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.

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.

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 37ºC 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.
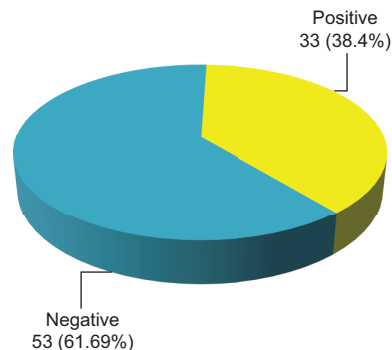

Fig.-1: *Distribution of the patients according to growth on sputum culture (n=86)*

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 house-wives, 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.