

Aspergillus hypersensitivity and allergic bronchopulmonary aspergillosis in patients with acute severe asthma in a respiratory intensive care unit in North India

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Summary

The prevalence of allergic bronchopulmonary aspergillosis (ABPA) in chronic asthma has been reported in various studies. However, no study has systematically evaluated the occurrence of *Aspergillus* hypersensitivity (AH) and ABPA in acute severe asthma (ASA). The aim of this study was to investigate the occurrence of AH and ABPA in patients with ASA. All patients with ASA admitted to the respiratory intensive care unit (ICU) of this institute underwent a prospective evaluation for ABPA using *Aspergillus* skin test (AST) as a screening tool. Patients with positive AST were labelled as AH and were further investigated for ABPA. Patients with ASA were compared with historical control group of 755 outpatient bronchial asthma patients previously reported. Of the 357 ICU admissions, 57 (43 females, 14 males; mean age 43.5 years) patients were admitted with a diagnosis of ASA. The occurrence of AH was 50.9% [95% confidence interval (CI) 38.3–63.4; 29/57 patients] whereas the prevalence of ABPA was 38.6% (95% CI 27.1–51.6; 22/57 patients) in patients with ASA. The occurrence of AH and ABPA was significantly higher in the ASA group compared with the outpatient bronchial asthma group (38.5% and 20.5%, respectively). The prevalence of serological ABPA (ABPA without central bronchiectasis) was also higher in the ASA group compared with the outpatient bronchial asthma group (45.4% vs. 23.9%). The occurrence of AH and ABPA is very high in patients with acute asthma admitted to a respiratory ICU. Furthermore, the occurrence of high percentage of serological ABPA calls for the use of AST as a routine screening tool for ABPA in all patients with acute asthma at discharge.

Key words: Allergic bronchopulmonary aspergillosis, *Aspergillus* hypersensitivity, acute severe asthma, bronchial asthma.

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is the most frequently recognised manifestation of allergic aspergillosis. It is an immunologically mediated lung

damage caused by hypersensitivity to the antigens of the fungus, *Aspergillus fumigatus* (Af).¹ This disease is generally believed to complicate the course of 1–2% of patients with bronchial asthma and between 2% and 15% of patients with cystic fibrosis.² In most cases, lung biopsy is not required for the diagnosis, and the diagnosis can be made on clinical, radiological and serological grounds. The disorder needs to be diagnosed early and treated appropriately to prevent the irreversible complications of the disease – bronchiectasis, lung fibrosis and in a minority of patients, end-stage lung disease and respiratory failure. Despite its description a

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little more than half a century ago, the true prevalence of ABPA among asthmatics remains speculative. One important reason for this may be attributed to the lack of a uniform diagnostic criterion and standardised tests.³ Another important reason is the lack of standardised protocol for screening all asthmatics.⁴ Diagnostic criteria for ABPA include the presence of bronchial asthma, immediate skin test reactivity to *Af*, elevated serum IgE levels – total and *Af*-specific, pulmonary infiltrates (transient or fixed), central bronchiectasis, peripheral blood eosinophilia and the presence of serum precipitins against *Aspergillus* antigen. However, none of these criteria is individually specific for ABPA and many patients in different stages of the disease may not fulfil all the criteria.⁵

The occurrence of ABPA in the course of bronchial asthma is known to worsen asthma control leading to repeated exacerbations. However, no study has systematically evaluated patients with acute severe asthma (ASA) for *Aspergillus* hypersensitivity (AH) and/or ABPA. We have recently described the prevalence, outcome and the risk factors predicting outcome of ABPA in 755 stable outpatients with bronchial asthma.^{6,7} In this study, we describe the prevalence of ABPA in patients with ASA admitted to the respiratory intensive care unit (ICU) of this institute.

Materials and methods

This was a prospective study conducted in the respiratory ICU of this institute between July 2006 and December 2007. All patients admitted with a diagnosis of ASA were eligible for inclusion in this study. In order to be included in the study, the patient had to fulfil all of the following inclusion criteria⁸: (i) respiratory rate more than 30 breaths min⁻¹; (ii) peak expiratory flow less than 200 l min⁻¹; and (c) inability to speak in sentences in one breath or SpO₂ less than 92% or pulsus paradoxus more than 10 mmHg. Patients with any of the following conditions were excluded: (i) smoking history of more than 10 years; (ii) chronic obstructive pulmonary disease or ABPA; (iii) pulmonary infiltrates consistent with pulmonary oedema or pneumonia; and (iv) pregnancy. An informed consent was obtained from all the patients as per protocol and the study was approved by the institutional ethics committee.

A detailed history and physical examination was performed and all patients on discharge underwent an intradermal skin test for *Af*.^{6,7} The *Aspergillus* skin test (AST) was performed using *Af* antigen (Aspergillin;

Hollister-Stier Laboratories, Spokane, WA, USA). The test was read every 15 min for 1 h. The test was defined as positive if a wheal and erythema developed within 1 min, reached a maximum after 10–20 min, and resolved within 1–2 h. If the skin test was positive, the patients were further investigated for ABPA with IgE levels (both total and *Af* specific), *Aspergillus* precipitins and high-resolution computerised tomography (HRCT) of the chest. *Aspergillus fumigatus* precipitins were detected by the Ouchterlony gel diffusion techniques according to the method of Longbottom and Pepys.⁹ Levels of serum IgE (total) and IgE (for *Af*) were assayed with commercially available kits using the quantitative enzyme-linked immunosorbent assay (Demeditec diagnostics GmbH, Kiel, Germany) and the fluorescent enzyme immunoassay (UniCap Systems; Pharmacia Upjohn, Stockholm, Sweden). High-resolution CT of the thorax (IV contrast was not administered) was performed on a 16-row, multiple detector, CT scanner (LightSpeed Plus; GE Medical Systems, Slough, UK) with a 512 matrix size. The scans [120 kV; 10 mA; window width, 1500 Hounsfield units (HU); and window level, 600 HU] were obtained with a scan time of 3 s in the supine position at full-end inspiration from the lung apex to base. The image acquisition was contiguous and the images (1.25 mm at 10-mm intervals) were reconstructed using the high-spatial-frequency algorithm.

Patients were classified to have AH if only the skin test was positive but all other investigations were negative or ABPA if the *Af* skin test was positive and IgE levels [both total (more than 1000 IU l⁻¹) and *Af* specific IgE (more than 0.35 kUA l⁻¹)] and *Aspergillus* precipitins were raised. Patients were further classified as serological ABPA (ABPA-S) or ABPA with central bronchiectasis (ABPA-CB) based on the absence or presence of central bronchiectasis, respectively. Patients were followed up for 1 year following discharge from the ICU. The current cohort of ASA was compared with a historical control group of 755 outpatients with bronchial asthma, which we had previously reported,^{6,7} to ascertain any difference in presentation between the two groups of patients.

The statistical software package spss (SPSS version 10.0; Chicago Inc., Chicago, IL, USA) was used for statistical analysis. Data are presented in a descriptive fashion as means with 95% CI or percentages with 95% CI wherever applicable. Differences between the means of continuous variables were analysed using Mann–Whitney *U*-test and differences between categorical variables were analysed using chi-squared test. A *P*-value of less than 0.05 was considered statistically significant.

Table 1 Baseline characteristics of the 57 patients admitted with acute severe asthma

Variables	<i>Aspergillus</i> skin test positive (n = 29)	<i>Aspergillus</i> skin test negative (n = 28)	Total
Gender (M : F)	9 : 20	5 : 23	14 : 43
Age, years	44.9 (38.6–50.9)	42 (36.7–47.3)	43.3 (39.4–47.3)
Duration of asthma, years	11.6 (8.5–14.7)	9.2 (6.2–12.3)	10.3 (8.2–12.5)
Body mass index, kg m ⁻²	23.1 (21.7–24.4)	23.4 (21.7–25.1)	23.2 (22.2–24.3)
Heart rate, beats min ⁻¹	119.8 (113.9–125.6)	113.5 (106.6–120.5)	116.5 (112–121.1)
Respiratory rate, breaths min ⁻¹	37.1 (33.4–40.8)	36.9 (34.7–39.1)	36.9 (34.9–39.1)
PEF, l min ⁻¹	95.1 (72.6–117.5)	87.9 (75.1–100.7)	91.4 (79–103.8)
pH	7.42 (7.39–7.45)	7.43 (7.41–7.44)	7.43 (7.41–7.44)
PaO ₂ /FiO ₂ ratio	300.6 (270–331.3)	278.5 (249.9–307.1)	288.7 (268.3–309.2)
PaCO ₂ levels	38.2 (33.5–42.9)	38.1 (32.2–43.9)	38.2 (34.4–41.9)

FEV1, forced expiratory volume in the first second; PEF, peak expiratory flow.

All the values are expressed as mean (95% CI) unless otherwise stated.

Results

During the study period, there were 357 admissions in the respiratory ICU. Sixty-one patients were admitted with a diagnosis of ASA; four patients were excluded as they were later diagnosed to have chronic obstructive pulmonary disease. Finally, 57 (43 females, 14 males) patients met the inclusion criteria and were enrolled in the study. The baseline characteristics of the study population are shown in Table 1. The mean age of the study population was 43.3 years with a mean duration of asthma of 10.3 years. Forty-seven patients had presented to this facility for the first time and were being treated elsewhere; 10 patients were diagnosed with acute asthma in our chest clinic but were not compliant with the management. None of the patient gave any history to suggest ABPA (fever, weight loss, malaise, expectoration of brownish black mucus plugs or haemoptysis), and the chest radiograph was interpreted as normal in all the patients. All patients were managed in the RICU as per standard protocol, and

none of the patient required endotracheal intubation and invasive ventilation.

Twenty-nine of the 57 (50.9%; 95% CI 38.3–63.4) patients were diagnosed to have AH as evidenced by a positive AST whereas 22 out of the 57 patients (38.6%; 95% CI 27.1–51.6) were diagnosed to have ABPA. The prevalence of ABPA in *Aspergillus*-hypersensitive acute asthma was 75.9% (Table 2). High-resolution CT revealed the presence of central bronchiectasis in 12 of the 22 [54.5% (95% CI 34.7–73.1)] patients with ABPA (classified as ABPA-CB) whereas the remaining 10 patients had no evidence of bronchiectasis and were classified as ABPA-S. We also compared this group of ASA patients with the group of historical outpatient clinic bronchial asthma patients in whom we had previously reported the prevalence of ABPA.^{6,7} The occurrence of AH, occurrence of ABPA and the prevalence of serological ABPA was higher in patients with ASA when compared with historical group of outpatient bronchial asthma patients (Table 2).

Table 2 Comparison of the occurrence of *Aspergillus* hypersensitivity (AH) and allergic bronchopulmonary aspergillosis (ABPA) in patients with acute severe asthma (n = 57, 14 males) vs. historical control^{6,7} of outpatient bronchial asthma patients (n = 755, 411 males)

Variables	Acute severe asthma	Outpatient bronchial asthma	P-value
Occurrence of AH and ABPA			
Occurrence of AH	29/57 (50.9%, 38.3–63.4)	291/755 (38.5%, 35.1–42.1)	0.053
Occurrence of ABPA	22/57 (38.6%, 27.1–51.6)	155/755 (20.5%, 17.8–23.6)	0.002
Prevalence of ABPA in AH	22/29 (75.9%, 57.9–87.8)	155/291 (53.3%, 47.5–58.9)	0.02
Characteristics of ABPA			
Age, years	45.5 (37.9–53.2)	33.9 (32.1–35.9)	
Gender (M : F)	7:15	79:76	0.09
Total IgE levels (IU ml ⁻¹)	3237 (1991–4482)	6434 (5524–7345)	0.0004
<i>Aspergillus fumigatus</i> -specific IgE (kUA l ⁻¹)	2 (6.5–10.3)	8.4 (6.5–10.3)	0.0002
Prevalence of serological ABPA in ABPA	10/22 (45.4%, 26.9–65.3)	37/155 (23.9%, 17.8–31.2)	0.026

Three more patients could be classified as ABPA if the IgE cut-off value was decreased to 500 IU l⁻¹. However, these patients were not treated with glucocorticoids and were followed up with a repeat total IgE level performed at 6 months; all three patients showed a spontaneous decline in the IgE levels. All patients diagnosed as ABPA were treated with oral glucocorticoids and underwent remission at 6 weeks (35% decline in IgE levels). To exclude the false negative AST because of the use of glucocorticoids, 18 of the 28 (10 patients did not follow up and the AST could not be done) skin-test negative patients were subjected to a repeat AST after 6 months of cessation of glucocorticoids, and all were found to be negative.

Discussion

Although there are reports of ABPA complicating the course of severe asthma¹⁰ and presentation of ABPA as acute asthma¹¹, no study has systematically studied the prevalence of ABPA in ASA. The development of ABPA in bronchial asthma is known to worsen asthma control¹² and can cause repeated exacerbations, and was the prime reason for the conduct of this study. This study shows a high prevalence of AH and ABPA (51% and 39%, respectively) in patients admitted with a diagnosis of ASA in a respiratory ICU. Interestingly, 46% of the patients with ABPA had normal HRCT (serological ABPA), and all patients with ABPA had a normal chest radiograph implying that the condition could not have been diagnosed if active screening was not undertaken. In fact, the prevalence of AH and ABPA is far higher than in outpatients with bronchial asthma. The high prevalence of ABPA is not unique to our Chest clinic but has also been reported from other asthma clinics across the globe. In a recent meta-analysis (20 studies, 5092 asthmatics), we have demonstrated a prevalence of AH and ABPA in outpatients with bronchial asthma of 28% and 12.9%, respectively.³ This study reveals an even higher prevalence of ABPA in patients with ASA.

There is a close association between fungal sensitisation and asthma severity.¹³ In a recently published survey, the frequency of sensitisation to *Alternaria* or *Cladosporium* was a powerful risk factor for severe asthma in adults.¹⁴ Previous studies have shown that exposure to environmental fungi increased the risk of death from asthma¹⁵ and also acute attacks of asthma requiring ICU admission.¹⁶ In a study published in 1978, 28% of the asthmatics from Cleveland and 23% from London had immediate skin reactivity to *Aspergillus*, which was related to the severity of airway

obstruction.¹⁷ In another study on AH without ABPA, the duration of asthma was longer and the age of onset of asthma was significantly earlier.¹⁸ It has also been demonstrated that treatment with itraconazole of severe asthmatic patients with fungal sensitisation was associated with significant improvements in the quality of life.¹⁹

An early diagnosis of ABPA is highly desirable as appropriate therapy with glucocorticoids can prevent bronchiectasis and lung fibrosis, which represent permanent lung damage. The need for a screening protocol also depends on the prevalence of the disease, and this study suggests that the prevalence of ABPA in a respiratory ICU is sufficiently high to justify the use of a protocol (routine screening of all ASA patients with an AST for diagnosis) for screening. Despite a high prevalence in asthma clinics, ABPA continues to be diagnosed infrequently in clinical practice. The under-diagnosis of ABPA can be ascribed, in part, to a lack of routine skin testing in most asthma clinics.⁴ Another important reason is the lack of uniform diagnostic criteria, and thus the variations in diagnostic criteria between centres may be an equally important source of diagnostic uncertainty. Many centres use a cut-off of 500 IU ml⁻¹¹²⁰⁻²² to define ABPA, whereas others use a cut-off of 1000 IU ml⁻¹.^{6,7,23,24} Even in the current study, more patients could be classified as ABPA if the threshold of IgE levels was decreased from 1000 to 500 IU ml⁻¹. However, as a protocol, we generally closely follow-up patients with IgE levels between 500 and 1000 IU ml⁻¹ and chose to treat only if the IgE levels are persistently above 1000 IU ml⁻¹ signifying ongoing inflammatory lung damage (Fig. 1).

A routine use of computerised tomography of the chest has been justified as a screening modality for ABPA.²¹ However, central bronchiectasis on HRCT chest can occur in patients with asthma without ABPA.²⁵ Conversely, patients with ABPA can have a normal HRCT chest, i.e. serological ABPA. Even in the current study, almost 46% of the patients had a normal CT of the chest. In addition, more patients with serological ABPA were prevalent in the ASA group (45.4%) vs. the outpatient bronchial asthma group (23.9%). This is probably because patients with serological ABPA will be missed on the chest radiograph and this condition cannot be diagnosed unless active serological screening is performed. On the other hand, patients with classic ABPA with pulmonary opacities are detected by the chest radiograph relatively early in the course and treated with glucocorticoids. This probably accounts for a higher proportion of ABPA with central bronchiectasis (who often have coexistent

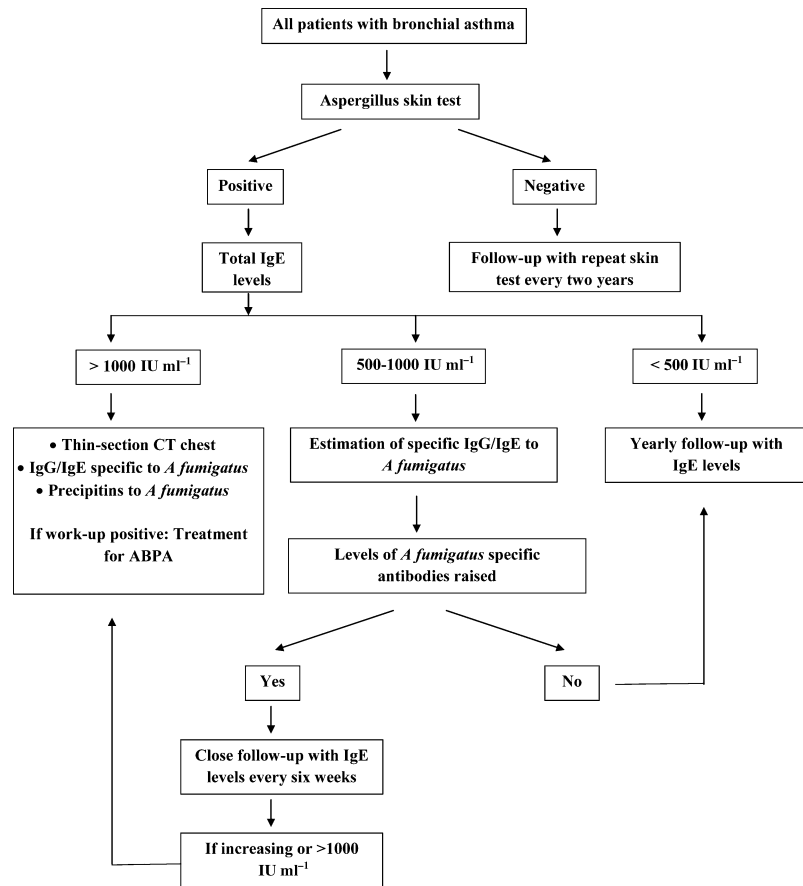


Figure 1 Algorithm for the work-up of allergic bronchopulmonary aspergillosis followed in our Chest Clinic.

pulmonary opacities demonstrated on chest radiograph) in the outpatient group.

In this study, we have used the intradermal method for screening patients with asthma, as this is the method performed in our centre. The intradermal test is believed to be associated with a higher complication rate than the skin prick test. In a recent meta-analysis, we demonstrated that the intradermal test is more sensitive than skin prick tests (28.7% vs. 24.8%, respectively).³ Hence, wherever feasible, a skin prick test should be performed and if negative, confirmed with an intradermal test.

In many ICUs, allergologists are not readily available but the blood can be tested for *Af*-specific IgE. Hence, an important question arises whether *Af*-specific IgE can replace AST as a screening modality for ABPA. An elevated level of specific antibodies to *Af* is considered the hallmark of the disease and is measured by fluorescent enzyme immunoassay tests.⁶ A cut-off value of IgG/IgE more than twice the pooled serum samples from patients with *Aspergillus*-hypersensitive asthma can help in the diagnosis of ABPA from patients with

asthma and AH.²⁶ We currently use a cut-off of 0.35 kUA l⁻¹ of *Af*-specific IgE for the diagnosis of ABPA [the mean *Af* specific IgE level of 25 patients with AH and asthma was found to be 0.152 kUA l⁻¹ using the fluorescent enzyme immunoassay (UniCap Systems; Pharmacia Upjohn)]. Thus, the important point to be considered is that a positive cut-off for *Af*-specific IgE is twice the levels of *Af*-specific IgE in asthmatics who demonstrate positive results on AST. This means that many patients would be AST positive but will have normal values for *Af*-specific IgE.

Majority of the patients who were skin test negative remained negative after 6 months of cessation of steroids and the IgE levels also remained stable in patients with values between 500 and 1000 IU ml⁻¹. Thus, another important aspect, which has emerged from this study is that 7–10 days of glucocorticoid therapy is unlikely to affect the performance of AST. This is important because in many instances, screening is postponed for 3–6 months and many patients are lost to follow-up; thus, the screening of this group of patients is greatly missed.

In conclusion, there is a high occurrence of *Aspergillus* sensitisation and ABPA in patients with acute asthma. Similarly, there is a high prevalence of serological ABPA in this group justifying the need for a routine screening for AH and ABPA with an AST. Moreover, 7–10 days of glucocorticoid therapy is unlikely to affect the screening tests routinely employed in the diagnosis of ABPA.

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