Original Article

Patterns of infections in chronic obstructive pulmonary disease exacerbations and its outcome in high dependency area, intensive care setting in a tertiary care hospital

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ABSTRACT

Background and Objectives: Chronic obstructive pulmonary disease is a common problem in both developed and developing nations. It is directly linked with smoking. It is associated with frequent exacerbations and then hospitalizations. A large percent of Gross domestic product is spent on its management. We conducted a hospital-based study in such patients who got admitted with exacerbation, whether infective or noninfective, and who required invasive ventilation during management. Such kind of study has not been reported from our country so far. The aim of this study is to determine the prevalence, etiology, and sensitivity of infective exacerbations and its impact on the outcome with the use of invasive ventilation. **Materials and Methods:** We enrolled 150 admitted patients for the study and recorded their clinical and laboratory parameters. The respiratory specimen was obtained by different ways and sent for culture and drug sensitivity. The outcome was noted with the use of invasive ventilation, and prognostic values of different variables were ascertained. **Results:** The infective exacerbation was seen in 65% and organisms involved were Gram-negative bacteria, with a predominance of *Acinetobacter* in 35%, *Klebsiella* in 32%, *Pseudomonas* in 17.5%, and *Escherichia coli* in 5%. The number of hospitalization days of the 150 patients ranged from 5 to 40 days with a mean of 16.39 ± 11.45 days. The number of Intensive Care Unit days range was 0–25 days with a mean of 7.35 ± 7.9 days. The number of days of invasive ventilation range was 2–18 days with a mean of 3.28 ± 5.2. The number of days on Bi-level positive airway pressure ventilation (BiPAP) was between 2 and 22 with a mean of 6.15 ± 5.7 days. The outcome was significant between the survivors/nonsurvivors in terms of a number of days of invasive ventilation required ($P < 0.004$). **Conclusion:** There was higher mortality among patients admitted with multiorgan dysfunction and multiple infiltrates on chest X ray, and there was significant advantage in outcome on invasive ventilation.

Key words: Bi-level positive airway pressure, bronchoalveolar lavage, C-reactive protein, chronic obstructive pulmonary disease and acute exacerbations, Clinical and Laboratory Standards Institute, pharyngeal swab

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Access this article online	
Quick Response Code:	Website: www.caijournal.com
	DOI: 10.4103/2225-6482.191369

How to cite this article: Bashir S, Muzamil J, Guru FR, Mohsin N, Nabi F, Kanwar MS. Patterns of infections in chronic obstructive pulmonary disease exacerbations and its outcome in high dependency area, intensive care setting in a tertiary care hospital. Community Acquir Infect 2016;3:77-86.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease characterized by an inexorable decline in respiratory function, exercise capacity, and health status.[1] The prevalence of COPD is increasing worldwide as is tobacco usage.[2] Increasing environmental pollution is another factor. Intermittently there are exacerbations of COPD symptoms which vary in severity and frequency during the course of patient's illness. These exacerbations are important not only because of their short-term impact on an individual's quality of life but also because of their long-term effects on health status, morbidity, and mortality. Indeed frequency of exacerbations is one of the most important determinants of health-related quality of life.[3] COPD exacerbations are a significant cause of hospital admission and readmission, and the burden placed on health resources.[4] In-hospital mortality of acute exacerbation of COPD (AECOPD) can vary from 6% to 42%.[5] Various factors such as baseline lung function, cause of acute exacerbation, severity of illness, nutritional status of the patient, and need for mechanical ventilation are responsible for such a wide range of mortality. Numerous causes of AECOPD have been identified, the most common being lower respiratory tract infection. Published data suggest that 50–70% of exacerbations are due to respiratory infections by bacteria, atypical organisms, and respiratory viruses,[6] 10% are due to environmental pollution (depending on season and geographic placement),[7] and up to 30% are of unknown etiology.[5] Bacteria are isolated from sputum in 40% to 60% of patients with acute exacerbation of chronic bronchitis. The three predominant bacterial species isolated are nontypeable *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*.

Viral infections of the respiratory tract are a common cause of morbidity. It is unclear whether a patient with COPD is more susceptible to these infections than healthy individuals. Some studies have isolated viruses more frequently in COPD patients while some have not.[8-11] Certainly, exacerbations have been associated with a prodrome of coryzal symptoms and are more frequent in winter months when viral infections are more frequent in the community.[12] Many studies have provided only indirect evidence of a viral etiology of AECOPD as they have relied on the presence of serological conversion as a marker of infection[8,13] although some recent studies have used more robust techniques including viral culture and polymerase chain reaction to identify viral RNA or DNA sequences.[10,14]

There is a paucity of data from India addressing these issues. This prospective study was therefore planned to determine the microbiologic etiology of severe COPD exacerbation requiring ventilatory support, their existing sensitivity pattern, and the association with patient outcome.

Aims and objectives

- To determine the prevalence of infection in the AECOPD requiring invasive ventilation
- To find out the microbiological etiology of AECOPD and their antimicrobial susceptibility pattern
- To evaluate the association between factors such as age, smoking status, comorbid illnesses, hospital course, and the type of organism isolated.

MATERIALS AND METHODS

The study was conducted at the Department of Respiratory Medicine in collaboration with the Department of Microbiology at Indraprastha Apollo Hospitals, New Delhi. It was a hospital-based prospective study conducted in the various medical Intensive Care Units (ICUs) and various wards of Indraprastha Apollo Hospitals. A total number of patients enrolled were 150.

Inclusion criteria

Patients with a history of COPD admitted with acute respiratory failure and requiring invasive ventilation having a history of recurrent cough with expectoration, dyspnea, and history of exposure to risk factors for the disease were enrolled in this prospective study.

A clinical evidence of exacerbation of COPD was either in the form of increased cough, sputum production, change in character of sputum, increased shortness of breath, and other typical signs resulting in respiratory failure.

Exclusion criteria

Patients excluded were those having the previous diagnosis of bronchial asthma or neoplasia, immunosuppressed state, and patient hospitalized within 1 month prior to the present admission.

For all the patients included in the study, a detailed history and physical examination were performed at admission. Informed consent was obtained from patient or next of kin. The following variables were recorded for each patient enrolled in the study.

Host factors - age, gender, duration of COPD, previous history of exacerbations, smoking habits and alcohol status, duration in years, comorbidities (diabetes, hypertension, chronic renal disease, malignancy, tuberculosis, etc.), and environment pollutant exposure such as Chula smoke, history of tuberculosis, and history of intubations.

The following laboratory parameters were noted: Hemoglobin, total leukocyte count (TLC), arterial blood gases (pH, pCO_2, paO_2, and bicarbonate), urea, creatinine, albumin, proteins, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, and chest radiograph (CXR).

Participants were investigated for microbiological evidence of infection within 48 h of admission using specimens such as pharyngeal swab, tracheal aspirate, bronchoscopic bronchoalveolar lavage (BAL), and C-reactive protein (CRP) or blood culture. If the patient developed ventilator-associated pneumonia (VAP), bronchoscopy was repeated to confirm the diagnosis and for microbiological analysis. The criteria for VAP included:

- Appearance of a new or progressively increasing infiltrates on CXR
- Fever
- Leukocytosis
- Purulent tracheal secretions (diagnosis of pneumonia was made when three of the above criteria, which include criteria 1, were present).

Microbiological analysis was performed at the Department of Microbiology, Indraprastha Apollo Hospitals. Samples were transported to the laboratory immediately where they were Gram-stained and examined. The samples were then cultured to ascertain the microbial patterns.

The following aerobic culture media were used 5% sheep blood agar, MacConkey's agar, and Chocolate agar. Isolated strains were identified by standard microbiological techniques. The antimicrobial susceptibility testing was performed by disc diffusion method as per Clinical and Laboratory Standards Institute guidelines. Ziehl–Neelsen staining for acid-fast bacillus and fungal culture was performed on BAL sample only.

Then, the outcome was assessed by the following parameters:

- Survivor or nonsurvivors
- Number of hospitalization days
- Invasive ventilation required or not
- Number of ventilated days
- Number of BiPAP days
- Antimicrobial susceptibility pattern.

OBSERVATIONS AND RESULTS

We prospectively studied 150 patients who were admitted with a diagnosis of AECOPD and required invasive ventilation in the various medical wards and ICUs of the Indraprastha Apollo Hospitals, New Delhi, between December 2010 and April 2012. All the patients included in the study had severe exacerbations of COPD. The following observations were made on data analysis of these patients.

The age range was 42–82 years with the median age of the study participants was 59 years. The majority of the patients were between 50 and 60 years. The male to female ratio was 2.3:1. The majority of the patients were smokers (80%). The duration of smoking was 2–45 years with a mean duration of 14.8 ± 8.5 years. The duration of COPD was 1–17 years with a mean of 7.9 years (±3.7). The duration of COPD exacerbation was in the range of 2–10 days. A large majority of the patients had comorbidities (120/150). Hypertension being the most common in 45% patients, followed by tuberculosis (23.5%), and diabetes mellitus in 20% of patients, and chronic kidney disease was present in 7.5% patients.

The study revealed that sixty patients had a history of tuberculosis (40%) and around 112 patients had a history of previous exacerbations of COPD (75%) [Table 1]. There was a previous history of intubation in 25% of the participants. Thirty percent of the patient had a history of exposure to Chula smoke, and 35% of them gave a history of alcohol intake [Table 1].

The CXR infiltrates were present in 65%, unilateral infiltrates were seen in 47.5%, and bilateral infiltrates were seen in 17.6% patients. Chest X-ray was normal in 35% patients. The CRP was positive in 72.5% patients.

All of the patients had received antibiotics prior to the sampling of the respiratory tract. All patients had received a combination of antibiotic from the onset of symptoms. The most commonly used antibiotic was amoxicillin-clavulanic acid followed by azithromycin.

All the patients were investigated for the microbiological evidence of infection within 48 h of admission. The pharyngeal swab was obtained in all the 150 patients, normal flora was seen in 60%, and 15% samples were sterile. *Klebsiella* was the most common organism seen in 15% and *Pseudomonas* and *Acinetobacter* in 5% each [Figure 1].

Tracheal aspirate was sterile in 45%, normal flora in 17.5%. *Acinetobacter* was the most common organism seen in

Table 1: Clinical characteristics of patients

Age	59.6±11.05 (42-82)
Gender	
Male	105 (70%)
Female	45 (30%)
Duration of COPD years	7.9±3.7 (1-17 years)
Duration of exacerbation	5.3±2.1 (2-10 years)
Co-morbidities	
HTN	40 (27.50)
HTN + DM	15 (10%)
HTN + TB	7 (5%)
HTN+ CKD	15 (10%)
DM	15 (10%)
Malignancy	3 (2.5%)
TB alone	25 (17.5%)
CKD	3 (2.5%)
NONE	30 (20%)
Past H/o PTB	60 (40%)
Past H/o exacerbation	112 (75%)
Past H/o intubation	37 (25%)
Smoking	120 (80%)
Alcohol intake	52 (35%)
Chulla smoke	45 (30%)

20%. *Klebsiella* was seen in 10% and *Escherichia* coli in 5% [Figure 2].

BAL was done in 99 patients, 42 were sterile. *Acinetobacter* was the most common present in 24 patients, *Klebsiella* in 12, *Pseudomonas* in 6, *E. coli* in 6, and normal flora in 9 [Figure 3].

When the results from nonbronchoscopic BAL and bronchoscopic BAL were considered together, microorganisms were isolated from 65% patients with AECOPD. Gram-negative bacteria were isolated with a predominance of *Acinetobacter* in 35%, *Klebsiella* in 32%, *Pseudomonas* in 17.5%, and *E. coli* in 5% [Figure 4].

The patients were divided into two groups based on whether bacteria could be isolated from either the pharyngeal swab, tracheal aspirates, BAL fluid or not. Bacterial positivity was seen in 86.4% of males and 13.6% of females. About 27.3% of positive cultures were seen in patients below 50 years and 22.7% in patients above 70 years of age. About 81.8% of patients had bacterial positivity who gave a previous history of exacerbations. CRP positivity was seen in 72.5% of patients who showed bacterial positivity too.

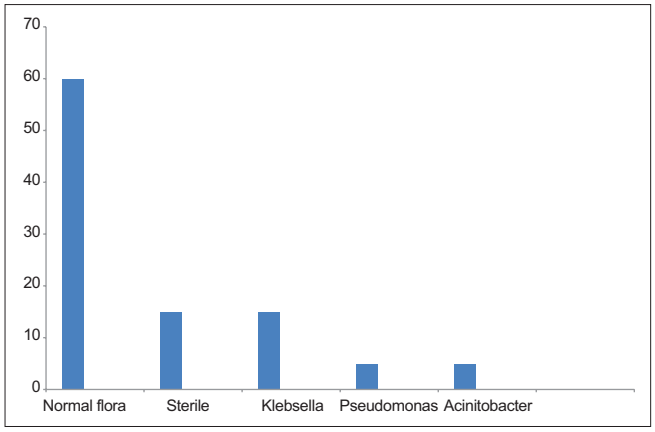

Figure 1: *Klebsiella* followed by *Pseudomonas* was isolated among pathogens in pharyngeal aspirate

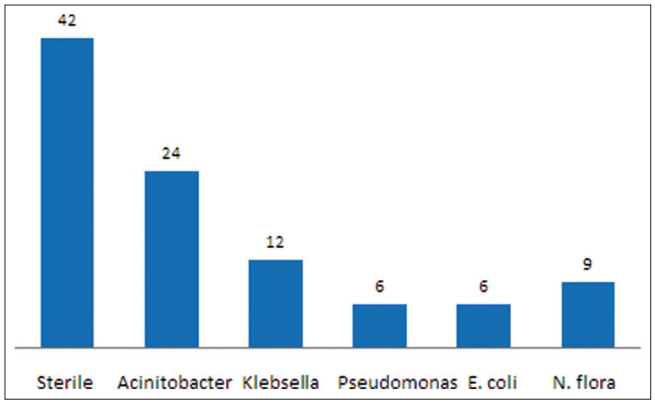

Figure 3: *Acinetobacter* followed by *Klebsiella* pathogen isolated in bronchoalveolar lavage

Patients with unilateral infiltrates had 59.1% positive bacterial isolation, while those with bilateral infiltrates had 27.3% positive isolates. The difference between the two groups in terms of gender, age, previous history of exacerbation, and CRP was not statistically significant.

The BAL fluid from all the patients was subjected to KOH preparation and fungal culture. Fungi were isolated in 12.5% patients. Majority were *Candida*, found in 12 and 3 patients had *Aspergillus* species. The majority of patients with fungal positivity were above 70 years; however, this difference in terms of age was not statistically significant.

Among the Gram-negative bacteria isolated from the respiratory tract samples, only seven were producers of extended spectrum of beta-lactamase (ESBL). *Klebsiella*, as well as *Acinetobacter*, isolates were 80% sensitive to cefoperazone-sulbactam. This was followed by polymyxin, piperacillin-tazobactam, meropenem, and imipenem. *E. coli* isolated in 5% patients were ESBL negative and sensitive to all antibiotics except amikacin [Figure 5].

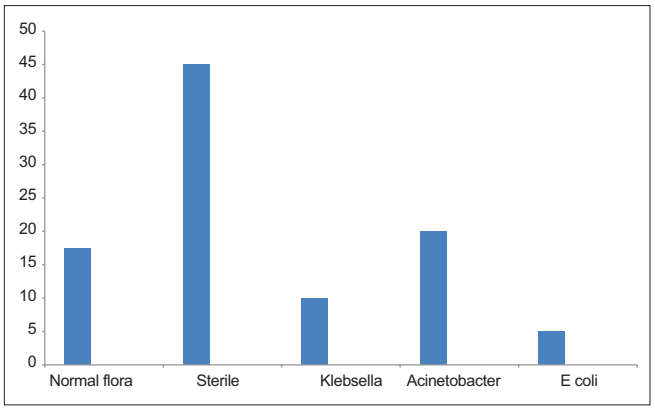

Figure 2: *Acinetobacter* followed by *Klebsiella* pathogens isolated in tracheal aspirate

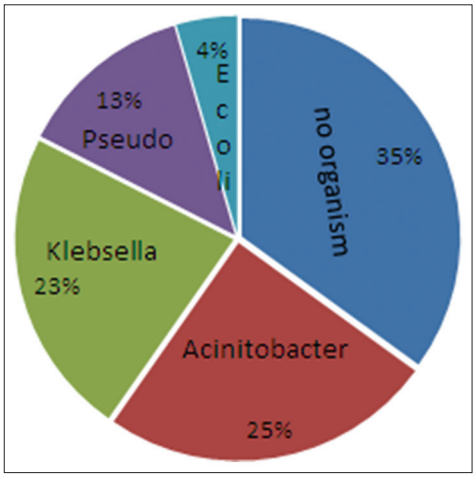

Figure 4: Pie diagram revealing *Acinetobacter* followed by *Klebsiella* organisms isolated from all types respiratory secretions

The number of hospitalization days of the 150 patients ranged from 5 to 40 days with a mean of 16.39 ± 11.45 days. The number of ICU days range was 0–25 days with a mean of 7.35 ± 7.9 days. The number of days of invasive ventilation range was 2–18 days with a mean of 3.28 ± 5.2. The number of days on BiPAP was between 2 and 22 with a mean of 6.15 ± 5.7 days [Table 2]. The outcome was assessed in terms of survival and nonsurvival. Of the total 150 patients, 127 were alive and 23 died.

The outcome variables between the two groups were statistically significant in terms of invasive ventilation requirement ($P = 0.005$). Among survivors, only 45 out of 127 patients were intubated. All the 23 patients who died had been intubated.

The outcome in terms of number of hospitalization days ($P = 0.04$), number of ICU days ($P = 0.031$), and number of days of noninvasive ventilation ($P = 0.045$) was not statistically significant. The outcome was significant between the two groups in terms of a number of days of invasive ventilation required ($P < 0.004$).

The outcome in terms of gender revealed that all the 23 patients who died were males and all the females who presented with AECOPD were alive. This difference between the two groups was not statistically significant.

The outcome in terms of CRP between the two groups was not statistically significant ($P = 0.464$). The outcome analysis in terms of pH, pCO_2, HCO_3, hemoglobulin, TLC, urea, creatinine, total protein, albumin, SGOT, SGPT, and serum alkaline phosphatase was not statistically significant [Table 3].

The analysis in terms of CXR infiltrates revealed that 15% of the patients with unilateral infiltrates and 40% of the patients with bilateral infiltrates died. No patient with a normal CXR died. This difference, however, was statically significant ($P = 0.0021$). The analysis of CXR infiltrates in terms of number of hospitalization days, number of ICU days, number of days of invasive ventilation, and number of BiPAP days were all statistically significant ($P < 0.001$) [Table 4].

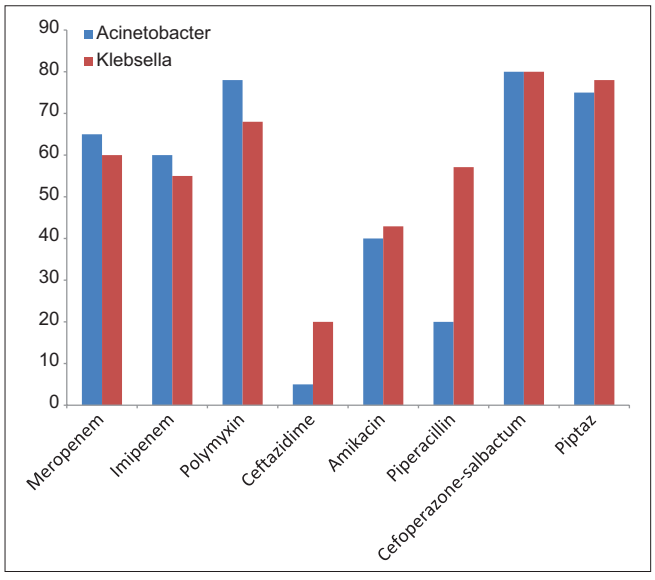

Figure 5: Organisms were sensitive to cefoperazone, piperacillin, and carbapenems

DISCUSSION

COPD is a major cause of mortality worldwide. Exacerbations of COPD are thought to be caused by the interaction

Table 2: Course in hospital

Hospitalization (days)	16.39±11.45
ICU stay (days)	7.35±7.9
Invasive ventilation (days)	3.28±5.2
Use of BiPap (days)	6.15±5.7
Outcome	
Alive	34 (85%)
Dead	6 (15%)

Table 3: Comparison of laboratory parameters

Lab parameter	Outcome	Mean	St. Deviation	*P*
Ph	Alive	7.3438	0.07652	0.447
	Dead	7.3133	0.10482	
PCO_2	Alive	60.02	13.400	0.288
	Dead	52.33	8.869	
PO_2	Alive	61.43	14.376	0.404
	Dead	65.33	9.709	
HCO_3	Alive	31.32	4.977	0.592
	Dead	29.50	4.593	
Hb	Alive	11.17	2.518	0.956
	Dead	10.97	2.032	
TLC	Alive	1.08E4	4185.312	0.985
	Dead	1.13E4	7697.186	
Ur	Alive	46.50	50.165	0.019
	Dead	119.00	103.309	
Cr	Alive	1.168	1.1726	0.447
	Dead	1.967	2.3611	
Albumin	Alive	3.22	0.283	0.061
	Dead	3.35	0.476	
SGOT	Alive	36.97	13.037	0.071
	Dead	49.83	20.074	
SGPT	Alive	37.00	16.739	0.255
	Dead	40.67	11.501	

Table 4: Comparison of chest radiograph in terms of outcome

Chest radiograph	Hospitalization (days)	ICU stay (days)	Invasive ventilation (days)	BiPap use (days)
Unilateral infiltrates				
Mean	20.37	10.42	4.21	6.95
Std. Deviation	12.509	8.611	5.213	5.532
Bilateral infiltrates				
Mean	21.14	11.29	7.29	10.29
Std. Deviation	8.707	6.993	7.365	7.410
Normal				
Mean	7.33	1.21	0.00	3.00
Std. Deviation	3.601	1.578	0.000	2.184
P value	0.000	0.000	0.00	0.004

between host factors, bacteria, viruses, and changes in air quality to produce increased inflammation in the lower airways. Most of the patients who present with AECOPD receive empirical antimicrobials in the emergency room only. The choice of initial antimicrobial therapy is purely empirical and based on existing pattern of microbial etiology of AECOPD prevalent in that area.

Deciding on the appropriate antibiotic at the outset is extremely important as studies have found that inappropriate initial antibiotic treatment is independently associated with increased ICU mortality.[15] However, conversely many controlled trails have shown little or no benefit on treatment with antimicrobial agents.[16,17] This has been attributed to small patient numbers, inappropriate selection of patients, and the choice of antibiotics used in these studies. Because bacterial infections are mucosal and some are likely to resolve spontaneously, the difference between antibiotic and placebo treatment may be difficult to detect, particularly in exacerbations that have not been characterized and when a proportion might not even have been bacterial in origin. The discrepancies in the result from these trails emphasize the need for determination of the existing prevalence of exacerbations caused by bacterial infections, proper identification of patients likely to have a bacterial exacerbation, and knowledge of the prevalent microorganisms and their antimicrobial susceptibility patterns.

This prospective study describes the clinical course and microbiology of 150 patients with COPD with acute or acute on chronic respiratory failure requiring invasive mechanical ventilation admitted to a tertiary care hospital in New Delhi, India, between December 2010 and April 2012. In our study, majority of the patients (35%) were in the age group 50–60 years. The prevalence of COPD is highest in older age group due to the cumulative effect of exposure to risk factors of cigarette/bidi/Chula smoke and the natural decline in forced expiratory volume in 1 s (FEV_1). Exposure to risk factors leads to an accelerated decline in FEV_1 leading ultimately to the clinical manifestation of COPD. Few patients who manifest the disease in the third or fourth decade of life usually have a genetic abnormally in the form of alpha-1 antitrypsin deficiency. The male to female ratio was 2.3:1 in our study cohort. This male predominance in COPD is seen across the world, though the increase in the number of female tobacco smokers is gradually narrowing down this difference. In our country, exposure to Chula smoke is an important risk factor for the development of COPD in the female population, along with the rise in the number of female smokers.[17]

Overall, tobacco accounts for an estimated 80–90% risk of developing COPD.[17] In this study as well, 80% of the patients were smokers, out of which none had quit smoking. Other factor which has been found to be associated with COPD is exposure to indoor air population in the form of exposure to human fuels (Chula smoke).[18] In a developing country like India, still a large number of people live in cramped, closed spaces, and cook food over Chula without proper ventilation for the ensuing smoke. Thirty percent of our patients had a history of exposure to Chula smoke, which might have accounted for their COPD.

The number of published articles on CAP in patients with AECOPD is very small. In a prospective, multicentric, Spanish study, 124 hospitalizations for CAP among patients with COPD were investigated.[19] Despite the importance of this study, the acute episodes were investigated from the viewpoint of CAP and not AECOD, so there was no comparison between these cases and cases of AECOPD without CAP. Lieberman *et al*. analyzed 240 hospitalizations of 213 patients of AECOPD out of which 23 (10%) have chest infiltrates classified as pneumonia.[20] Paired sera were obtained for each of the hospitalizations and were tested serologically for 12 pathogens. No significant differences were found between the two groups for any of the parameters related to COPD, comorbidity, or the clinical type of the exacerbation. However, compared to nonpneumonic acute exacerbations (NPAEs), patients with pneumonic acute exacerbations (PNAE) had lower pO_2 values at hospital admission ($P = 0.004$), higher rates of ICU admission (P - 0.007), requirement of invasive ventilation ($P = 0.01$), mortality ($P = 0.007$), and longer hospital stay ($P = 0.001$). In 22 PNAE hospitalizations (96%) and in 153 NPAE hospitalizations (71%), at least one infectious etiology was identified ($P = 0.001$). In PNAE, compared to NPAE, viral and pneumococcal etiologies were more common; however, the rate of atypical pathogens was similar.

In our study, 65% of patients had infiltrates on the chest X-ray. Five percent had unilateral whereas 17.6% had bilateral infiltrates. The comparison of demographic data and clinical background in patients shows no significant difference between the PNAE group and the NPAE group. Similar to the study by Lieberman *et al*., the presence of infiltrates was associated with higher rate of isolation of microorganisms, an increased incidence of complications, increased morbidity, and mortality.[20] Patients with unilateral infiltrates on CXR had 59.1% isolation, and those with normal CXR had 13.6% positive isolation in our study.

The study of the role of bronchial infection in AECOPD has yielded conflicting results. Most studies were conducted in patient with mild-to-moderate exacerbation treatable on an outpatient basis, and the majority was designed as trials evaluating the effect of antimicrobial treatment which may be regarded as an indirect means to evaluate the role of bacterial infection in acute exacerbations.[16,21] Early studies evaluating the microbial flora of patients with chronic bronchitis relied on sputum cultures.[21-24] However, sputum is especially vulnerable to sampling errors and oropharyngeal contamination, and therefore, nowadays considered to represent an inadequate tool for the evaluation of the role of bacteria in acute exacerbation. Important insights into

the distal bacterial flora have been provided by studies using protected specimen brush (PSB) with quantitative cultures. Monsó *et al*. showed that 25% of patients with stable COPD were colonized with bacterial pathogens as compared with around 50% during acute mild to moderate exacerbations.[25] Fagon *et al*. investigated patients with AECOPD requiring mechanical ventilation using the PSB technique and found positive bacterial results in 50% of cases.[26] In another bronchoscopic study by Pela *et al*., 52.5% specimens of AECOPD revealed significant bacterial growth as compared to 25% patients with stable COPD.[27] The predominant microorganism was *S. pneumoniae*. The mortality rate and the duration of both mechanical ventilation and hospitalization were not different in patients with or without positive microbiological results. Thus, these studies suggested that bronchial infection by bacterial pathogens may have a role in up to 50% of cases of acute exacerbations.

A detailed evaluation of the lower respiratory tract by various techniques significantly increases the yield of pathogens. Soler *et al*. found evidence for pathogens in 72% patients of AECOPD by a comprehensive microbiological evaluation including TBAS, BAL, and serology.[28] Among these techniques, serology had the highest independent impact on this increased yield. Moreover, the rate of Gram-negative bacilli (GNB) and *Pseudomonas* spp. was unexpectedly high in their study. In the present study, 65% of the lower respiratory tract samples were positive for bacteria, and all were Gram-negative.

Infections due to GNB and *Pseudomonas* sp. are of special concern in the treatment of acute severe exacerbation as these organisms require specific and prolonged antimicrobial treatment with the higher generation of antibiotics. In the studies using bronchoscopic methods, these pathogens were only infrequently found in outdoor patients, with a rate of 5% and 7%.[29] However, they were only isolated with increasing frequency (16% and 28%) in mechanically ventilated patients.[28] Our study also demonstrated 65% GNB with a predominance of *Acinetobacter* spp. in 35%, *Klebsiella* in 32%, and *Pseudomonas* in 17.5% of patients. These findings indicate that the empirical treatment of all patients of AECOPD cannot be standardized with a set of antimicrobials. Treatment has to be individualized, and all efforts should be made to achieve a microbiological diagnosis. On the other hand, patients who present with severe exacerbations, especially those requiring mechanical ventilation, should be covered adequately for infection with Gram-negative bacteria, especially *Acinetobacter* and *Pseudomonas*. The bacterial isolate recovered by various techniques in COPD patients in different studies with a comparison to our study is depicted in Table 5.

In the present study, the rate of isolation of bacteria is slightly higher as compared to the previous studies. The foremost cause for this discrepancy is the presence of highly advanced microbiological laboratory at our hospital or a higher incidence of critically ill patients being evaluated at our center. Almost 100%

Table 5: Bacterial isolates in various studies

Study	Subject	Diagnostic methods	Antibiotic pretreatment	% bacterial pathogen positive	Bacterial pathogens isolated, (%)
Fagon *et al.* [15]	50 ICU patients receiving mechanical ventilation	PSB	NA	50	*Haemophilus parainfluenzae*, 11 (22) *S. pneumonia*, 7 (14) *H. influenzae*, 6 (12) *M. catarrhalis*, 3 (6) *P. aeruginosa*, 3 (6) Other gram negative, 6 (12) Other gram positive, 9 (18)
Monso *et al.* [14]	29 outpatients	PSB	NA	51.7	*H. influenzae,* 10 (34.4) *S. pneumoniae,* 3 (10.3) *P. aeruginosa,* 2 (6.9) *M. catarrhalis,* 2 (6.9)
Soler *et al.* [17]	50 ICU patients receiving mechanical ventilation	PSB, BAL, Endotracheal aspirate	42%	46	*H. influenzae,* 11 (22) *P. aeruginosa,* 9 (18) *S. pneumoniae,* 4 (8) *M. catarrhalis,* 4 (8) Other gram negative, 6 (12)
Pela *et al.* [18]	40 outpatients	PSB	NA	52.5	*S. pneumoniae,* 10 (25) *Alpha hemolytic streptococci,* 6 (15) *M. catarrhalis,* 2 (5) *H.influenzae,* 1 (2.5) *P. aeruginosa,* 1 (2.5) Other gram negative, 1 (205) Other gram positive, 1 (2.5)
Current study	150 ICU patients requiring mechanical ventilation	PSB, BBAL, NBBAL	100%	65%	*Acinetobacter sp,* (35%) *Klebseilla* (32.5%) *Pseudomonas sp* (17.5%) *E. coli*, (5%) *Citrobacter* (2.5%)

of our patients had received antibiotics prior to admission. The over-the-counter usage of oral antibiotics is quite common in our country. It is likely that patients received antibiotics for some time before being brought to our hospital (being a tertiary care center). All of them received a combination of antimicrobials for atypical coverage and few received high-end antibiotics which include piperacillin-tazobactam and cefoperazone-sulbactam. This could have eradicated the sensitive community acquired bacteria like *S. pneumoniae* and may be the reason why these bacteria were not isolated in our study.

There was no significance difference in gender, mean age, CXR infiltrates between the patients with GNB as compared to the patients without. The duration of exacerbation tended to be lesser in patients where bacteria were identified although it did not reach statistical significance. This can be explained by the fact that longer the duration of exacerbation, more the changes that the patient would have sought for over-the-counter treatment with antimicrobials. Blood gas parameters and biochemical parameters including baseline TLC were also not significance different between the two groups.

This finding is similar to the result obtained from the study Soler *et al*. where the presence of GNB and *Pseudomonas/Stenotrophomonas* sp. could not be predicted by age, smoking states and alcohol status, current glucocorticoid therapy, FEV_1% predicted, or number of previous hospitalizations.[28] Although there was a tendency of GNB and *Pseudomonas/Stenotrophomonas* spp. to occur more frequently in elderly patients in both the studies and in those being most frequently hospitalized, these differences did not reach statistical significance. Since our study focused on a fairy homogeneous population of severe exacerbations requiring mechanical ventilation, lack of relation of patient factors with bronchial isolates may not be representative of COPD exacerbations in general.

In our study, the presence of bacteria did not influence the severity of acute clinical illness, nor did it affect the length of mechanical ventilation, ICU, or hospital stay. This observation is in accordance with the findings of others.[26,28] These findings may support the view that bacterial infections may not represent the only cause of acute exacerbations.

In our study, *Pseudomonas*, as well as *Acinetobacter*, isolates were 80% sensitive to cefoperazone-sulbactam, followed by polymyxin, piperacillin-tazobactam, meropenem, and imipenem. *E. coli* isolated in 5% patients was ESBL negative and sensitive to all antibiotics, except amikacin.

Majority of our isolates were beta-lactamase producers and hence multidrug resistant (MDR). This trend is probably due to the extensive use of antimicrobial in the current setting. In a recent study done by Nseir *et al*., quantitative tracheal aspirates were performed on 857 patients with severe exacerbations of COPD, and 304 bacteria were isolated (>10 CFU/mL) in 206 patients (30%).[30] This includes 75 MDR bacteria (24%). Previous antimicrobial treatment and previous intubation were independent risk factors for MDR bacteria. ICU mortality rate was higher in patients with MDR bacteria than in patients without MDC bacteria (44% *vs*. 25%; $P < 0.001$) rates were significantly higher in patients with bacteria other than MDR. Inappropriate initial antibiotic treatment was independently associated with increased ICU mortality.

In our study, fungi were demonstrated in the BAL fluid in 12.5% cases. Majority of the isolates were *Candida* sp. found in 12 *Aspergillus* sp. were isolated in three cases. In our study, the majority of patients with fungal positivity were above 70 years; however, this difference in terms of age was not statistically significant. The difference in terms of gender, previous history of exacerbation, tuberculosis, CRP, and CXR infiltrates was not statistically significant between the two groups who showed fungal positivity and negativity.

One of the aspects evaluated in our prospective study was hospital mortality. In-hospital mortality was 15% in our cohort which is similar to other studies where it has been found to be 6–42%.[5,31-33] The baseline lung function, cause of acute exacerbation, severity of illness at the time of presentation, nutritional status of the patient, and need for invasive ventilation are some of the factors.

We found no difference in the preintubation pH and $PaCO_2$ between survivors and nonsurvivors. Some studies have shown arterial blood gas parameters, especially pH and $PaCO_2$ to be important predictors of mortality. However, most of these studies were done on stable COPD outpatients. In contrast, studies on hospitalized patients with COPD have found no association between respiratory blood gas parameters and hospital mortality although they had value as predictors of long-term outcome.[34] In a landmark study done on patients with AECOPD, Connos *et al*. also did not find pH and $PaCO_2$ to be independently related to survival.[5]

Fungi have not been commonly described as a cause of AECOPD. *Candida* sp. is frequently isolated from the respiratory tract, but they are usually regarded as colonizers. *Aspergillus* sp. though not so commonly isolated as *Candida* sp. has been seen to colonize the respiratory tract of patients with structural lung diseases, especially those on chronic steroid treatment or those admitted in a hospital or nursing care facility for prolonged periods.

The role of prognostic factors like previous history of AECOPD, previous intubations, have been used in predicting outcome in patients with COPD has been addressed through multiple well-controlled studies.[35] It has been found that Acute Physiologic Assessment and Chronic Health Evaluation II score is useful in predicting mortality in AECOPD though the timing of scoring after admission has varied in different studies. We compared various baseline parameters between the survivor and nonsurvivor group.

Serum albumin reflects the underlying nutritional status of the patients and is also affected by the severity of acute illness. In a chronic inflammatory condition like COPD, depletion of fat-free mass is seen in at least 40–50% clinically stable patient with moderate to severe disease.[36] We also found that the levels of liver enzymes were significantly higher in the nonsurvivor group. This may be due to a more florid cytokine response, hypotension leading to ischemic hepatitis, and sepsis-induced multiorgan dysfunction syndrome in these patients.

CONCLUSION

This is the first kind of study from India which takes into account the AECOPD with factors causing it, need for invasive ventilation, recovery of microorganisms, its sensitivity, and its effect on survival. Gram-negative bacteria were the most common organisms recovered. In-hospital mortality was 15% and was among the patients having multiorgan dysfunction and infiltrates on chest X-ray. There was a significant advantage in outcome in patients who required invasive ventilation.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Stockley RA. Neutrophils and the pathogenesis of COPD. Chest 2002;121 5 Suppl: 151S-5S.
2. Lopez AD, Murray CC. The global burden of disease, 1990-2020. Nat Med 1998;4:1241-3.
3. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157(5 Pt 1):1418-22.
4. Pauwels R, Calverley P, Buist AS, Rennard S, Fukuchi Y, Stahl E, *et al.* COPD exacerbations: The importance of a standard definition. Respir Med 2004;98:99-107.
5. Connors AF Jr, Dawson NV, Thomas C, Harrell FE Jr, Desbiens N, Fulkerson WJ, *et al*. Outcomes following acute exacerbations of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understanding Prognosis and Preferences for Outcomes and Risks to Treatment). Am J Respir Crit Care Med 1996;154:959-67.
6. Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. Chest 1995;108 2 Suppl: 43S-52S.
7. Sunyer J, Sáez M, Murillo C, Castellsague J, Martínez F, Antó JM. Air pollution and emergency room admissions for chronic obstructive pulmonary disease: A 5-year study. Am J Epidemiol 1993;137:701-5.
8. Carilli AD, Gohd RS, Gordon W. A virologic study of chronic bronchitis. N Engl J Med 1964;270:123-7.
9. Monto AS, Bryan ER. Susceptibility to rhinovirus infection in chronic bronchitis. Am Rev Respir Dis 1978;118:1101-3.
10. Smith CB, Golden CA, Kanner RE, Renzetti AD Jr. Association of viral and *Mycoplasma pneumoniae* infections with acute respiratory illness in patients with chronic obstructive pulmonary diseases. Am Rev Respir Dis 1980;121:225-32.
11. Greenberg SB, Allen M, Wilson J, Atmar RL. Respiratory viral infections in adults with and without chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;162:167-73.
12. Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. Respir Care 2003;48:1204-13.
13. Stenhouse AC. Viral antibody levels and clinical status in acute exacerbations of chronic bronchitis: A controlled prospective study. Br Med J 1968;3:287-90.
14. Seemungal TA, Harper-Owen R, Bhowmik A, Jeffries DJ, Wedzicha JA. Detection of rhinovirus in induced sputum at exacerbation of chronic obstructive pulmonary disease. Eur Respir J 2000;16:677-83.
15. Nseir S, Di Pompeo C, Cavestri B, Jozefowicz E, Nyunga M, Soubrier S, *et al.* Multiple-drug-resistant bacteria in patients with severe acute exacerbation of chronic obstructive pulmonary disease: Prevalence, risk factors, and outcome. Crit Care Med 2006;34:2959-66.
16. Nicotra MB, Rivera M, Awe RJ. Antibiotic therapy of acute exacerbations of chronic bronchitis. A controlled study using tetracycline. Ann Intern Med 1982;97:18-21.
17. Sachs AP, Koëter GH, Groenier KH, van der Waaij D, Schiphuis J, Meyboom-de Jong B. Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. Thorax 1995;50:758-63.
18. Jindal SK, Aggarwal AN, Gupta D. A review of population studies from India to estimate national burden of chronic obstructive pulmonary disease and its association with smoking. Indian J Chest Dis Allied Sci 2001;43:139-47.
19. Torres A, Dorca J, Zalacaín R, Bello S, El-Ebiary M, Molinos L, *et al.* Community-acquired pneumonia in chronic obstructive pulmonary disease: A Spanish multicenter study. Am J Respir Crit Care Med 1996;154:1456-61.
20. Lieberman D, Lieberman D, Gelfer Y, Varshavsky R, Dvoskin B, Leinonen M, *et al.* Pneumonic vs nonpneumonic acute exacerbations of COPD. Chest 2002;122:1264-70.
21. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.
22. Gump DW, Phillips CA, Forsyth BR, McIntosh K, Lamborn KR, Stouch WH. Role of infection in chronic bronchitis. Am Rev Respir Dis 1976;113:465-74.
23. Lambert HP, Stern H. Infective factors in exacerbations of bronchitis and asthma. Br Med J 1972;3:323-7.
24. McHardy VU, Inglis JM, Calder MA, Crofton JW, Gregg I, Ryland DA, *et al.* A study of infective and other factors in exacerbations of chronic bronchitis. Br J Dis Chest 1980;74:228-38.
25. Monsó E, Ruiz J, Rosell A, Manterola J, Fiz J, Morera J, *et al.* Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. Am J Respir Crit Care Med 1995;152(4 Pt 1):1316-20.
26. Fagon JY, Chastre J, Trouillet JL, Domart Y, Dombret MC, Bornet M, *et al.* Characterization of distal bronchial microflora during acute exacerbation of chronic bronchitis. Use of the protected specimen brush technique in 54 mechanically ventilated patients. Am Rev Respir Dis 1990;142:1004-8.
27. Pela R, Marchesani F, Agostinelli C, Staccioli D, Cecarini L, Bassotti C, *et al.* Airways microbial flora in COPD patients in stable clinical conditions and during exacerbations: A bronchoscopic investigation. Monaldi Arch Chest Dis 1998;53:262-7.
28. Soler N, Torres A, Ewig S, Gonzalez J, Celis R, El-Ebiary M, *et al.* Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. Am J Respir Crit Care Med 1998;157(5 Pt 1):1498-505.
29. Martinez JA, Rodríguez E, Bastida T, Bugés J, Torres M. Quantitative study of the bronchial bacterial flora in acute exacerbations of chronic bronchitis. Chest 1994;105:976.
30. Nseir S, Di Pompeo C, Soubrier S, Cavestri B, Jozefowicz E, Saulnier F, *et al.* Impact of ventilator-associated pneumonia on outcome in patients with COPD. Chest 2005;128:1650-6.
31. Groenewegen KH, Schols AM, Wouters EF. Mortality and

mortality-related factors after hospitalization for acute exacerbation of COPD. Chest 2003;124:459-67.
32. Patil SP, Krishnan JA, Lechtzin N, Diette GB. In-hospital mortality following acute exacerbations of chronic obstructive pulmonary disease. Arch Intern Med 2003;163:1180-6.
33. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60:925-31.
34. Khilnani GC, Banga A, Sharma SK. Predictors of mortality of patients with acute respiratory failure secondary to chronic obstructive pulmonary disease admitted to an intensive care unit: A one year study. BMC Pulm Med 2004;4:12-8.
35. Schrier RW, Wang W. Acute renal failure and sepsis. N Engl J Med 2004;351:159-69.
36. Ai-Ping C, Lee KH, Lim TK. In-hospital and 5-year mortality of patients treated in the ICU for acute exacerbation of COPD: A retrospective study. Chest 2005;128:518-24.