and hypercholesterolemia as risk factors for stroke. Pak J Med Sci, 2003;42(1):17-22.

22. Park HY, Lee H, Koh W-J, et al. Association of blood eosinophils and plasma periostin with FEV1 response after 3-month inhaled corticosteroid and long-acting beta2-agonist treatment in stable COPD patients. International Journal of Chronic Obstructive Pulmonary Disease, 2016;11: 23-30.

23. Leigh R, Pizzichini MM, Morris MM, Maltais F, Hargreave FE, Pizzichini E. Stable COPD:predicting benefit from high-dose inhaled corticosteroid treatment. Eur Respir J, 2006;27(5):964–971.

24. Brightling CE, Monteiro W, Ward R, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomized controlled trial. Lancet, 2000;356:1480–1485.

25. Siddiqui SH, Guasconi A, Vestbo Jet al. Blood eosinophils: a biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2015;192(4):523–525.

26. Lee SY, Park HY, Kim EK, et al. Combination therapy of inhaled steroids and long-acting beta2-agonists in asthma-COPD overlap syndrome. Int J Chron Obstruct Pulmon Dis, 2016;11:2797–2803.

27. DiSantostefano RL, Li H, Rubin DB, et al. Which patients with chronic obstructive pulmonary disease benefit from the addition of an inhaled corticosteroid to their bronchodilator? A cluster analysis. BMJ Open, 2013;3:e001838

Chest Heart Journal
Vol. 42, No. 2, July 2018

*ORIGINAL ARTICLE*

# Assessing treatment Patterns of acute Exacerbation of Chronic Bronchitis (AECB) in Outpatient Settings- Bangladesh

**Mahmud Masum Attar[1], Iqbal Hasan Mahmood[2], Asif Mujtaba Mahmud[3], Abdullah Al-Karim[4]**

**Abstract:**

***Background:*** *Chronic obstructive pulmonary disease (COPD) is a heterogeneous group of disorder that is broadly defined and encompasses several clinical and pathologic entities, primarily emphysema and chronic bronchitis. Being a lifelong disease, COPD patients require constant care and special care is needed for acute exacerbation of their condition along with the proper assessment of their treatment pattern and medications. Though a global guideline for management of COPD (GOLD) along with other management protocols are available in different countries, but in Bangladesh there is no local guideline and little data regarding the treatment pattern and medications including the use of antibiotic during the exacerbation phase of COPD. Therefore, this study has been designed to assess the use of antibiotic during acute exacerbation of chronic bronchitis (AECB) in outpatient settings- Bangladesh.*

***Methods:*** *This was a multicenter, observational, prospective study. A total of 525 patients were planned to be enrolled in outpatient (Male & Female) > 18 years and presenting with suspected acute exacerbation of chronic bronchitis (AECB) where the physician intend to treat with antibiotic as well as signed informed consent to meet the inclusion criteria in this observational study from 20 centers. The physicians were selected randomly from a list of physicians who have post graduations in Respiratory Medicine and General practitioner with special training on Respiratory Medicine. Clinical diagnosis was based on sign, symptoms, radiological evidence and laboratory results as per routine practices. Patient data were collected by the investigators during baseline (Visit 1), intermediate (Visit 2) (if decided by the physicians) and at the end of antibiotic therapy. At visit 2 the effectiveness of the therapy in terms of therapeutic response and patients' compliance as per physicians' choice were assessed. Therapeutic response were evaluated in terms of Cure, Improvement, failure and relapse by the investigators.*

***Results:*** *Among the enrolled patients there were 435 (83%) male with age varied from 20~91 years (57.9±13.5). More than 80% of the patients were 50 years and older and only 55 (10.47%) was below 40 years old. The rural resident patients were larger than urban and semi urban (48.8% vs. 36.4% and 14.9%). 34.5% were employed, 34.9% were previously employed, 15.4% were retired person and 15.2% were house wife. There were 26.5% of current smoker, 51% of former smoker, and 22.5% of never smoker. Abnormal breath*

1. National Institute of Disease of Chest & Hospital, Dhaka, Bangladesh.
2. M. H. Samarita Medical College & Hospital, Dhaka, Bangladesh.
3. Asgar Ali Hospital, Dhaka, Bangladesh.
4. Sanofi Bangladesh Limited, Dhaka, Bangladesh.

**Corresponding to:** Dr. Mahmud Masum Attar, National Institute of Disease of Chest & Hospital, Bangladesh.
**Submission on:** 14 May, 2018 **Accepted for Publication:** 29 June, 2018
Available at http.//www.chabjournal.org

*sound was found in 91% of patients. Radiologically, 61% of patients had bronchitis, 23.8% had pneumonia, only 3.1% had tuberculosis and 12% had other provisional diagnosis such as pleural effusion and pulmonary fibrosis. Out of 525 only 11.4% patients have had spirometry report available including 4 patients had mild (FEV e"80% predicted), 38 had moderate (50% d"FEV1 <80% predicted), 15 had severe (30%d" FEV1 <50% predicted), and 3 patients had very Severe (FEV1< 30% predicted). Age of the patient, severity of disease, suspected organisms, local trend of antibiotic resistance, culture and sensitivity report, and patient's compliance were considered to choose antibiotic. Most commonly prescribed antibiotic was co-amoxiclav (45.2%) followed by cefuroxime (12.95%), cefixime (10.85%), ceftriaxone (10.28%), levofloxacin (8.76%) and azithromycin (7.6%).*

***Conclusion:** Patients with chronic bronchitis frequently develop AECB, a devastating illness if not appropriately managed. Not all patients with AECB need antibiotic therapy, but this intervention is valuable. It could be mentioned that in the AECB study while patients were treated at outdoor setting the physicians advised almost three fourth of the patients the chest x ray and more than 9 patients out of 10 were prescribed Co-amoxiclav, cefuroxime, cefixime, ceftriaxone, levofloxacin or azithromycin.*

***[Chest Heart Journal 2018; 42(2) : 120-128]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019589*

**Introduction:**

COPD is a heterogeneous group of disorder that is broadly defined and encompasses several clinical and pathologic entities, primarily emphysema and chronic bronchitis.[1] The global scenario of diseases is shifting from infectious diseases to non-communicable diseases, with chronic conditions such as heart disease, stroke and chronic obstructive pulmonary disease (COPD) now being the chief causes of death globally.[2] It is estimated that more than 64 million people have COPD worldwide. More than 3 million people died of COPD in 2005, which is equal to 5% of all deaths globally that year. Almost 90% of COPD deaths occur in low- and middle-income countries, where effective strategies for prevention and control are not always implemented or accessible.[3-5]

There is a global guideline for management of COPD-'Global Initiative for Chronic Obstructive Lung Disease (GOLD)[5]. In addition there are other management protocols developed according to local context in different countries.[6-8] But in Bangladesh there is no local guideline. Various institutions follow separate protocolos.[9-10] But being a lifelong disease[2], COPD patients require constant care and special care is needed for acute exacerbation of their condition. Moreover there is little data about how they are treated, what drugs are administered most commonly and for how long. It is also unclear what protocols are followed for management of acute exacerbation of COPD. So to explore the situation and find out this information, an observational study may be the best tool.

**Method:**

This is a multicenter, observational, prospective study. A total of 525 patients were planned to be enrolled in this observational disease registry study from 20 different centers from greater Dhaka and Comilla to see the current real life management patterns of acute exacerbation of chronic bronchitis (AECB) with various antibiotics at outdoor settings. The physicians were selected randomly from a list of physicians who have post graduations in Respiratory Medicine and General practitioner with special training on Respiratory Medicine. Clinical diagnosis was based on sign, symptoms, radiological evidence and laboratory results as per routine practices. Management of AECB and selection of antibiotics were as per the physician's discretion.

Data on participating physicians were collected on a self-questionnaire during the selection of the investigators. Patient data were collected at visit 1, visit 2 and any visit in between done as per the need of the physicians. Data on demography, clinical problems, diseases history, vaccination history, method of diagnosis,

concomitant diseases, treatment prescribed were collected in the data collection form (CRF) at visit 1 (Day 1). Patients were advised to come back at visit 2 (as per physician's decision) to assess the effectiveness of the therapy in terms of therapeutic response and patients' compliance as per physicians choice. During this Follow up visits patient's overall assessment to the therapy and occurrence of adverse events during treatment were also evaluated. Patients who completed follow-up visit at the end of antibiotic therapy were considered for analysis. Statistical analysis was mainly descriptive and was summarized as mean, median, standard deviation, minimum, maximum and percentages for continuous parameters and frequency and percentages for categorical parameters. Statistical analysis was done using SPSS 17.0.

The primary endpoint was the relative proportion of AECB patients treated with various antibiotics at outdoor settings. Secondary endpoints were profile of the patients, center specificities that may determine some therapeutic decisions: type of center, laboratory tests, traditions following local/international guidelines, treatment costs, COPD diagnosis method used by physicians, treatments prescribed for AECB, dose & duration of treatment with antibiotic, vaccination history against influenza and pneumonia and therapeutic response to different treatment modalities according to patients and physicians assessment. Clinical outcome (success) was categorized into 4 headings: a) Cure: disappearance of all pre-treatment signs and symptoms of infection, b) Improvement: improvement in, or partial disappearance of signs and symptoms without requiring further antibacterial therapy. c) Failure: no change in, or worsening of baseline signs and symptoms requiring modification of treatment, i.e., addition of or switch to another antibacterial therapy, and d) Relapse: initial amelioration in the clinical picture, a favorable response to therapy, followed by worsening or reappearance of some signs or symptoms either later during treatment or once off therapy.

**Safety analysis:**

There were 4 death cases and the investigators confirmed that the reason of death was aging and cardiorespiratory failure. As the investigators confirmed that the patients were not on Sanofi brand, death was not considered as reportable serious adverse event from sanofi end. Use of non-Sanofi brand was identified in 5 patients and was not eligible for AE reporting. Among the 43 patients, uses of non-Sanofi brand were confirmed by the investigators in 12 patients and were non-eligible for AE reporting. Use of Sanofi brand was confirmed in 26 patients of whom 3 were not considered for reporting AE due to identification of non-reportable event on Pharmacovigilance reevaluation. There were 5 patients for whom use of Sanofi brand was unknown to the investigators was also considered for AE reporting considering possibility of Sanofi Brand use. Finally 28 (5.3%) patients were considered for reporting non-serious AEs and the event was lack of efficacy or no improvement in sign and symptoms. There were no SAEs reported for Sanofi INN.

**Results:**

A total of 525 patients who were attended to the physicians with clinical features of AECB were enrolled in this study, however, four of them died due to complication of other comorbidity and another two patients were lost to follow up before their visit 2. Patients were recruted in 20 different sites in two districs of Bangladesh. 20 physicians who were specialized in the respiratory medicine and or experienced in this area participated in this study as investigators and recruited eligible patients from 20 centers (private hospital or chamber). Among the enrolled patients, there were 83% male and 17% female patients with age from 20~91 years (57.98±13.54). More than 80% of the patients were 50 years and older and only 10.47% was below 40 years old that might be cause of alpha 1- antitrypsin deficiency or any other gnetically transmitted diseases. The majority of the patients were (48.8%) were residing in rural areas than semi urban (14.9%) and urban (36.4%) areas. About 34.5% were employed, 34.9% were previously employed, 15.4% were retired person and 15.2% were house wife. There were 26.5% of current smoker, 51% of former smoker, and 22.5% of never smoker. The demographic characteristics of the patients at baseline are presented in Table 1

During the baseline visit 478 (91%) patients had abnormal breath sound and most common were wheezes and crackles. Two common laboratory

tests that the patients presented to their physicians during visit 1 were sputum culture and X-ray chest along with other routine blood tests. Radiologically 177 (61%) patients had bronchitis, 69 (23.8%) had pneumonia, only 9 (3.1%) had TB and 20 (12%) had other provisional diagnosis such as pleural effusion and pulmonary fibrosis were common. Out of 525 only 60 (11.4%) patients have had spirometry report available during their visit 1. 4 patients had mild (FEV e"80% predicted), 38 had moderate (50% d"FEV1 <80% predicted), 15 had severe (30%d" FEV1 <50% predicted), and 3 patients had very Severe (FEV1< 30% predicted). Table 2 showed clinical characteristics of the patients at baseline.

All the 525 patients were prescribed antibiotics either single or in with another one. Choice of antibiotics and their dosage and duration were determined by the physicians. Age of the patient, severity of disease, suspected organisms, local trend of antibiotic resistance, culture and sensitivity report, and patient's compliance were considered to choose antibiotic. Most commonly prescribed antibiotic was co-amoxiclav (45.2%) followed by cefuroxime (12.95%), cefixime (10.85%), ceftriaxone (10.28%), levofloxacin (8.76%) and azithromycin (7.6%). Table 3 indicated antibiotics and their dosage and duration.

Other antibiotics prescribed were doxycycline, moxifloxacin, clarithromycin, amikacin, ceftazidime, ciprofloxacin, linezolid, gentamycin, gemifloxacin. Most of the cases physicians' first choice was oral antibiotic (74.2%) and dosage, frequency of dosages and duration were as per physicians' discretion. Table 4 Prescribed antibiotics responses at final visit at baseline.

Most common concomitant diseases were cardiovascular (20.4%), diabetes mellitus (14.9%), hypertension (44.8% within 67 patients), anxiety and depression (9.8%). Table 5 below shown all concomitant diseases reported by the physician.

**Table-I**

*Patients demographic characteristics at baseline*

| | Total (n=525) |
|---|---|
| Age (years) | |
| Mean ±SD | 57.98±13.54 |
| Gender | |
| Male/Female | 435/90 |
| Locality [n (%)] | |
| Urban | 191 (36.4%) |
| Sub-urban | 78 (14.9%) |
| Rural | 256 (48.8%) |
| Occupational status | |
| Employed | 181 (34.5%) |
| previously employed | 183 (34.9%) |
| Retired person | 81 (15.4%) |
| Office based staff | 130 (24.8%) |
| Labour | 118 (22.5%) |
| Industrial staff | 81 (15.4%) |
| Engaged in agriculture | 70 (13.3%) |
| Businessmen | 41 (7.8%) |
| House wife | 80 (15.2%) |
| Others (student, painter, singer, ward boy, self-employed) | 5 (1%) |
| Smoking | |
| Former smoker | 268 (51%) |
| Current smoker | 139 (26.5%) |
| Never smoker | 118 (22.5%) |

**Table-II**

*Patients clinical characteristics at baseline*

| | | Total (n=525) |
|---|---|---|
| Vital Signs | Range | M±SD |
| Pulse Rate | 62-120 | 87.85±11.17 |
| Systolic | 80-200 | 125.71±18.97 |
| Diastolic | 50-120 | 78.99±9.97 |
| Respiratory Rate | 14-40 | 22.57±4.49 |
| Sign & Symptom | (n, %) | |
| Increased Dyspnea | 468 (89.14%) | |
| Increased Sputum Volume | 388 (73.90%) | |
| Chronic Cough | 495 (94.28%) | |
| Fever | 282 (53.71%) | |
| Abnormal Breath Sound | 478 (91.04%) | |
| Clinical diagnosis: | | |
| AECB with previous hospitalization | 162 (31%) | |
| AECB patients advised hospitalized | 79 (15%) | |
| AECB treated as out-patient | 446 (85%) | |
| Investigations | | |
| Sputum culture | 35 (6.66%) | |
| X-ray chest | 243 (46.3%) | |
| Bronchitis | 177 (61%) | |
| Pneumonia | 69 (23.8%) | |
| TB | 09 (3.1%) | |
| Other provisional diagnosis | 20 (12%) | |
| Normal radiological findings | 15 (2.85%) | |
| Chest X-ray advised at the visit 1 | 391 (74.5%) | |
| Spirometry | 60 (11.4%) | |
| Mild (FEV ≥80% predicted) | 04 (0.76%) | |
| Moderate (50% ≤ FEV1 <80% predicted) | 38 (7.23%) | |
| Severe (30% ≤ FEV1 <50% predicted) | 15 (2.85%) | |
| Very Severe (FEV1< 30% predicted) | 03 (0.57%) | |
| Spirometry at the visit 1 | 245 (46.7%) | |
| Vaccination history | | |
| Influenza | 33 (6.28%) | |
| Pneumonia | 30 (5.71%) | |
| Both influenza and pneumonia. | 25 (4.76%) | |
| Patients had never vaccinated (on either influenza or pneumonia) | 453 (86.28%) | |
| Unknown | 79 (15.04%) | |

**Table-III**

*Antibiotics and their dosage and duration. (Visit 1)*

| ANTIBIOTIC | Total Number | mg | Times daily No. of Patient | Duration No. of Patient |
|---|---|---|---|---|
| DOXYCYCLINE | 6 | 100 | 1 (3) | 14 (3) |
| | | | 2 (2) | 7 (2) |
| | | 200 | 2 (1) | 7 (1) |
| AZITHROMYCIN | 40 | 500 | 1 (30) | 5 (4) |
| | | | | 7 (18) |
| | | | | 10 (4) |
| | | | | 14 (4) |
| | | | 2 (10) | 7 (5) |
| | | | | 10 (1) |
| | | | | 14 (4) |
| CO-AMOXICLAV | 239 | 250 | 2 (2) | 10 (2) |
| | | 375 | 3 (15) | 7 (5) |
| | | | | 10 (10) |
| | | 500 | 2 (2) | 7 (2) |
| | | 625 | 2 (30) | 10 (4) |
| | | | | 14 (26) |
| | | | 3 (141) | 7 (78) |
| | | | | 10 (46) |
| | | | | 14 (17) |
| | | 1000 | 2 (14) | 7 (5) |
| | | | | 10 (9) |
| | | 1200 | 3 (35) | 5 (2) |
| | | | | 7 (28) |
| | | | | 10 (5) |
| CEFUROXIME | 68 | 250 | 2 (11) | 7 (3) |
| | | | | 10 (5) |
| | | | | 14 (3) |
| | | 500 | 2 (41) | 7 (28) |
| | | | | 10 (6) |
| | | | | 14 (7) |
| | | | 3 (4) | 7 (3) |
| | | | | 14 (1) |
| | | 750 | 2 (3) | 5 (3) |
| | | | 3 (2) | 7 (2) |
| | | 1500 | 2 (2) | 5 (2) |
| | | | 3 (5) | 7 (5) |
| CEFIXIME | 57 | 200 | 2 (53) | 7 (41) |
| | | | | 10 (12) |
| | | 400 | 2 (4) | 7 (2) |
| | | | | 10 (1) |
| | | | | 14 (1) |

*table continued*

| ANTIBIOTIC | Total Number | mg | Times daily No. of Patient | Duration No. of Patient |
|---|---|---|---|---|
| AMIKACIN | 14 | 500 | 2 (14) | 5 (5)<br>7 (6)<br>10 (2) |
| CEFTAZIDIME | 12 | 1000 | 3 (12) | 5 (4)<br>7 (7)<br>10 (1) |
| CEFTRIAXONE | 54 | 1000 | 1 (3)<br><br>2 (51) | 7 (1)<br>14 (2)<br>5 (6)<br>7 (30)<br>10 (15) |
| **CIPROFLOXACIN** | 3 | 500 | 2 (3) | 7 (3) |
| **CLARITHROMYCIN** | 14 | 250<br>500 | 2 (1)<br>2 (13) | 7 (1)<br>7 (10)<br>10 (3) |
| **CLAVULANIC ACID** | 5 | 250 | 2 (5) | 7 (2)<br>10 (2)<br>14 (1) |
| **GEMIFLOXACIN** | 4 | 320 | 1 (4) | 7 (4) |
| **LEVOFLOXACIN** | 46 | 500<br><br><br><br>750<br><br><br>1000 | 1 (40)<br><br><br><br>1 (4)<br><br><br>2 (2) | 5 (3)<br>7 (15)<br>10 (17)<br>14 (5)<br>7 (1)<br>10 (2)<br>14 (1)<br>10 (2) |
| **LINEZOLID** | 5 | 400 | 2 (5) | 7 (5) |
| **MOXIFLOXACIN** | 14 | 400 | 1 (14) | 7 (11)<br>14 (3) |

**Table-IV**

*Prescribed antibiotics responses at final visit at baseline*

| Antibiotic (Multiple responses) | Physicians assessment | | | | Total (n=590) |
|---|---|---|---|---|---|
| | Cure (n=187, %) | Improvement (n=371, %) | Failure (n=20, %) | Relapse (n=12, %) | |
| Azithromycin | 10, 25% | 28, 70% | 0, 0% | 2, 5% | 40 |
| Co-amoxiclav | 80 (33.5%) | 149 (62.3%) | 6 (2.5%) | 4 (1.7%) | 239 |
| Cefuroxime | 27 (40%) | 39 (57%) | 1 (1.5%) | 1 (1.5%) | 68 |
| Cefixime | 10 (17.5%) | 43 (75%) | 4 (7.5%) | 0 (0%) | 57 |
| Ceftriaxone | 17 (31.5%) | 30 (55.5%) | 3 (5.5%) | 4 (7.5%) | 54 |
| Levofloxacin | 24 (52.17%) | 19 (41.30%) | 2 (4.35%) | 1 (2.17%) | 46 |
| Others | 19 (22%) | 63 (73.3%) | 4 (4.7%) | 0 (0%) | 86 |

**Table-V**

*Below shown all concomitant diseases reported by the physician*

| Concomitant Disease | N (%) |
|---|---|
| Diabetes | 96 (14.9) |
| Infections | 33 (5.1) |
| Cardiovascular | 131 (20.4) |
| Osteoporosis | 20 (3.1) |
| Lung Cancer | 2 (0.3) |
| Anxiety and depression | 63 (9.8) |
| None | 218 (33.9) |
| Unknown | 13 (2.0) |
| Others (Multiple) | 67 (10.4) |
| Hypertension (HTN) | 30 (44.8) |
| BEP | 1 (1.5) |
| Bladder cancer | 1 (1.5) |
| PUD | 5 (7.5) |
| IHD (Ischemic Heart Disease) | 5 (7.5) |
| Chronic kidney disease (CKD) | 4 (6.0) |
| Cor pulmonale | 3 (4.5) |
| Chronic liver disease (CLD) | 1 (1.5) |
| Hypothyroidism | 2 (3.0) |

Others (Laryngeal carcinoma, TB, Thyroid disease, Pneumonia, Neurological, Bronchitis, Urinary Tract Infections, Senile tremor, Osteochondritis, Non Ulcer Dyspepsia, Respiratory Failure, Prostate Infection, Irritable bowel syndrome, Pneumothorax, Lumbar Spondylosis) 15, 22.4

Out of 525 patients 114 (21.7%) had a family history of AECB. With a range of 0-40 years 70% of the patients (365) had a history of AECB for 9 years or less. 25% (133) patients had history of AECB between 10-19 years and only 5% (27) had 20 years or more. Number of exacerbation per year was 0-12 times. 31% (162) had previous history of hospitalization due to AECB. During visit 1 after the examination physician advised only 79 (15%) AECB patients to be hospitalized for better management of their acute condition. The rest of 85% (446) was treated as out-patient.

**Discussion:**

This study was conducted to see the relative proportion of AECB patients treated with various antibiotics at outdoor settings. It was also intended to describe the profile of the patients, different diagnostic methods and different treatment options for AECB in real life practice in Bangladesh. 20 physicians who were specialized in the respiratory medicine and experienced in this area participated in this study as investigators and recruited eligible patients from 20 centers (private hospital or chamber). The most common investigations that were recommended and considered for the diagnosis and management of AECB patients were X-ray Chest, Complete Blood Count (CBC), Culture and Sensitivity, and Spirometry. Almost all the physicians reported that they were regularly following GOLD recommendation (Global Initiative for Chronic Obstructive Lung Diseases) in diagnosis and management of AECB[2]. They had also suggested that those patients should be vaccinated for Pneumonia and Influenza. All the 525 patients were prescribed antibiotics either any single one or in combination with another one. 172 (32.76%) of the patients were visited their physicians within 3-7 days of visit 1 as an optional follow up visit mainly due to either no change or worsening of their condition. During this visit an evaluation on clinical outcome was done by the physician and categorized as cured, improved, failure/no change and relapse. Out of 172 only two patients found cured, 145 improved, 24 no changed/failure, and one patient had relapsed. Modification of antibiotics either changes of their dosage was required for 90 patients. 13 patients were advised to be hospitalized during this intermediate visit for better management of their acute condition. At the final visit 508 (96.8%) of the patients had completed prescribed course of antibiotics and 17 (3.2%) were not able to complete it. Of them two patients were lost to follow up (LTFU), and four patients had died during the study. Five patients discontinued antibiotics due to economic reason and another four patients didn't want to continue it without explaining any reason. One patient discontinued due to worsening of his condition and another one had to take anti TB treatment. An evaluation on clinical outcome was done on the final visit by the physician and categorized as cured, improved, failure/no change and relapse. Out of 519 (4 deaths and 2 LTFU were excluded) evaluated patients 32.4% (170) found cured, 62.7% (329) improved, 2% (11) no changed/failure, and 1.7% (9) had relapsed. 10 patients were advised to be hospitalized.

In this study (AECB) the most common factors that the physicians considered to prescribe empirical antibiotics were cardinal symptoms of the patients followed by guidelines/ recommendations, local sensitivity/resistant patterns and cost of antibiotic treatment which were reflected in the responses of the Physician's questionnaire. All most all the physicians participated in this study reported that they were regularly following GOLD recommendation[2] (Global Initiative for Chronic Obstructive Lung Diseases) in diagnosis and management of AECB. Although many of these patient related factors and the causative organism related factors were considered during taking decision on the selection of antibiotic regimen by the physician in outdoor setting in Bangladesh but it could not be confirmed if the participating physicians systematically categorize the patient based on their historical information, lung function and shifting of associated organisms in the decision making.

This study has been conducted in 20 different centers from the two districts towns which do not represent entire population especially patient from the rural part of Bangladesh. A longer follow-up could evaluate the effect of antibiotic therapy in reducing the subsequent exacerbation in patient with chronic bronchitis.

**Conclusion:**

Patients with chronic bronchitis frequently develop AECB, a devastating illness if not appropriately managed. Not all patients with AECB need antibiotic therapy, but this intervention is valuable. It could be mentioned that in the AECB study while patients were treated at outdoor setting the physicians advised almost three fourth of the patients the chest x ray and more than 9 patients out of 10 were prescribed Co-amoxiclav, cefuroxime, cefixime, ceftriaxone, levofloxacin or azithromycin.

**Acknowledgement:**

This study was sponsored by Sanofi Bangladesh Limited. The sponsor participated in the study design and managed all operational aspects of the study, including monitoring data collection, statistical analysis and writing of the report. AAK is an employee of Sanofi Bangladesh Limited & also the CPL from the sponsor. MMA, IHM & AMM were investigators in this study. All authors contributed to the interpretation of the data and contributed to this publication and approved the final manuscript for submission to the target journal. They received no financial compensation for the authorship.

**References:**

1. American Thoracic Society/European Respiratory Society Task Force: Standards for the diagnosis and management of patients with COPD. Version 1.2. New York: American Thoracic Society, 2004. PDF available for download at thoracic.org/ sections/copd/ (accessed March 20, 2009).
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2006 MCR VISION, Inc.
3. World Health Organization, 2014. http:// www.who.int/respiratory/copd/World_ Health_Statistics_2008/en/; accessed at 17/ 7/14.
4. The global burden of disease: 2004 update, 2008.
5. World Health Organization, 2008, 'World health statistics 2008', http://www.who.int/ whosis/whostat/EN_WHS08_Full.pdf?ua=1; accessed at 17/7/14
6. Canadian Thoracic Society Recommendations for managing chronic obstructive pulmonary disease-2008 update-highlights for primary care.
7. NICE 2010, chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care.
8. American Thoracic Society 2004, 'COPD Guideline'.
9. Alam et al, 2010. 'Prevalence of COPD and its socioeconomic and lifestyle determinants in Bangladesh: Preliminary results from a population based study'. Primary Care Respiratory Journal 2010; 19(2): A1-A25.
10. Hossain A, Islam K.2009.' 'Prevalence and risk factors of chronic obstructive pulmonary disease (COPD) in Dhaka city Bangladesh'. Chest; 136(4_Meeting Abstracts): 90S-b-91S.

Chest Heart Journal
Vol. 42, No. 2, July 2018

## ORIGINAL ARTICLE

# Association between Diabetes Mellitus and Pulmonary Tuberculosis in Adults

**Md Saiful Islam Patwary[1], Mohammod Tanvir Islam[2], AKM Motiur Rahman Bhuiyan[3], Shamim Ahmed[4], Afroja Alam[5], Binoy Krishna Tarafder[6], Mohammad Kamruzzaman Mazumder[7], Muhammad Jamal Uddin[8], Md. Nazim Al – Azad[9], Mohammad Farhad[10], Debasish Kumar Ghosh[11], Md Zilan Miah Sarker[12]**

**Abstract:**

***Background:*** *Tuberculosis (TB) and diabetes mellitus (DM) are national and global pandemic. Bangladesh is among the top ten countries for both diabetes and tuberculosis prevalence. The coexistence of both diabetes and tuberculosis has a greater impact on the disease process and treatment outcome. Hence bidirectional screening for this coexistence may have a positive role in the better management of both disease conditions.*

***Methods and Materials:*** *A case-control study was conducted in the Department of Internal medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh among smear positive pulmonary TB patients as cases and non-TB controls. Participants were tested for fasting plasma glucose and glycosylated hemoglobin (HbA1c) for diagnosis of diabetes according to ADA guidelines.*

***Results:*** *Among 142 cases and 142 controls the mean (SD) age was 40.48±14.17 and 42.70± 13.17 years. BMI was <18.5 kg/m² in most of the tuberculosis patients. Among 142 TB cases 45 (31.7%) were diabetic and 74(52.1%) were prediabetic. Tuberculosis was associated with prediabetes (OR 18.5, CI 5.6 – 60.9) and diabetes (OR 21.2, CI 4.4 - 100).Tuberculosis (TB) cases with Diabetes mellitus were more from urban areas. The previously diagnosed diabetic cases have poor glycemic control during diagnosis of tuberculosis.*

***Conclusion:*** *In this case control study reconfirms the association of pulmonary tuberculosis and diabetes mellitus. The present study reveals risk of tuberculosis twenty one times more in diabetes mellitus cases and eighteen times more in prediabetes cases. This high frequency of diabetes mellitus suggest in adult patient should be tested for diabetes and patient with cough should be tested for tuberculosis.*

***Key words:*** *Diabetes mellitus, tuberculosis.*

***[Chest Heart Journal 2018; 42(2) : 129-136]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019590*

1. Medical Officer, UHC, Haimchar, Chandpur, Bangladesh.
2. Associate Professor, Department of Internal Medicine, BSMMU, Bangladesh.
3. Associate Professor , Department of Internal Medicine, BSMMU, Bangladesh.
4. Associate Professor, Respiratory Medicine, BSMMU, Bangladesh.
5. Associate Professor , Department of Internal Medicine, BSMMU, Bangladesh.
6. Associate Professor, Medicine, Colonel Malek Medical college, Manikgonj, Bangladesh.
7. Assistant professor, Medicine, Ibn sina medical college, kollanpur, Dhaka, Bangladesh.
8. OSD, DGHS, Mohakhali, Dhaka, Bangladesh.
9. Junior consultant, Medicine, Mugda Medical College & Hospital, Dhaka, Bangladesh.
10. OSD, DGHS, Mohakhali, Dhaka, Bangladesh.
11. Assistant Professor, (Endocrinology & Metabolism), Khulna Medical College, Khulna, Bangladesh.
12. Professor, Department of Internal Medicine, BSMMU, Bangladesh.

**Correspondence to:** Dr. Md Saiful Islam Patwary, Medical Officer, UHC, Haimchar, Chandpur, Mobile: 01711115325, Email: drsaiful.sohel@gmail.com

**Submission on:** 10 May, 2018 **Accepted for Publication:** 10 June, 2018
Available at http.//www.chabjournal.org

**Introduction:**

Tuberculosis (TB) is a major cause of morbidity and mortality throughout the world. Bangladesh stands sixth among the 22 high TB burdened areas and the annual incidence of TB is 225/ 100000 per year in this country. The prevalence is estimated to be 434 per 100,000 populations. The estimated TB mortality is 45 per 100,000 populations per year[1]. Bangladesh, along with India, China and few other countries are also overburdened with both Tuberculosis and Diabetes Mellitus. Number of diabetic patients around the world is escalating in such a steep way that by the year 2030, DM will become the 7th leading cause of death around the world[2]. It is to be mentioned that, 80% of diabetic death in the world occurs in the low income countries like Bangladesh[3]. Bangladesh remains in the list of top 10 DM burdened countries around the world and by the year 2030 the ranking is expected to go up[4]. Both diabetes and tuberculosis are global and national concern.

Recent studies show prevalence of diabetes mellitus in Bangladesh community prevalence: 30-35% abnormal glucose tolerance of which diabetes is 8-12%[5]. Besides 1.75% of adult population (total 1.58 million) had Impaired Glucose Tolerance[6].

In Bangladesh almost all are type 2 diabetes; type 1 is rare. About half of all people with diabetes are unaware of their disease. 80% of people with diabetes live in low and middle income countries. Diabetic population shows 8.4% of all cause mortality. Health spending on diabetes accounts for 10.8% of total health expenditure worldwide (1).Co-existence of DM in TB has a greater impact on disease process and treatment outcome.

Diabetes contributes to the global increase in incidence of tuberculosis and may become a threat to the TB control program in coming days[7]. DM has been identified as an important risk factor for development of active TB[8]. The incidence of tuberculosis is 2 to 5 times higher in diabetic patients than the non-diabetic ones[8]. A screening program in China showed significant number of new cases (3%) of DM in TB patients. Total number of DM cases was also higher in this population. Moreover they were able to find 7.8% new cases of impaired fasting glucose which could significantly help in the primary prevention of diabetes[9]. Prevalence of DM in TB was found to be much higher in Kerala (44%), Mexico (36%) and Texas (39%)[10,11].

In China overall prevalence of DM in patients with TB was 12.4%. Health facilities serving urban populations and hospitals had a higher prevalence of DM compared with health facilities serving rural populations and clinics[9].

The innate and adaptive immune responses necessary for the prevention of tuberculous proliferation is hampered in diabetic patients[8]. TB patients with DM have different manifestations of the disease and unfavorable treatment outcome[12]. It has been found that these patients have more cavitatory lesions on chest x-ray, less sputum positivity and a paucity of clinical presentation[13]. Both treatment failure and number of death are high in this group of people. According to Baker et al they have a risk ratio (RR) for the combined outcome of failure and death of 1.69 (95% CI, 1.36 to 2)[14]. DM has a 2 fold higher risk of death[15]. Dooley et al also showed in the same study that the time for sputum culture conversion was longer in pulmonary TB cases with diabetes. Treatment failure among diabetic patients was also higher than the non-diabetic TB patients (4.1% vs. 6.7%)[15]. Diabetic patients are more prone to develop multidrug-resistant TB and they are more than 5 times likely to become infected with drug-resistant strains[16].

TB patients with anti-tuberculer drugs in diabetic patients can be troublesome as drugs like rifampicin can induce hyperglycemia directly or by indirect interaction with ongoing oral hypoglycemic agents[17,18]. TB infection is also responsible for reversible impaired glucose tolerance[19]. In diabetic patients the plasma concentrations of isoniazid and rifampicin is found to be lower[20].

This steep rise of the curve of diabetic prevalence will have an impact on the global prevalence of tuberculosis also. So detecting diabetes early in TB cases will be needed for better management of these "Tubercular diabetic" patients[7]. Extensive works have been done in China, India

and other countries where diabetes has been screened in TB patients and found to be higher[9,10,21]. Diabetic patients were also screened for TB in these countries and a higher prevalence was also evident there[22,23]. Bidirectional screening was also done for DM and TB in some places. Currently world health organization (WHO) also recommends for such bi-directional screening as detecting early the co-existence of these diseases can lead to better management of both cases[24].

**Methods:**

This study was conducted as a case-control study. Smear positive PTB patients were as cases, non TB patients were as controls. Cases were collected from DOTS corner and Outpatients Department (OPD) of BSMMU and 'TB control and training institute', Chankharpol, Dhaka. Controls were collected from Medicine OPD, BSMMU.

This study was carried out during a period of 1st Jan 2015 to 31st December 2015 in the Department of Internal Medicine, BSMMU, Dhaka. A total of 142 patients were cases and 142 were controls. Samples were collected by convenient sampling technique as per inclusion and exclusion criteria. PTB was diagnosed by history ( fever, cough for 3 weeks or more, weight loss) & bacteriological confirmation by sputum for Acid Fast Bacilli & GeneXpert. TB was excluded by history (cough, low grade intermittent fever, night sweating in past 3 weeks and unexplained weight loss in the past month), physical examination and relevant investigations (CBC, CXR, FBS, HbA1c). Study purpose was explained to the patient and informed written consent was taken before collection of data. The findings were entered into the structured questionnaire and data sheet. Patient blood samples were obtained and sent to Biochemistry department to determine the FBS, HbA1C for both cases and controls. Complete blood count was done in hematology and chest x-ray was done in radiology department for only controls. Later reports were collected and entered into the data sheet. Persons fulfilling American Diabetes Association (ADA) diagnostic criteria 2014 for DM was enrolled as diabetic. For patients with self-reported DM, we also measured FBS, HbA1C level to see current glycaemic status. All available patients who fulfilled the inclusions criteria were selectedand analyzed. HbA1c was measured using the NGSP certified Bio-Rad D-10$^{TM}$ Hemoglobin $A_1C$ Program 220-0101, USA. All data were expressed as frequencies and mean (±SD or ± SE). Student's unpaired t- test for quantitative data and Chi-Square test for qualitative data were performed by using the statistical package for social science (SPSS) program[23]. Pearson's correlation test was used to see correlation among different variables. P values ≤0.05 was considered as significant. Multiple Logistic regression analysis was done to estimate the role of prediabetes and diabetes as a risk factor for tuberculosis.

**Results:**

A total of 284 subjects were enrolled in the study among which 142 were cases (smear positive pulmonary TB) and 142 were control. The age range of the subjects were between 18 and 70 years with the mean age of case group 40.48 ± 14.17 years and control group 42.70±13.17 (table i). Table I shows the baseline characteristics of the cases and controls.

There was no statistically significant difference between the duration of cough and weight loss among cases. Out of 142 cases previous history of pulmonary TB was present in 13 (4.6%).Among cases equal number were smoker and non-smoker (50%); Among controls non-smokers (58.50%) were more than smokers though the difference was not statistically significant. Most of the cases (60.6%) were under-weight while the participants of control group had normal weight (68.3%); differences in BMI among case and control groups were statistically significant (p value <0.001). (Table II).

Among 142 TB cases, DM was present in 45 (31.7%) (Previously known DM 32, newly diagnosed DM 13). 74(52%) cases were prediabetic. Normal fasting glucose was found in 23(16.2%). Among 142 controls, DM was found in 13(9.2%) (Previously known 5, newly diagnosed 8) and prediabetes was found in 30(21.1%), normal glucose tolerance in 99(69.7%) and were statistically significant (p<0.001).(Table III).

**Table-I**

*Baseline characteristics of cases and controls*

| | Case (N=142) | Control (N=142) | P |
|---|---|---|---|
| Age (years)* | 40.48±14.17 | 42.70±13.17 | 0.176 |
| BMI kg/m² * | 17.34±3.09 | 23.73±2.61 | <0.001 |
| Education** | | | |
| Illiterate | 68 (47.9%) | 34(23.9%) | <0.001 |
| Primary | 53 (37.3) | 42 (29.6%) | |
| SSC/HSC | 17 (12%) | 53(37.3) | |
| Degree & above | 4 (2.8%) | 13 (9.2%) | |
| Occupation** | | | |
| Cultivator | 4 (2.8%) | 14(9.9%) | 0.012 |
| Service | 41 (28.9%) | 44(31%) | |
| Business | 29 (20.4%) | 28(19.7%) | |
| Housewife | 35 (24.6%) | 41(28.9%) | |
| Others(day labor) | 33 (23.2%) | 15(10.6%) | |
| Gender ** | | | |
| Male | 102 (71.8%) | 94 (66.2%) | 0.306* |
| Female | 40 (28.2%) | 48 (33.8%) | |
| Residence** | | | |
| Rural | 22(15.5%) | 44(31%) | |
| Urban | 120(84.5%) | 98(69%) | 0.002 |

**Table-II**

*BMI category of study subjects*

| BMI in Kg/m² | Case(N=142) | Control(N=142) | P |
|---|---|---|---|
| <18.5 | 86 (60.60%) | 1 (0.70%) | |
| 18.5-24.9 | 53 (37.30%) | 97 (68.30%) | <0.001 |
| 25-29.9 | 2 (1.40%) | 43(30.30%) | |
| >30 | 1 (0.70%) | 1(0.70%) | |

(Done by $X^2$ test)
(<18.5-under weight, 18.5-24.9-Normal, 25-29.9-Over weight,>30-Obese)
BMI-Body Mass Index)

**Table-III**

*Distribution of NFG, Prediabetic, DM in case and control*

| | Case(N=142) | Control(N=142) | P |
|---|---|---|---|
| NFG | 23 (16.2%) | 99(69.7%) | <0.001 |
| Prediabetic | 74 (52.1%) | 30(21.1%) | |
| DM | 45(31.7%) | 13(9.2%) | |

The frequency of DM was higher in those aged 36 years or more. Patients with TB and DM were older than those with only TB. (Table IV)

Out Of 284 subjects mean fasting plasma glucose in cases were 6.77±2.98 and 5.42±1.58 in controls. HbA1c in cases were 7.15±2.28 and 5.724±1.52 among control. The difference was statistically significant (P value <0.001) (Table V)

In the study known diabetic cases were 32. Majority of patients' FPG (84.4%)& HbA1c (93.8%) were uncontrolled.

Multiple Logistic regression analysis showed odds ratio for the risk of tuberculosis associated with urban areas (5.0, CI1.7-14.7), history of smoking (2.8, CI 1.0 – 7.5), previous history of DM (12.4, CI 1.7- 88.4) prediabetes (18.5, CI5.6 – 60.9) and for diabetes (21.2, CI 4.4 - 100). (Table VI).

**Table-IV**

*Age group distribution of DM & prediabetic cases*

| Age in years | NFG | Prediabetes | DM | P value |
|---|---|---|---|---|
| 18-35 | 17(73.9%) | 36(48.6%) | 9(20.0%) | |
| 36-50 | 5(21.7%) | 23(31.1%) | 18(40.0%) | <0.001 |
| 51-70 | 1(4.3%) | 15(20.3%) | 18(40.0%) | |

(Done by $x^2$ test, NFG-Normal Fasting Glucose, DM-Diabetes Mellitus)

**Table-V**

*FPG & HbA1c value in study subjects*

| | Case(N=142) | Control(N=142) | P value |
|---|---|---|---|
| FPG | 6.77±2.98 | 5.42±1.58 | <0.001 |
| HbA1c | 7.15±2.28 | 5.724±1.52 | <0.001 |

(Done by student's t- test)

(FPG: Fasting plasma glucose, HbA1c: Glycosylated haemoglobin A1c )

**Table-VI**

*Multiple analysis for association between Residence, Previous DM, Smoking, Prediabetes, Diabetes in cases (n=142) and controls (n=142)*

| Characteristic | Odds Ratio | 95% Confidence Interval |
|---|---|---|
| Residence | | |
| Rural | Ref | Ref |
| Urban | 5.0* | 1.7-14.7 |
| No Pervious history of DM | Ref | Ref |
| Previous history of DM | 12.4* | 1.7 – 88.4 |
| No H/O smoking | Ref | Ref |
| H/O smoking | 2.8 | 1.0-7.5 |
| Impaired Fasting Glucose | Ref | Ref |
| Prediabetes | 18.5* | 5.6 – 60.9 |
| Diabetes | 21.2* | 4.4 – 100 |

DM - Diabetes mellitus, ref - Reference

*p value less than 0.05;

Done by- Multiple logistic regression analysis

**Discussion:**

The frequency of diabetes mellitus was higher among patients with active pulmonary TB, which was almost five times higher than the estimated population prevalence of DM in Bangladesh[5]. Our findings were in conformity with reports of high prevalence of DM in TB from Mexico, Tanzania, India, Pakistan, China, and Indonesia [25,26,27,28]. The wide range of prevalence of DM in different studies might be due to the socio-demographic characteristics of source populations in the localities. Previous literature supports that DM is an important risk factor for the occurrence of TB[8,29].

Although the direct mechanism has not yet been clearly identified, reduced immunity in diabetic patients might play a major role in increasing the risk of tuberculosis. People with diabetes have reduced chemotaxis and oxidative killing potential than those of non-diabetic control[30].

The overall presence of prediabetes among newly pulmonary TB cases in this study were higher than the report from Indonesia[28], India[10] and Guinea[31] Tanzania[21].This positive association may be due to stress-induced hyperglycemia caused by tuberculosis. Possible explanation of

high blood glucose level in tuberculosis is insulin resistance caused by severe infection[32].

This study also demonstrated that significant proportion of new cases of diabetes mellitus was detected in patients with pulmonary tuberculosis. These findings are an alarming signal that DM should be considered and investigated in all tuberculosis patients. These findings were similar in another study in India[33,10]. This high proportion of undiagnosed cases may indicate less awareness of DM by the public and lack of access to health care services for the diagnosis of DM[10, 34]. High prevalence of diabetes mellitus in developing countries may be also another cause.

High incidence of tuberculosis has been reported in diabetic patients. Tuberculosis increases the risk of diabetes; it is not clear. In general infection (tuberculosis) often worsens hyperglycemia[35]. Tuberculosis infection can stimulate free fatty acid synthesis and secretion[36], which mediates insulin resistance by elevating pro inflammatory cytokines, specifically tumor necrosis factor-±.

Some studies suggest that tuberculosis can cause diabetes, even in those not previously known to have diabetes mellitus[28]. However; it is unclear whether diabetes mellitus persists in these patients or whether diabetes is more prevalent with tuberculosis than with other infectious diseases.

In this current study patient those were previously diagnosed as DM, their FPG and HbA1c were uncontrolled and failed to reach target HbA1c level[37]. Diabetes was newly diagnosed in cases and their median HbA1c was significantly lower than those with previously diagnosed DM[38.] Previous diagnosed of diabetes mellitus patients have poorly controlled glycosylated haemoglobin levels.[10] The association between diabetes mellitus and TB reported in this and other case-control studies may reflect an elevated risk of TB among diabetes patients. Poorly controlled diabetes may impair the cell-mediated immune response and neutrophil function and hyperglycemia alone may provide a better environment for bacterial growth and increased virulence of various microorganisms[39].

In this study, most of cases were age over 35 years and whose was diabetics age also above 35 years. This may be related to the fact that Type 2 DM is seen more frequently in the higher age group. The mean age of the patients with TB and DM was higher than in those with tuberculosis alone. This is similar to the other study[21,40]. We assume that old age is acted as a confounding factor for this finding.

Greater number of men was diagnosed with tuberculosis than women. The finding is also compatible with other studies[40]. Male were more exposed, smoker, interpersonal and social interaction for socioeconomic and cultural reasons. In addition, men may delay seeking treatment at health clinics[41].

The body mass index was less in cases. This was true for both newly diagnosed and previously diagnosed diabetes mellitus cases. Our age group suggests more prevalent type 2 DM where we expect BMI to be higher, but coexistence with tuberculosis was probably the reason behind our findings of low BMI in TB-DM cases. Same result was matched in other study[40].

Illiterate subjects were more in our tuberculosis cases. Illiteracy is a risk factor for tuberculosis mortality and findings also pointed towards the vulnerability of uneducated persons to tuberculosis. Lack of education is correlated with poor social conditions, lower perception of health problems, less self-care, and delay in seeking health service.

The major part of the cases of this study was from urban areas. Rapid urbanization and overcrowded living conditions in urban areas are possible factors. The increased prevalence of diabetes in urban areas is responsible for the urban incidence of smear-positive tuberculosis greater than rural areas[42].

In this study odds ratio for the risk of tuberculosis associated with urban area, previous history of DM, prediabetes and for diabetes were higher than study in Indonesia[28].

The strength of study is that glycosylated haemoglobin levels & fasting plasma glucose levels were measured on all patients. HbA1C measurement provides blood glucose levels over a period 2–3 months and is not subject to the

rapid swings. Both were separately diagnostic criteria for diagnosis of diabetes mellitus[37].

**Conclusion:**

Diabetes is a risk factor for tuberculosis. The increasing diabetes prevalence may be a threat to TB control. So diabetes prevention and proper treatment may reduce TB mortality & drug resistance. Diabetes is an important co-morbid feature to be sought in patient with TB.

**References:**


1. National guidelines for the management of TB –DM . 2014; first edition, 57.
2. Alwan A. Global status report on noncommunicable diseases 2010; World Health Organization.
3. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. 2006;. 3( 11) : 442. 318
4. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes estimates for the year 2000 and projections for 2030. Diabetes care. 2004; 27(5): 1047-1053.
5. Report on Diabetes camp. 2015; Farida Huq foundation.
6. International Diabetes Federation. Diabetes Atlas, 6th edn. Brussels, Belgium: International Diabetes Federation.2013; 33.
7. Bailey SL, Grant P. 'The tubercular diabetic': the impact of diabetes mellitus on tuberculosis and its threat to global tuberculosis control. Clinical Medicine. 2011; 11(4): 344-347.
8. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. 2008; 5( 7): 152.
9. Li L, Lin Y, Mi F, Tan S, et al. Screening of patients with tuberculosis for diabetes mellitus in China. Tropical Medicine & International Health. 2012; 17(10): 1294-1301.
10. Balakrishnan S, Vijayan S, Nair S, et al. High diabetes prevalence among tuberculosis cases in Kerala, India. 2012; *7*(10): 502.
11. Restrepo BI, Camerlin AJ, Rahbar M, et al. Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases. Bulletin of the World Health Organization. 2011; 89(5): 352-359.
12. Wang CS, Yang CJ, Chen HC, et al. Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis, Epidemiology and infection. 2009; 137(02): 203-210.
13. Banerjee S, Banerjee M., Diabetes and tuberculosis interface.J Indian Med Assoc. 2005; 103: 318, 320, 322 .
14. Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review, BMC medicine, 2011; .9 (1 ): 81.
15. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infectious Diseases, 2009; 9: 737–746.
16. Bashar M, Alcabes P, Rom WN, Condos R. Increased incidence of multidrug-resistant tuberculosis in diabetic patients on the Bellevue Chest Service (1987 to 1997). 2001; 120: 1514–9.
17. Takasu N, Yamada T, Miura H et al. Rifampicin-induced early phase hyperglycemia in humans. Am Rev Respir Dis, 1982; 125: 23–7.
18. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin: clinical relevance. Clin Pharmacokinet, 2003; 42: 819–50.
19. Oluboyo PO, Erasmus RT. The significance of glucose intolerance in pulmonary tuberculosis tubercle, 1990; 71( 2): 135-138.
20. Babalika A, Ulusb I H, Bakircic N, et al. Plasma Concentrations of Isoniazid and Rifampin Are Decreased in Adult Pulmonary Tuberculosis Patients with Diabetes Mellitus, Antimicrob. Agents Chemother, 2013; 57(11): 5740-5742.
21. Restrepo BI, Camerlin AJ, Rahbar M, et al. Cross-sectional assessment reveals high

diabetes prevalence among newly-diagnosed tuberculosis cases. Bulletin of the World Health Organization, 2011; 89(5): 352-359.

22. Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. 2008; 5(7): 152.

23. Jali MV, Mahishale V, Hiremath MB. Screen all patients with tuberculosis for diab. 24. World Health organization. 2009. Global tuberculosis control: a short update to the report. Geneva: WHO etes. Curr Sci, 2013; 104: 158.

25. Stevenson CR, Forouhi NG, Roglic G, Williams BG, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosisincidence. BMC Public Health. 2007; 7: 234.

26. Shetty N, Shemko M, Vaz M, D'Souza G. An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. Int J Tuberc Lung Dis. 2006; 10: 80–86.

27. Faurholt-Jepsen D, Range N, Praygod G, et al. Diabetes is a risk factor for pulmonary tuberculosis: a case-control study from Mwanza, Tanzania. 2011; 6( 8): 215

28. Alisjahbana B, van Crevel R, Sahiratmadja E, et al. Diabetes mellitus is strongly associated with tuberculosis in Indonesia. Int J Tuberc Lung Dis, 2006; 10: 696–700.

29. Leung CC, Lam TH, Chan WM, et al. Diabetic control and risk of tuberculosis: a cohort study. American Journal of Epidemiology , 2008; 167(12): 1486-1494.

30. Rayfield EJ, Ault MJ, Keusch GT, et al. Infection and diabetes: the case for glucose control. Am J Med, 1982; 72: 439–450.

31. Balde NM, Camara A, Camara LM, et al. Associated tuberculosis and diabetes in Conakry, Guinea: prevalence and clinical characteristics. The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease, 2006; 10(9): 1036-1040.

32. Gearhart MM, Parbhoo SK. Hyperglycemia in the critically ill patient. AACN Clin Issues, 2006; 17: 50–55.

33. Viswanathan V, Kumpatla S, Aravindalochanan V, et al. Prevalence of Diabetes and Pre-Diabetes and Associated Risk Factors among Tuberculosis Patients in India. 2012; 7(7): 1367.

34. Hjelm K, Mufunda E. Zimbabwean diabetics' beliefs about health and illness: an interview study.BMC International Health and Human Rights. 2010; 10: 7

35. Wolf G. Serum retinol-binding protein: a link between obesity, insulin resistance, and type 2 diabetes. Nutr Rev. 2007; 65: 251–256.

36. Podell BK, Ackart DF, Kirk NM, et al. Non-diabetic hyperglycemia exacerbates disease severity in Mycobacterium tuberculosis infected guinea pigs, 2012; 7: 824.

37. American diabetic association. Classification and Diagnosis of diabetes mellitus. Diabetes Care. 2014; 38(1): 8-16.

38. Kornfeld H, West K, Kane K, et al. High Prevalence and Heterogeneity of Diabetes in TB Patients from South India: A Report from the Effects of Diabetes on Tuberculosis Severity (EDOTS) Study, 2016.

39. Geerlings SE, Hoepelman AIM. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunology & Medical Microbiology. 1999; 26: 259–265.

40. Blanca I Restrepo, Aulasa J Camerlin, Mohammad H Rahbar, et al. Bull World Health Organ. 2011; 89: 352–359.

41. Chan-Yeung M, Noertjojo K, Chan S L, Tam C M. Sex differences in tuberculosis in Hong Kong, International Journal of Tuberculosis and Lung Disease. 2002; 6(1): 11–18.

42. Catherine R, Stevenson, Nita G Forouhi, et al. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence· BMC Public Health. 2007; 7: 234.

Chest Heart Journal
Vol. 42, No. 2, July 2018

## *ORIGINAL ARTICLE*

# Association of ABO And RH Blood Group with Hypertension – An Observational Study

**Sobroto Kumar Roy[1], Pinaki Ranjan Das [2], Md. Zakir Hossain[3], Md. Amzad Hossain[4], AHM Nazmul Ahsan[5], Md. Mesbahul Karim Ruble[6]**

**Abstract:**

***Objective:*** *The principle aim is to find out the association of ABO and Rh blood group with hypertension.*

***Methods:*** *This cross-sectional study was conducted at hypertension and research centre, Rangpur. A total of 1128 hypertensive patients were included in this study by purposive sampling method. Staging of hypertension was done according to The JNC 7 Hypertension Guidelines. ABO and Rh blood group are determined by agglutination method.*

***Result:*** *This study demonstrated that majority (58.1%) patients were within 40 to 60 years of age. 63.7% patients were male and 36.3% were female. 65% patients were from rural area and the rest 35% from urban area. Socio-demographic data demonstrate that 48.6% was service holder, businessman 13.5%, farmer 12.2% and others occupation includes 25.7% like retired person, student etc. Majority (40.7%) patients were poor; middle class 31.7% and 23%were rich. Maximum observed systolic blood pressure was 170 mm of Hg and minimum 110 mm of Hg. Maximum diastolic blood pressure was 120 mm of Hg and minimum 60 mm of Hg. Out of 1128 hypertensive patients 21% patients had normal BMI, 66.7% overweight, 8.8% moderately obese and 3.5% patients were under weight.*

*ABO blood group of this hypertensive study subjects showed 41.3% ($p<0.001$) were blood group B, group A 32.2% ($p=0.25$); group O 14.0% ($p<0.001$) and 12.5% ($p<0.001$) were blood group AB. Rh typing of the study patients showed 92.6% ($p<0.001$) was found Rhesus positive and only 7.4% ($p<0.001$) was Rhesus negative. Among the Rh positive group 32.1% ($p=0.25$) was A positive, 35.5% ($p<0.001$) B positive, 12.5% ($p<0.001$) AB positive and 12.4% ($p<0.001$) was found O positive respectively. Among Rh negative group 0.1% ($p=0.44$) was A negative, 5.8% ($p<0.001$) B negative, 00%% ($p>0.05$) AB negative and 1.6% ($p=0.001$) was found O negative respectively in comparison with another study where Rh positive blood group were A-21.58%, B-34.58%, AB-8.85%, O- 30.70% and Rh negative group were A- 0.82%, B-0.96%, AB-0.64%, O-1.87% respectively.*

*The prevalence of hypertension was more in Rh positive blood group 92.6% ($p<0.001$), particularly in Rh B positive 35.5% ($p<0.001$) and significantly less in A, AB and O blood group which were found statistically significant.*

***Conclusion:*** *The prevalence of hypertension is more in Rh B positive and significantly less in other ABO blood group.*

***Key Word:*** *Hypertension, ABO blood group, Rh blood group.*

***[Chest Heart Journal 2018; 42(2) : 137-141]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019591*

1. Junior Consultant , Medicine, Sadar Hospital, Gopalgonj, Bangladesh.
2. Assistant Registrar, Cardiology, National Institute of Cardiovascular Disease, Dhaka, Bangladesh.
3. Professor & Head, Department of Medicine, Shaheed Ziaur Rahman Medical College, Bogura, Bangladesh.
4. Assistant Proefssor, Medicine, Shaheed Suhrawardy Medical college, Dhaka, Bangladesh.
5, Associate Proefssor, Medicine, Shaheed Suhrawardy Medical college, Dhaka, Bangladesh.
6. Assistant Proefssor, Respiratory Medicine, Shaheed Suhrawardy Medical college, Dhaka, Bangladesh.

**Correspondence to:** Dr. Sobroto Kumar Roy, Junior Consultant , Medicine, Sadar Hospital, Gopalgonj, Bangladesh.

**Submission on:** 14 May, 2018 **Accepted for Publication:** 29 June, 2018
Available at http.//www.chabjournal.org

**Introduction:**

Hypertension has proven to be a silent killer contributing to many deaths and considerably increasing morbidity worldwide.[1] Hypertension is rapidly emerging as a major public health problem in developing countries.[2] 25%of world adult population is already hypertensive. Almost three quarters of the hypertensive population are in developing countries.[3] Nationwide survey on NCD conducted in Bangladesh in 2010 indicated that the prevalence of hypertension is 17.9%.[4] Twelve million people suffers from hypertension in Bangladesh.[5] Essential hypertension generally is regarded as a polygenic disorder.[6]

The ABO blood group system was discovered by Austrian scientist, Karl Landsteiner, who found three different blood types (A, B and O) in 1900 from serological differences in blood called the Landsteiner Law.[7] In 1902, DesCasterllo and Sturli discovered the fourth type, AB.[8] The genes of ABO blood group have been determined at chromosome locus.[9-12]

The blood group of a person depends upon the presence or absence of two genes, A and B. In some study of different parts of the world it has been shown that there are some correlation between ABO and Rh blood group with hypertension. But population based study on association of hypertension with ABO blood group and Rh typing lacking in our country.

In most cases the cause of hypertension is unknown, there may be some genetic influence though yet not established. ABO blood group and Rh typing in each individual is also genetically determined.

So this association might helps in the identification of hypertension, its early prevention, treatment and prevention of target organ damage.

**Materials & Methods:**

This cross-sectional study was conducted at Hypertension Research Centre, Rangpur - A Hypertension care and Research centre from July, 2012 to December, 2012. A total of 1128 patients were included in this study by purposive sampling method. All the patients were diagnosed cases of hypertension (BP >140/90 mm of Hg). This study included adult patient aged e"18 years. All cases of secondary hypertension were excluded by history, physical examination and relevant investigations. Blood pressure was measured with a well-calibrated sphygmomanometer. Staging of hypertension was done according to The Seventh Report of the Joint National Committee on Prevention, detection, Evaluation and treatment of High Blood Pressure. ABO and Rh blood group of all hypertensive patients are determined by agglutination method.

**Results:**

This study intended to find the association between hypertension and ABO blood group. The findings derived from data analyses were presented below.

**Table-I**

*Distribution of age and sex of the study subjects (n = 1128)*

| Age (years) | Sex | | Total |
|---|---|---|---|
| | Male | Female | |
| 18-40 | 315 (27.92%) | 140 (12.41%) | 455 (40.3%) |
| 40-60 | 385 (34.13%) | 270 (23.93%) | 655 (58.1%) |
| > 60 | 18 (1.6%) | 00 (00%) | 18 (1.6%) |
| Total | 718 (63.7%) | 410 (36.3%) | 1128 (100%) |

In this study, out of 1128 hypertensive patients majority 655 (58.1%) were between 40-60 year of age and about 718 (63.7%) were male and 410 (36.3%) were female. (Table-I).

Socio-demographic data demonstrated that educational status of the study subjects included majority 314 (27.8%) were graduate and Occupation comprised majority were Service holder 548 (48.6%). Most 733 (65%) patients were from rural areas and the rest (35%) was from urban areas. Among 1128 hypertensive patients most of the 751 (66.7%) patients were overweight.

Majority of the study patients 851(75.4%) had no family history of hypertension. (Table-II).

Association of ABO and Rh blood group with hypertension:

In this study among the 1128 subjects 466(41.3%) belongs to ABO blood group B, 363(32.2%) blood

**Table-II**

*Socio-demographic characteristics of the study subjects (n = 1128)*

| Variables | | Sex | | Total |
|---|---|---|---|---|
| | | Male | Female | |
| Educational | Primary | 207 | 63 | 270 (23.9%) |
| Qualification | Secondary | 87 | 175 | 262 (23.2%) |
| | Higher Secondary | 81 | 24 | 105 (9.3%) |
| | Graduate | 286 | 28 | 314 (27.8%) |
| | Postgraduate | 57 | 120 | 177 (15.7%) |
| Total | | 718 | 410 | 1128 (100%) |
| Occupation | Farmer | 138 | 00 | 138 (12.2%) |
| | Service | 428 | 120 | 548 (48.6%) |
| | Businessman | 152 | 00 | 152 (13.5%) |
| | Others | 00 | 290 | 290 (25.7%) |
| Total | | 718 | 410 | 1128(100%) |
| Residence | Rural | 195 | 200 | 395 (35%) |
| | Urban | 523 | 210 | 733 (65%) |
| Total | | 718 | 410 | 1128 (100%) |
| BMI | Normal | 163 | 73 | 236 (20%) |
| | Overweight | 466 | 249 | 715 (66.7%) |
| | Obese | 48 | 80 | 128 (10.3%) |
| | Under weight | 41 | 08 | 49 (3.5%) |
| Total | | 718 | 410 | 1128 (100%) |
| Family history HTN | Yes | 100 | 53 | 153 (13.56%) |
| | No | 618 | 357 | 975 (86.44%) |
| Total | | 718 | 410 | 1128 (100%) |

group A, 158(14.0%) blood group O and 141(12.5%) subjects belongs to blood group AB respectively.

Majority1045 (92.6%) belongs to Rh blood group positive and only 83 (7.4%) are Rh blood group negative (Table-III).

Among the Rh positive blood group 362 (32.1%) was A positive, 401 (35.5%) B positive, 141 (12.5%) AB positive and 140 (12.4%) was found O positive respectively. Among Rh negative group 1 (0.1%) was A negative, 65 (5.8%) B negative, 0 (00%) AB negative and 18 (1.6%) was found O negative respectively (Table IV).

**Table-III**

*ABO & Rh blood group distribution of the study subjects (n=1128)*

| Variables | | Sex | | Total No. ( %) | p value |
|---|---|---|---|---|---|
| | | Male | Female | | |
| Blood Group | A | 240 | 123 | 363 (32.2) | $0.25^{ns}$ |
| | B | 267 | 199 | 466 (41.3) | $<0.001^{s}$ |
| | AB | 141 | 00 | 141 (12.5) | $<0.001^{s}$ |
| | O | 70 | 88 | 158 (14.0) | $<0.001^{s}$ |
| Total | 718 | 410 | 1128 (100) | | |
| Rh type | Positive | 635 | 410 | 1045 (92.6) | $<0.001^{s}$ |
| | Negative | 83 | 00 | 83 (7.4) | $<0.001^{s}$ |
| Total | | 718 | 410 | 1128 (100) | |

**Table-IV**

*ABO & Rh blood group distribution of the study subjects (n=1128)*

| Blood group with Rh type | Sex | | Total No. ( %) | p value |
|---|---|---|---|---|
| | Male | Female | | |
| A (+ve) | 239 | 123 | 362 (32.1) | $0.25^{ns}$ |
| A (-ve) | 1 | 0 | 1 (0.1) | $0.44^{ns}$ |
| B (+ve) | 202 | 199 | 401 (35.5) | $<0.001^{s}$ |
| B (-ve) | 65 | 0 | 65 (5.8) | $<0.001^{s}$ |
| AB(+ve) | 141 | 0 | 141 (12.5) | $<0.001^{s}$ |
| O (+ve) | 52 | 88 | 140 (12.4) | $<0.001^{s}$ |
| O (-ve) | 18 | 0 | 18 (1.6) | $0.001^{s}$ |
| Total | 718 | 410 | 1128 (100) | |

**Discussion**

In this study among 1128 hypertensive patients majority (58.1%) were 40 to 60 years of age and 63.7% were male and 36.3% female with Male female ratio 1.75:1. Hypertension is more common in men than in women of same age. Sex difference in the prevalence of hypertension may be mainly attributed to the differences in dietary habit, life style choice, salt intake, Physical activity level and some genetic polymorphism. [13]

Among 1128 hypertensive patients only 13.56% patients had positive family history and majority (75.4%) patients had no family history of hypertension. Majority of the study subjects 66.7% were overweight.

Positive family history is associated with hypertension prevalence double that found in patients with negative history and is independent with weight. When over weight is also present, however hypertension prevalence is three to four times as high. [14]

In this study among the 1128 subjects blood group B was found in 41.3% (p<0.001), group A in 32.2% (p=0.25), group O in 14.0% (p<0.001) and blood group AB in 12.5% (p<0.001) respectively (Table III).

The relative frequency of O, A, B and AB blood group in Western Europe are 46%, 42%, 9% and 3% respectively.[15]

In the United States, the frequency of O, A, B and AB blood group is 45%, 41%, 10% and 4%. [16]

In a study of our country showed prevalence of ABO blood group are A - 22.40%. B - 35.54%, AB – 9.49%, O – 32.57%. [17]

This study shows prevalence of hypertension is high in group B and significantly low in blood group O. So there was significant association found between hypertension with blood group B and O (p value is <0.05 which is statistically significant).

In this study majority 92.6% (p<0.001) was found Rhesus positive and only 7.4% (p<0.001) was Rhesus negative. Among the Rh positive group 32.1% (p=0.25) was A positive, 35.5% (p<0.001) B positive, 12.5% (p<0.001) AB positive and 12.4% (p<0.001) was found O positive respectively. Among Rh negative group 0.1% (p=0.44) was A negative, 5.8% (p<0.001) B negative, 00% (p>0.05) AB negative and 1.6% (p=0.001) was found O negative respectively.

Significant association was found in B and O positive blood group (p value is <0.001).

In a study of Belgium reported an association between the ABO blood group and blood pressure among 42, 000 Belgian men. [18] They found that those with ABO blood type AB had the highest values of SBP and DBP.

**Conclusion & Recommendation:**

The prevalence of hypertension is more in Rh B positive and significantly less in other ABO & Rh blood group.

The limitation of the present study is data were collected from single center. Further multi-

center study was recommended to validate the finding of the present study.

**References:**


1. Kotchen TA, Hypertensive Vascular Disease; In: Longo DL, Fauci SA, Kasper DL, Hauser SL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine ,18 th edition. New York: McGrawHill publishers, 2012; 2042-59.
2. Hypertension Study Group. Prevalence, awareness, treatment and control of hypertension among the elderly in Bangladesh and India: A multicentre study. Bull World Health Organ. 2001; 79:490–500.
3. Kearny PM, Global burden of Hypertension: analysis of worldwide data. *Lancet 2005*; 365:217-23.
4. Rahman M, Chowdhury MAJ et al.NCD Risk Factor Survey. BSM 2010;1- 35.
5. Sultana M H. Non-adherence to drug treatment in patients of essential hypertension. BMRC Bull; 2009; 35: 76-78.
6. McKusick V. Genetics and the nature of essential hypertension. *Circulation* 1960;22:857-863.
7. Landsteiner K: Zurr Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkungenm des Blutserums und der Lymphe. *Zentralbl Bacteriol* 1900; 27: 357-362.
8. von Decastello A, Struli A: "Ueber die Isoagglurtinine im serum gesunder und kranker Menschen". Mfinch men Wschr 1902; 49: 1090-1095.
9. Watkins WM: Biochemistry and genetics of the ABO, Lewis, and P blood group system, In: Advances in Human Genetics (Harris H & Hirschhorn K eds.). Plenum Press, New York, 1980, 136-136.
10. Larsen RD, Ernst RK, Nair RP, Lowe JB. Molecular cloning, sequence, and expression of a human GDP-L-fucose: b-D-galactoside 2-alpha-L-fucosyltransferase cDNA that can form the H blood group antigen. *Proc Natl Acad Sci* USA 1990: 87 (17):6674-6678.
11. Yamamoto F, Hakomori S. Sugar-nucleotide donor specificity of histo-blood group A and B transferases is based on amino acid substitution. *J Biol Chem* 1990;265 (31) : 19257-19262.
12. Bennett EP, Steffensen R, Clausen H, weghuis DO, Geurts van kessel A : Genomic cloning of the human histo-blood group and locus.*Biochem Biophys Res Commun* 1995;206 (1) :318-325.
13. Ruixin Y, Jinzhen W, Shangling P, Weixiong L, Dezhai Y, Yuming C. Sex differences in environmental and genetic factors for hypertension. The American journal of medicine 2008;121(9):811-819.
14. Stamler R, Stamler J, Reidlinger WF, Algera G, Roberts RH. Family (Parentaral) history and prevalence of hypertension. JAMA 1979;241(1):43-46.
15. Guyton AC, Hall JE. Blood groups; transfusion;Tissue and Organ transplantation. In: Textbook of medical physiology. 10th ed. New Delhi: Prism Saunders; 2000. 413-7.
16. Ganong WF. Blood types. In: Review of medical physiology. 21st ed. New York: McGraw-Hill; 2003. p. 539-42.
17. Pathan AH, Apu As, Jamaluddin ATM, Asaduzzaman M, Rahman MZ, Rahman A, et al. Bangladesh J. *Life Sci*.2008;20(2): 131-135.
18. Kesteloot H, Van Houte O. An epidemiologic survey of arterial blood pressure in a large male population group. *Am J Epidemiol*. 1974; 99:14-29.

Chest Heart Journal
Vol. 42, No. 2, July 2018

## CASE REPORT

# Surgical Extraction of a Huge Pacemaker Lead Vegetation causing Infective Endocarditis

**S.M.A Zulkernine Palash[1], Mohammad Delwar Hossain[2], Tamjid Mohammad Najmus Sakib Khan[3], Thahera Meher[4], Md. Kamrul Hassan[5], Saiful Islam Khan[6], Niaz Ahmed[7], Sohail Ahmed[8], Md. Zulfiqur Haider[9]**

**Abstract:**

*Infections of implantable intracardiac devices such as pacemakers are relatively rare but serious complications. In this paper we report removal of a huge vegetation in RV lead of permanent pacemaker though open surgical approach using extracorporeal circulation which was giving rise to lead endocarditis. A new epicardial lead was placed as the patient was pacemaker dependent. Though the culture of the extracted material didn't reveal any organism but the patient was improved a lot after operation from both symptomatic (subsidence of fever) & hemodynamic point of view. In follow-up OPD visit she was found to be recovered well without any complication. In conclusion, explantation of the entire pacemaker system in is necessary to cure lead endocarditis in addition to appropriate antibiotic therapy.*

***[Chest Heart Journal 2018; 42(2) : 142-146]***

*DOI: http://dx.doi.org/10.33316/chab.j.v42i2.2019592*

**Introduction:**

The use of implantable intra-cardiac devices such as pacemakers (PM) has improved the life span of patients. That's why pacemaker implantation has rapidly become a routine procedure since the first implantation of a completely implantable pacemaker by Elmqvist and Senning in 1958. One of the important complications of pacemakers is infective endocarditis from the leads as the source. Infection of the pacemaker pouch and wire may occur in 1-7% of implanted pacing systems, whereas lead endocarditis, which is a more serious condition, accounts for <10% of these complications,[1] with an incidence rate ranging from 0.06%5 to 0.6%.[2] Mortality rates in cardiac device endocarditis have been reported to be 30-35%[3]. Clinical findings of leads endocarditis are subtler than that of native valve infective endocarditis and thus the diagnosis is frequently delayed. Occurrence of lead vegetations (LVs) is described,[4-6] often as anecdotal cases[7-8]and mainly with reference to

1. Specialist, Cardio-thoracic and vascular Surgery, Apollo Hospitals Dhaka, Bangladesh.
2. Senior Registrar, Cardio-thoracic and vascular Surgery, Apollo Hospitals Dhaka, Bangladesh.
3. Registrar, Cardio-thoracic and vascular Surgery, Apollo Hospitals Dhaka, Bangladesh.
4. Registrar, Cardio-thoracic and vascular Surgery, Apollo Hospitals Dhaka, Bangladesh.
5. Registrar, Cardio-thoracic and vascular Surgery, Apollo Hospitals Dhaka, Bangladesh.
6. Specialist, Cardio-thoracic anaesthesia, Apollo Hospitals Dhaka, Bangladesh.
7. Consultant, Cardio-thoracic anaesthesia, Apollo Hospitals Dhaka, Bangladesh.
8. Consultant, Cardio-thoracic and vascular Surgery, Apollo Hospitals Dhaka, Bangladesh.
9. Senior Consultant, Cardio-thoracic and vascular Surgery, Apollo Hospitals Dhaka, Bangladesh.

**Correspondence to:** Dr. S.M.A Zulkernine Palash, Specialist, Cardio-thoracic and vascular Surgery, Apollo Hospitals Dhaka, Bangladesh.

**Submission on:** 20 May, 2018 **Accepted for Publication:** 20 June, 2018
Available at http.//www.chabjournal.org

feasibility, safety, and clinical outcomes of lead extraction (LE).[4,6,9]The reported prevalence of LV may change widely, due to the imaging technique involved and the phase of the illness. Treatment of cardiac device endocarditis is still controversial. Though medical treatment has been reported to be successful in some cases[10,11], there is increasing evidence that the entire pacing system should be removed to achieve complete infection eradication[12]. In this report we describe surgical extraction of a huge vegetation in RV lead of PPM which developed 12 years after its implantation. We will focus mainly on the surgical management of lead endocarditis.

**Case History:**

A 50 year - old female, who was implanted a pacemaker(PM) for sick sinus syndrome, changed the PM generator after long 12 years as it was not working properly. She developed local wound infection at the generator implantation site 1 year after the change. It was treated by wound debridement and secondary closure. Wound was healed properly but two months later she developed high grade intermittent fever. Initially she was treated by different medicine specialists with antibiotic courses but fever used to recur soon after finishing the antibiotics. She was investigated thoroughly including transthoracic echocardiography (TTE) but no specific cause found. At last a multidisciplinary medical board was held in chest disease hospital and decided to repeat TTE in another facility. Second echocardiography revealed a large vegetation around RV lead of PM. Meanwhile she developed septic shock with drug induced hepatitis and admitted into our hospital under cardiology.

On admission she was found tachycardic( 120 b/ min, regular), hypotensive ( BP: 80/50 mmHg), requiring inotropic support, febrile (Temp- $102^0$F). Laboratory values showed neutrophilic leukocytosis (TLC- 14.8 X $10^9$ / L), increased C-reactive protein (CRP- 7.85 mg/dl ), mildly raised bilirubin (2.2 mg/dl). Other routine laboratory values were normal. Septic workup done. But no growth found in the blood. Urine C/s showed candida albicans (> 105 CFU/ml ). Broad spectrum antibiotic with antifungal started after consultation with Microbiologist. After hemodynamic stabilization transesophageal echocardiography (TEE) done and found huge vegetation mass (4x4x3) cm attached to RV lead (Fig-1) around tricuspid valve and Right Atrium extending to SVC. RA lead tip also had vegetation. Despite broad spectrum antibiotic & antifungal coverage her total WBC count & CRP continued to rise. Multi- disciplinary medical board was arranged and decided to go for Surgical intervention.

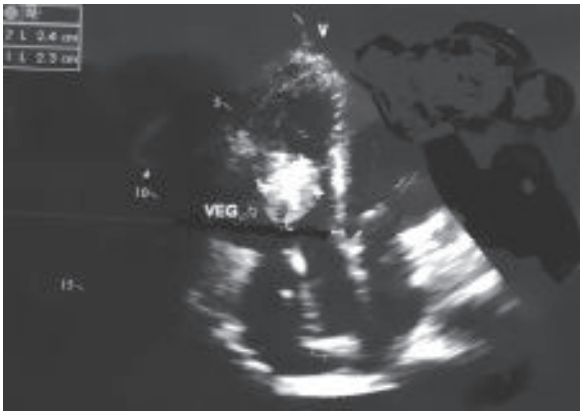



**Fig.-1:** *Showing huge vegetation in RV Lead near tricuspid valve.*

Patient was operated by cardiac surgery team. Through median sternotomy approach right atrium (RA) was opened after establishing extracorporal circulation. Large vegetations were found involving tips of both RA & RV leads*(Fig-2)*. The lead tips *(Fig-3a)*along with the vegetations were extracted*(Fig-3b)*.Patency of

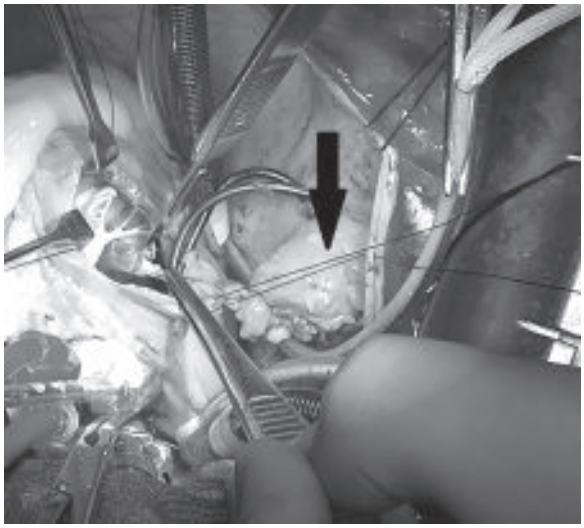
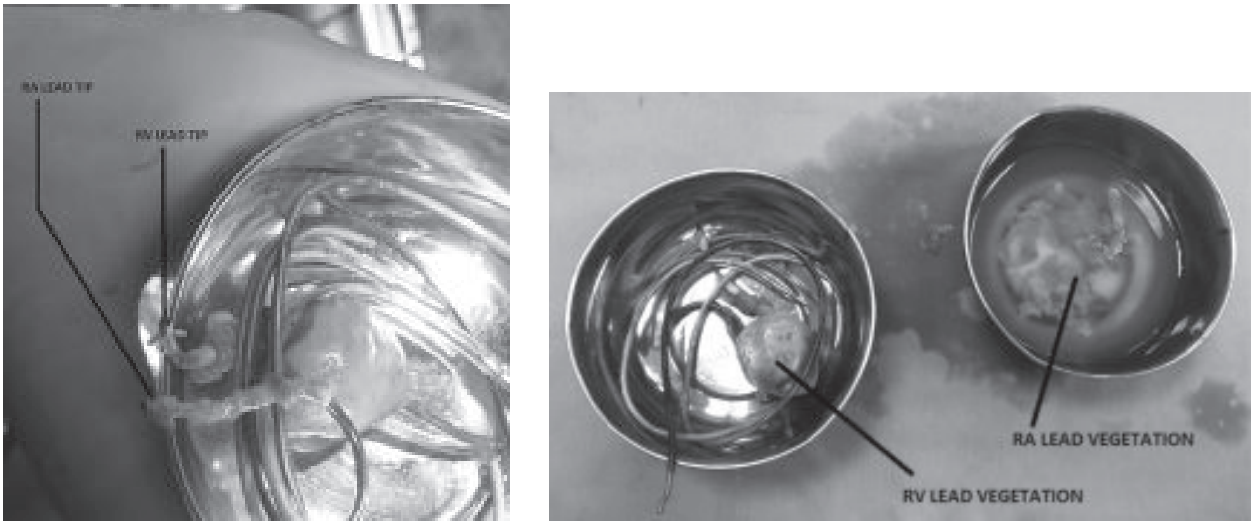


**Fig.-2:** *Vegetation (Black Arrow) around RV lead.*




(a) (b)

**Fig.-3:** *(a) Figure showing tips of extracted RA & RV leads. (b) Extracted Vegetations along with Pacemaker lead.*

Tricuspid valve was checked. Upper part of the RV lead was adherent to the SVC. The lead was removed through releasing the adhesion by exploring the SVC after total circulatory arrest (TCA), done at $18^0$C. Then closure of RA done after rewarming and the patient was slowly weaned from cardiopulmonary bypass (CPB). An epicardial pacing lead was placed over the Left Ventricle *(Fig-4)* which was then passed through a tunnel made on the left side of the chest & was kept in situ in a subcutaneous pocket in left infra-clavicular region.

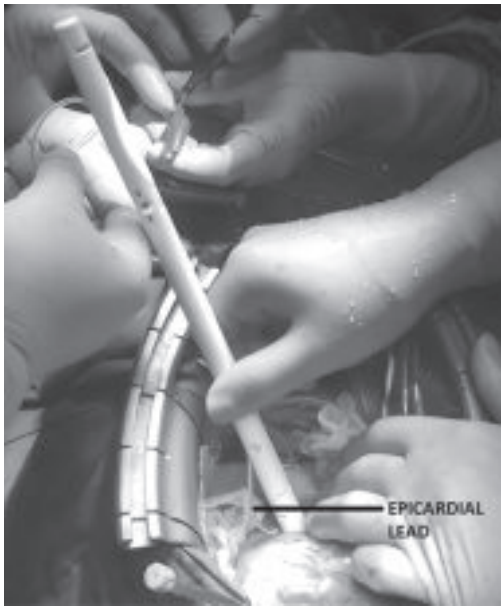



**Fig.-4:** *Figure showing placement of epicardial lead on Left ventricle (LV).*

Her postoperative course was smooth & uneventful. A New PM generator was placed on the left side (new pocket) on $4^{th}$ postoperative day (POD) and connected with the epicardial lead. It was set in VVI mode & working perfectly. Postoperative echo done on 8th POD which revealed no significant abnormality *(Fig-5).*Vegetations were sent for Histopathology and cultures (Bacterial and fungal). Histopathology didn't revealed any granuloma or malignancy. No bacterial or fungal growth was found in the culture. After operation her total WBC count, CRP and LFT was reduced back to normal level. We consulted with Microbiologist regarding

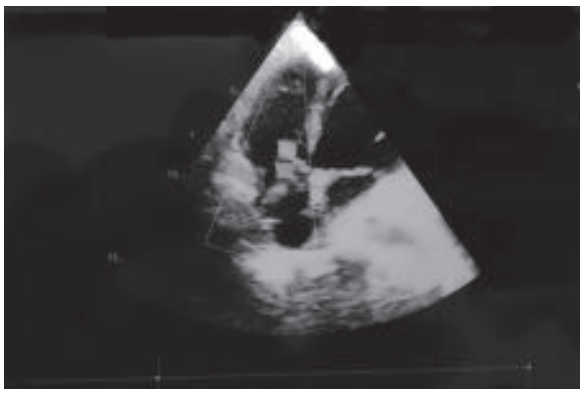


**Fig.-5:** *Postoperative echo showing no vegetation.*

antibiotics, who advised to continue i.v. antibiotics and antifungal for 6 weeks. She was discharged from hospital on 10th POD and on follow up at OPD she recovered well with overall improvement of general condition and no recurrence of fever. Surgical wound healed without any complication and follow up TTE was negative for vegetation.

**Discussion:**

Pacemaker (PM) related infections are usually limited to PM pocket. But it may involve the leads only or whole PM system. The incidence of pacemaker infection is currently reported to range from 0.5% to 1.5%, [7,8]. Recent studies report a prevalence of Lead vegetation (LV) in ~ 10%16 to 23%29 of patients with CDI. However, these figures may fluctuate widely according to the presence/absence of systemic involvement, and may be higher in patients with CDRIE/ systemic infection when compared with populations that also contain patients with pocket infections.

Clinical presentation of cardiac device-related infection (CDI) may be local, systemic, or both. Local manifestations are more common[9] and include signs and symptoms of inflammation at the device placement site,[10] possibly accompanied by fever. A chronic open skin lesion, with negative local bacteriological analyses (so-called 'chronic draining sinus'), may often be the only sign in the absence of evident infection. The intravascular segment of the lead is frequently involved in these infections.[11-12]. Infection of the pacing leads results in more severe clinical symptoms, because vegetation attached to the leads may cause infective endocarditis and promote thrombus formation in the superior vena cava and right atrium and ventricle, leading to the development of septicemia and the acute or recurrent formation of a pulmonary embolism.

The diagnosis of pacemaker infections is established by the nature of the clinical symptoms and the results of blood testing as well as ultrasonographic and radiologic imaging. However Apart from general symptoms such as fever and malaise, peripheric clinical findings of infective endocarditis are not observed frequently in these patients; hence the diagnosis is especially hard, frequently delayed and sometimes even missed. The average time from symptom onset to diagnosis is 3–4 months. Risk factors for cardiac pacemaker related infective endocarditis are diabetes, malignancy, cachexia, use of steroids and immunosuppressive treatment [3]. Our patient was non-diabetic but there had been 8 months from symptom onset to diagnosis. Blood culture positivity in these patients are less common than patients with native valve endocarditis. But in one study carried by Victor et al. [6] reported that blood cultures were positive 85% of patients with vegetation. In our case, no growth was found in the culture of blood or extracted vegetations. Echocardiography is a sensitive method for detecting

intracardiacvegetations adherent to the pacing leads. However, reviews suggest that TTE is inadequate. Victor et al. [6] evaluated 23 patients with lead endocarditis and found that TTE was capable of diagnosis in only 30% of patients, whereas TEE was able to diagnose 91% of the patient population. Additionally, TEE may give detailed information about the tricuspid valve. A recent study showed that concomitant valve infection is associated with increased mortality[10]. Therefore, in patients with permanent pacemaker, evaluation of fever should always include a TEE examination.

Extraction of whole pacemaker system including generator leads & vegetation should be the corner stone of treatment in patients with lead endocarditis. Choo et al.[5] suggested that without extracting the infected material, the infection cannot be controlled even if correct antibiotics are used according to antibiogram result. Our case was also an example for this conclusion. There are two different techniques for lead extraction. The first one is direct percutaneous extraction and the other option is surgical thoracotomy. Percutaneous technique can be used if the vegetation is smaller than 10 milimeters and the tricuspid valve is not involved, the time from implantation is shorter than 1–2 years and the patient is not pacemaker dependent. In other situations, surgical extraction and placement of a epicardial lead must be considered[3,9]. In our case the open surgical approach through median sternotomy & extra corporeal circulation was used as the vegetation was large and attached SVC. Moreover, this procedure has several advantages over the intravascular extraction methods, besides being associated with a similar low

overall risk. Specifically, the risk of mechanical injury to cardiac structures and dissemination of vegetations is less because the leads are not exposed to mechanical stress and blood circulation through the right heart is interrupted during the procedure. However, the extraction of infected leads through a purse-string suture with the heart beating, as described by Niederh • auser and associates[10], still carries the risk of incompletely removing vegetations, with subsequent dissemination. An open heart operation also allows additional surgical procedures to be performed in the right heart, such as reconstruction of the tricuspid valve or the removal of intra-cardiac vegetations and thrombi, which was necessary in all patients.

The preoperatively started antimicrobial therapy should be continued for at least 4-6 weeks after implantation of the new pacemaker. The new pacemaker was implanted through a different implantation site, usually the contra lateral pectoralis region or the upper abdominal area[11,12]. In our case both strategy was followed and patient remained free of infection on subsequent OPD visit.

**Conclusion:**

In patients with pacemakers and risk factors for endocarditis, fever must suggest lead endocarditis and TEE must be performed for accurate diagnosis. In addition to appropriate antibiotic therapy, extraction of infected material is needed for the cure. The removal of infected leads during extracorporeal circulation prevents mechanical injury as well as the spread of infection and allows additional intra-cardiac procedures to be performed, if necessary. Complications were rare, except in patients who present lately in a critically ill condition and septic shock.

**References:**


1. Arber N, Pras E, Copperman Y, Schapiro JM, Meiner V, Lossos IS et al. Pacemaker endocarditis. Report of 44 cases and review of the literature. Medicine (Baltimore) 1994;73:299–305.
2. del Rio A, Anguera I, Miro JM, Mont L, Fowler VG Jr, Azqueta M et al. Surgical treatment of pacemaker and defibrillator lead endocarditis: the impact of electrode lead extraction on outcome. Chest 2003;124:1451–9.
3. Bluhm G. Pacemaker infections: a clinical study with special reference to prophylactic use of some isoxazolylpenicillins. Acta Med Scand1985;699:1e62.
4. Massoure PL, Reuter S, Lafitte S, Laborderie J, Bordachard P, Clementy J et al. Pacemaker endocarditis: clinical features and management of 60 consecutive cases. Pacing ClinElectrophysiol2007;30:12–9.
5. Catanchin A, Murdock CJ, Athan E. Pacemaker infections: a 10-year experience. Heart Lung Circ2007;16:434–9.
6. Grammes JA, Schulze CM, Al-Bataineh M, Yesenosky GA, Saari CS, Vrabel MJ et al. Percutaneous pacemaker and implantable cardioverter-defibrillator lead extractionin 100 patients with intracardiacvegetations defined by transesophageal echocardiogram. J Am CollCardiol2010;55:886–94.
7. Kerut EK, Hanawalt C, Everson CT. Role of the echocardiography laboratory in diagnosis and management of pacemaker and implantable cardiac defibrillator infection. Echocardiography 2007;24:1008–12.
8. 18. Calton R, Cameron D, Cusimano RJ, Merchant N, Chauhan V. Successful laserassisted removal of an infected ICD lead with a large vegetation. Pacing ClinElectrophysiol 2006;29:910–3.
9. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR et al. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. Mayo Clin Proc 2008;83:46–53.
10. Lee JH, Geha AS, Ratehalli NM, Cmolik BL, Johnson NJ, Biblo LA, et al. Salvage of infected ICDs: management without removal. Pacing ClinElectrophysiol 1996;19:437e42.
11. Turkisher V, Priel I, San M. Successful management of an infected implantable cardioverter defibrillator with oral antibiotics and without removal of the device. Pacing ClinElectrophysiol 1997; 20:2268e70.
12. Myers MR, Parsonnet V, Bernstein AD. Extraction of implanted transvenous pacing leads: a review of a persistent clinical problem. Am Heart J 1990;121:881-8.