

Original Research Article

Aspergillus spp. infection as a cause of acute exacerbations of chronic obstructive pulmonary disease: a prospective observational study

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ABSTRACT

Background: Majority of exacerbations of COPD (AECOPD) are due to infections. Usual agents causing AECOPD are gram negative bacteria, but rarely viruses and fungi are also implicated. However, the role of fungal infection, especially *Aspergillus spp.* in the clinical deterioration of COPD still remains unclear. This prospective observational study looks at the prevalence of aspergillus infection in AECOPD. The Objectives of this study were to analyse the prevalence and risk factors associated with *Aspergillus* infection in AECOPD, and to investigate the clinical outcomes.

Methods: Patients admitted with AECOPD for a period of 3 months from 1st October 2017 to 31st December 2017 were prospectively included from ICU and general ward of Pulmonary Medicine department of a tertiary care hospital. Clinical, radiological and microbiological data were collected at admission and during the hospital stay. Clinical course and outcome are recorded.

Results: There were 104 cases of AECOPD during the study period out of which 96 were males and 8 were females. 17 patients had evidence of aspergillus infection and diabetes was found to be an independent risk factor for aspergillus infection.

Conclusions: *Aspergillus* infection is an important cause of COPD exacerbation and this is directly related to diabetes mellitus.

Keywords: AECOPD, *Aspergillus* infection, Sebraud's agar

INTRODUCTION

Exacerbations of chronic obstructive pulmonary disease (COPD) are frequent events in the natural history of the disease, considerably increasing the morbidity and mortality.^{1,2} Acute exacerbations of COPD (AECOPD) are characterized clinically by worsening of dyspnea, increased sputum production and/or changes in sputum purulence.³ There is evidence suggesting that infectious

agents, induces AECOPD by increasing bronchial and systemic inflammation.^{4,5}

Microbial infections account for the etiology of 75% of AECOPD.⁶ However, the role of microorganisms other than bacteria has not been well established. Viral infections causing AECOPD are frequently reported. *Aspergillus spp.* may be responsible for important clinical events from saprophytic colonization of the airways to rapidly invasive and life-threatening disseminated

diseases. This is attributed to the reduced immune status of the host due to the presence of underlying lung disease, comorbid illness such as diabetes and use of broad-spectrum antibiotics and corticosteroids.⁷⁻⁹ Some retrospective studies have analyzed the incidence of *Aspergillus fumigatus* isolation from lower respiratory tract samples in AECOPD patients and shown that COPD patients are an important group which are affected by either colonization or proven aspergillosis.¹⁰

In one of the largest studies investigating the prevalence of *Aspergillus spp.* in COPD patients, *Aspergillus* was isolated from respiratory samples of 36 patients out of a total of 1756 patients.¹¹ However, it remains unclear whether COPD patients are colonized by *Aspergillus spp.* or they have invasive pulmonary disease. It is difficult to define the influence of this organism as a causal agent of exacerbations unless invasive infection is proved by histopathological examination. This study is intended to analyze the prevalence and risk factors associated with *Aspergillus* infection in AECOPD and to investigate the clinical outcomes in a cohort of COPD patients requiring admission to the hospital with an AECOPD.

METHODS

Data was prospectively collected from patients hospitalized due to a COPD exacerbation in a tertiary teaching hospital between 1st October 2017 and 31st December 2017. Approval from institutional ethics committee (IEC) is obtained. Only known COPD patients as per previous hospital records and on treatment for COPD for more than one year were included. All patients admitted in the pulmonary medicine ward or ICU were evaluated clinically and investigated with CBC, X ray chest PA, spirometry, sputum culture, fungal smear and culture, Bronchoscopy and bronchial washings for bacterial and fungal culture and CT thorax in selected cases. Diagnosis of COPD exacerbation, decision to hospitalize, time of discharge and choice of pharmacological therapy were taken by the physician in charge.

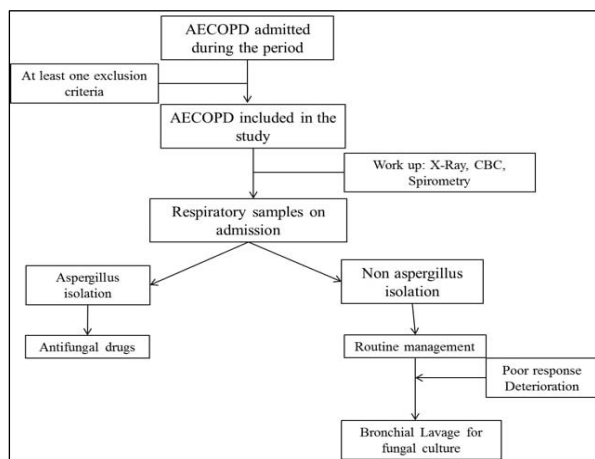


Figure 1: Flow diagram of patient inclusion.

All the patients were put on standard treatment for exacerbations as per GOLD guideline. Those who do not show expected improvement or deteriorate during the hospital stay were re-evaluated with bacterial and fungal culture (Figure 1). Patients with active tuberculosis, asthma, immunosuppression (innate or acquired) or any other clinical respiratory diseases were excluded. Clinical course and outcome of all patients were recorded. Outcome reported are discharge or death.

Data collection

Demographic variables, presence of any comorbid conditions (hypertension, diabetes or OSA), smoking status, use of steroids (systemic or inhaled) were recorded on admission to hospital. Symptoms/signs of the AECOPD together with physiological and laboratory data were collected at onset. Other variables such as length of stay (LOS), frequency of patients in whom admission to the intensive care unit (ICU) was needed, or requirement of non-invasive mechanical ventilation (NIMV) were also recorded.

The number of AECOPD events in the year preceding hospitalization was assessed based on treatment records. Only exacerbations requiring emergency room visits or admissions were included.

Microbiological analysis

Spontaneous sputum samples were obtained on admission and subsequently if the clinical response is not satisfactory or if the patient deteriorate. Sputum was examined by gram stain, KOH smear, bacterial culture and fungal culture. Samples were processed by the clinical microbiology laboratory of the hospital using standard procedures, including Sabouraud's agar culture, for the isolation of fungal species. Cultures were incubated at 32°C-37°C for at least 7 days and the number of visible colonies recorded. After seven days, filamentous colonies were examined, and *Aspergillus spp.* identified based on macroscopic and microscopic methods.

Statistical analysis

Data were analyzed using SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as absolute numbers and relative frequencies, while continuous variables are presented as the mean, standard deviation (SD) in parametric data, or median with the interquartile (IQR) range in non-parametric data. Categorical variables were compared using the χ^2 test or fisher's exact test, as appropriate.

RESULTS

Number of subjects treated for COPD exacerbation during the study period was 104. Out of these 72 (69.2%) patients were above the age of 65 years.

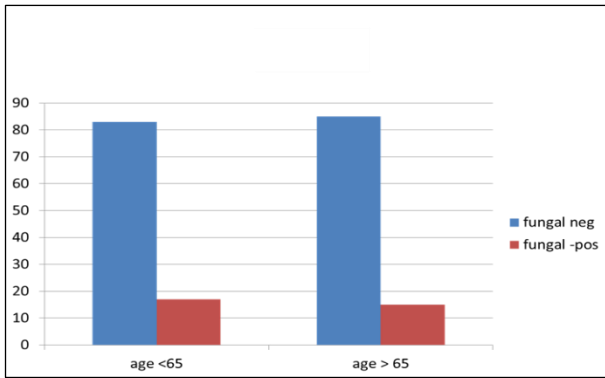


Figure 2: Characteristics of *Aspergillus spp.* infection in AECOPD.

Among those above 65 years 17% had fungal cause for exacerbation and those below 65 years 15% had fungal cause for exacerbations (Figure 2 and Table 1).

Table 1: Relationship between age group and fungal infection.

| Age group | n | No. fungal growth | Fungal growth |
|------------|----|-------------------|---------------|
| >65 years | 72 | 60 (83.3%) | 12 (16.7%) |
| < 65 years | 32 | 27 (84.4%) | 5 (15.6%) |
| P value | | | 0.895 |

Study subjects include 96 (93.3%) males and 8 (6.7%) females (Table 2).

Table 2: Sex distribution among AECOPD patients.

| Sex distribution | n | No. fungal growth | Fungal growth |
|------------------|----|-------------------|---------------|
| Male | 96 | 82 (85.4%) | 14 (14.6%) |
| Female | 8 | 5 (62.5%) | 3 (37.5%) |
| P value | | | 0.092 |

All the males were reformed smokers and 2 females were smokers. All the female patients had exposure to biomass fuels.

Among the study subjects, 17 (16.3%) patients had COPD exacerbation due to aspergillus infection. So, when we take a cut off of 65 years, there is no significant difference in the prevalence of fungal infections in AECOPD (Table 1). All the patients had treatment with inhaled corticosteroid and antibiotics during previous exacerbation and during the present admission.

Hence use of these two agents cannot be attributed to the increased rate of fungal infections. There were 17 diabetic patients in this cohort out of which 35% has aspergillus infection whereas among the non-diabetic 12.5% only had fungal infection.

This appears to be statistically significant (Figure 3 and Table 3).

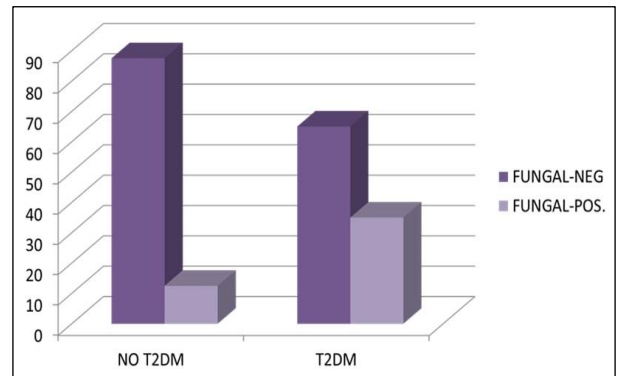


Figure 3: *Aspergillus spp.* infection in relation to T2 DM.

Table 3: Correlation between T2DM and *Aspergillus spp.* infection.

| Diabetic Status | n | No fungal growth | Fungal growth |
|-----------------|----|------------------|---------------|
| T2DM | 87 | 76 (87.4%) | 11 (12.6%) |
| No T2DM | 17 | 11 (64.7%) | 6 (35.3%) |
| P value | | | 0.032 |

There was no evidence of bacterial infection among 58% of those having fungal infection.

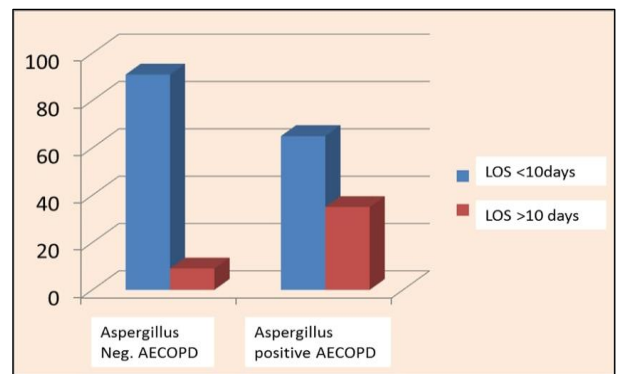


Figure 4: Relationship between *Aspergillus spp.* infection in AECOPD and LOS.

Whereas 42% of them had coexistent bacterial growth and predominant organisms are gram negative bacilli.

Table 4: Correlation between LOS and *Aspergillus spp.* infection.

| Length of hospital stay (LOS) | n | No fungal growth | Fungal growth (%) |
|-------------------------------|----|------------------|-------------------|
| < 10 days | 90 | 79 | 12 |
| >10 days | 14 | 8 | 38 |
| P value | | | 0.037 |

When we looked at duration of hospital stay it is found that 95% of patients who had a hospital stay of more than 10 days had *Aspergillus spp.* infection (Figure 4 and Table 4).

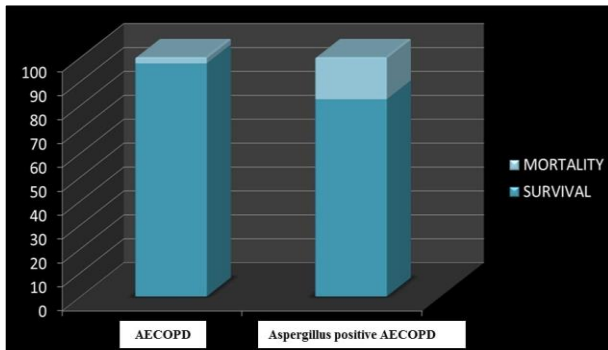


Figure 5: Outcome due to *Aspergillus spp.* infection in AECOPD.

This is found to be statistically significant. Case fatality among AECOPD patients in this study was 7 (6.6%) and death among those having aspergillus infection was 3 (17.5%) (Figure 5 and Table 5).

Table 5: Deaths among AECOPD.

| Mortality | N | No fungal growth | Fungal growth |
|-----------|----|------------------|---------------|
| Death | 7 | 4 (57.1%) | 3 (42.9%) |
| No death | 97 | 83 (85.6%) | 14 (14.4%) |
| P value | | | 0.084 |

DISCUSSION

There is a risk for developing pulmonary Aspergillosis in older patients with severe COPD, and other comorbidities who might have received prolonged treatment with corticosteroids and/ or broad-spectrum antibiotics. This is the first study in this part of the country to prospectively determine the prevalence of infection with *Aspergillus spp.*, associated risk factors and outcome in a cohort of AECOPD patients requiring hospitalization. We have shown that the prevalence of *Aspergillus spp.* isolation in this cohort was 16.3% on admission. The independent risk factor associated with *Aspergillus spp.* infection in this cohort was diabetes mellitus which is clinically and statistically significant with a p value of 0.032. *Aspergillus spp.* isolation was associated with clinically and statistically significant outcomes such as increased duration of hospital stay (p value 0.037) and death.

In a hilly agricultural district of Wayanad where the predominant cultivation is coffee and tea, we were looking for different causal factors leading to AECOPD. This is mainly because during ripening of coffee beans fungal flakes are released to the atmosphere in large quantities. So, we thought of looking aspergillus infection during this period, that is October to December. The

prevalence of *Aspergillus spp.* isolation is found to be equal or higher in this study when compared to earlier studies. In a study by Pashley CH et al, the isolation of *Aspergillus fumigatus* in sputum culture was significantly higher using a research approach compared to the standard method for mycological investigations.¹² There are few previous studies, reporting different prevalence rates of fungal isolation in respiratory samples from patients with COPD.¹³⁻¹⁵ Recently, a large, retrospective study conducted by Guinea J et al, analyzed the incidence of *Aspergillus fumigatus* isolation from lower respiratory tract samples in patients admitted for AECOPD in a tertiary hospital.¹⁶ They reported 239 isolations of *Aspergillus spp.* (16.3 per 1000 admissions), and present study shows much higher prevalence (16.3%).

There is no doubt that COPD patients are a population at risk for *Aspergillus spp.* colonization.^{10,17} In a previous study of critically ill patients, *Aspergillus spp.* isolation from respiratory secretions was significantly associated with both an underlying diagnosis of COPD and treatment with corticosteroids.¹¹ However, we could not establish a positive correlation with either steroid therapy or antibiotic therapy as all our patients had both steroids and antibiotics during previous admissions for AECOPD as well as during this admission. But there are studies establishing the relationship between pulmonary infection with *Aspergillus spp.* and the use of intravenous corticosteroids in COPD patients admitted to the ICU for severe exacerbation.¹⁸

The concurrent isolation of other pathogens, especially gram-negative bacteria was observed in 47.2% of patients with AECOPD in this series. Although the role of bacterial infection in COPD exacerbations remains controversial, *Pseudomonas aeruginosa* is usually isolated in patients with advanced COPD stages.¹⁹⁻²¹ Patients with previous severe exacerbations are more likely to receive a higher number of antibiotic therapy courses, and this could be the key factor in promoting further *Aspergillus spp.* isolation. Prospective studies focusing on this specific population are much needed to determine whether *Aspergillus spp.* isolation is the cause or the consequence of more infectious exacerbations with concurrent isolation of *Pseudomonas aeruginosa*. At the same time Bafadhel M et al, did not report association between the use of either inhaled (ICS) or oral corticosteroids (OCS) and an increased rate of *Aspergillus spp.*²²

There are two clinically significant outcomes we observed in present study. AECOPD due to *Aspergillus* infection prolonged the hospital stay of these patients. In a prospective study Huerta A et al, reported that patients with *Aspergillus spp.* isolation had significantly higher LOS compared to those patients without *Aspergillus spp.* isolation (7.5±5.0days versus 11.8±9.2days, p = 0.02).²³ Mortality among these patients was marginally higher when aspergillus isolation was established. It is reported that the mortality rate in association with aspergillus

infection in COPD patients is high because of the difficulty surrounding its diagnosis.²⁴ However Huerta A et al, did not find any significant differences in any of the other clinical outcomes when comparing patients with and without *Aspergillus spp.* isolation.²³

Limitation of this study is that, it is limited to hospitalized AECOPD during a period of 3 months when fungal spores are expected to be high due to coffee ripening season. A larger study throughout the year may be needed to establish a seasonal variation.

CONCLUSION

In summary, we found a high prevalence of *Aspergillus spp.* isolation in a cohort of COPD patients with severe AECOPD requiring hospitalization. Diabetes mellitus is found to be an independent risk factor for *Aspergillus* isolation. *Aspergillus* isolation is correlated with longer duration of hospital stay and slight increase in death rate when comparing patients with and without *Aspergillus spp.* isolation.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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