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Original Article

Paediatrics Section

# Clinical Spectrum of Aspergillosis in Children with Severe Asthma: A Retrospective Observational Study

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## ABSTRACT

**Introduction:** *Aspergillus* species can affect the respiratory system of genetically predisposed asthma patients. Allergic Broncho-Pulmonary Aspergillosis (ABPA) is one of the manifestations of aspergillosis. Most research on ABPA has been conducted in the adult population, with very few studies including paediatric patients.

**Aim:** To examine the clinical spectrum of aspergillosis in severely asthmatic children aged between 2 and 18 years admitted to the Paediatric Intensive Care Unit (PICU).

**Materials and Methods:** This retrospective observational study was conducted from September 2021 to August 2022. Out of 76 children aged between 2 and 18 years who presented with asthma over one year, 24 children fulfilling the inclusion criteria (severe asthma requiring PICU admission) were included in the study by convenient sampling. Children were diagnosed with ABPA and Severe Asthma with Fungal Sensitisation (SAFS) based on the ISHAM (International Society for Human and Animal Mycology) work group criteria (history of asthma, raised *Aspergillus*-specific and total Immunoglobulin E (IgE), presence of *Aspergillus*-specific IgG, eosinophilia, and positive radiological findings). Descriptive statistics elaborated in the form of mean and standard deviation.

**Results:** A total of 24 patients with acute severe asthma were admitted to the PICU over one year. Nearly 60% (15/24) of the patients fulfilled the criteria for subgroup A (comprising poorly controlled asthma, eosinophilia, or positive radiological findings). Among them, six (25%) patients had total serum IgE levels > 1000 IU/mL, three (12.5%) had levels between 500-1000 IU/mL, and six (25%) had levels <500 IU/mL. Among these patients, 60% (9/15) had elevated *Aspergillus*-specific IgE and IgG levels. As per the ISHAM work group criteria, 6/24 (25%) patients were diagnosed with S-ABPA (Serological ABPA) and 3/24 (12.5%) patients were diagnosed with SAFS.

**Conclusion:** *Aspergillus* sensitivity is increasingly being detected in asthmatic children, requiring further work-up, especially in patients with poorly controlled asthma.


**Keywords:** *Aspergillus* sensitivity, Bronchopulmonary disease, Respiratory infection

## INTRODUCTION

Asthma is a chronic inflammatory disease of the respiratory tract that manifests as coughing, wheezing, shortness of breath, and chest tightness. Its onset is heterogeneous with various phenotypes like allergic, non allergic, late-onset, obesity-related, and asthma with persistent airflow limitation [1]. Dust, house mites, pollens, animal dander, and fungal moulds are some of the well known risk factors for allergic asthma [2]. The *Aspergillus* species is commonly associated with fungi and affects the respiratory tract of genetically susceptible individuals [3]. The clinical spectrum includes allergic manifestations, saprophytic colonisation of the respiratory tract, and invasive aspergillosis [4]. Allergic aspergillosis may manifest as Allergic Sinusitis (AAS), ABPA, or *Aspergillus*-Induced Asthma (AIA) [4]. ABPA is a known clinical entity in adults, but paediatric data is limited [5]. These patients may present with poorly controlled asthma not responding to conventional asthma medications, along with *Aspergillus* sensitivity and radiological changes [5]. The clinical and radiological manifestations differ from case to case. There is no single definitive test to diagnose this clinical entity [6]. In 1977, Rosenberg M et al., proposed diagnostic criteria for the same, which were used until the ISHAM work group provided a simplified criterion in 2013 [7,8]. SAFS, a new subgroup of asthma, has recently been described [9]. It is characterised by fungal sensitisation with little or no colonisation. This subset of asthma patients represents the transition phase between asthma and ABPA. Patients with SAFS may go on to develop ABPA because of progressively increasing Th2 immune response [10].

A systematic review and meta-analysis demonstrated that the prevalence of *Aspergillus* Sensitisation (AS) in bronchial asthma ranges from 15-48%, with a pooled prevalence of 28% (95% CI, 24%-34%) [11]. A similar frequency of AS has been documented in recently published studies as well [12,13]. Most of the available data is based on studies done in adult patients [11-13], with only a few studies including paediatric patients [4,14]. Also, no diagnostic criteria have been specifically defined for paediatric patients to date. Hence, present study was planned in view of insufficient paediatric data.

Hence, the present study was conducted to study the clinical spectrum of aspergillosis in severely asthmatic children aged between 2 and 18 years who were admitted to the PICU and to classify severely asthmatic *Aspergillus*-sensitive children into various categories of *Aspergillus* manifestations.

## MATERIALS AND METHODS

This retrospective observational study was conducted in the Department of Paediatrics at Shree Guru Gobind Singh Tricentenary Medical College, Hospital, and Research Institute, located in Gurugram, Haryana, India. It is a tertiary-level healthcare facility located at outskirts of Gurugram and mainly serves the nearby rural population. All the case records during one-year period (September 2021-August 2022) were enrolled after taking ethical approval from the hospital's ethical committee (IEC/FMHS/F/18/8/23/96). Data collection and analysis of case records were conducted from July 2023 to August 2023.

**Inclusion criteria:** Paediatric patients aged 2-18 years who were admitted to the PICU with acute exacerbation of asthma within the study duration were included in the study.

**Exclusion criteria:** Patients who were taking oral steroids already at presentation or who were previously taking steroids and stopped them less than three months ago, or had underlying congenital disorders or anomalies, were excluded from the study.

**Sample size:** Sampling was done by convenience sampling. Children aged 2-18 years presenting with a diagnosis of asthma were observed. Those with mild to moderate exacerbation of asthma were admitted to the paediatric ward and received treatment as per the standard protocols. Children with severe exacerbation or poorly controlled asthma who were admitted to the PICU were enrolled in the study.

**Data Collection:** Baseline characteristics of these patients were recorded, including age, gender, clinical findings, presence of any co-morbidity, drug history, number of acute exacerbations per year, anthropometric parameters, and whether diagnosed with controlled, partially controlled, or poorly controlled asthma (as per Global Initiative for Asthma (GINA) guidelines) [1].

Patients with poorly controlled asthma or blood eosinophilia (>500 cells/µL) and positive radiological findings were categorised as subgroup A and further evaluated for evidence of aspergillosis. These patients were screened for aspergillosis using serum total Immunoglobulin (Ig) E (>1000 IU/mL), *Aspergillus*-specific IgE/IgG, chest X-ray findings, and chest Computed Tomography (CT) findings, if available. Patients with positive results for aspergillosis were categorised as ABPA (as per ISHAM workgroup criteria) or SAFS (as per the diagnostic criteria proposed by Denning DW et al.) [8,15].

The ISHAM workgroup criteria for ABPA are as follows: A) Predisposing conditions: 1) Bronchial asthma; 2) Cystic fibrosis. B) Criteria: a) Obligatory (both should be present): 1) Positive Type-I *Aspergillus* skin test (immediate cutaneous hypersensitivity reaction) or raised *Aspergillus*-specific IgE levels (>0.35 kUA/L); 2) Elevated total serum IgE levels (>1,000 IU/mL). b) Other criteria (at least two of three): 1) Presence of *Aspergillus*-specific IgG antibodies; 2) Radiographic findings consistent with ABPA; 3) Absolute eosinophil count >500 cells/µL [8]. Radiographic findings suggestive of aspergillosis include fleeting opacities, tramline sign (parallel lines), ring shadows, High Attenuation Mucous (HAM), gloved finger or wine glass appearance on plain chest X-ray. Additionally, CT may show evidence of central bronchiectasis, bronchial wall thickening, occluded bronchi, and air-fluid levels [16].

The diagnostic criteria for SAFS include: 1) Poorly controlled asthma with frequent asthma exacerbations; 2) Positive fungi-specific skin prick test (not necessarily specific to *Aspergillus* species) or presence of antifungal IgE (> 0.4 kU/L); 3) Total serum IgE <1,000 IU/mL. SAFS patients do not exhibit mucoid impaction or bronchiectasis [15].

## STATISTICAL ANALYSIS

Data was entered into a Microsoft Excel sheet and analysed using Statistical Package for Social Sciences (SPSS) version 23.0. Descriptive statistics elaborated in the form of mean and standard deviation.

## RESULTS

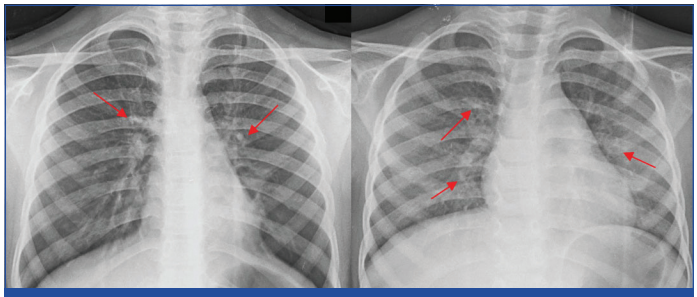
During the defined one-year study period, 76 patients presented with asthma to the paediatric department, during the defined one-year time, 76 asthmatic patients presented to paediatric unit either through outpatient department (OPD) or admitted through emergency department. Among them, 49 (64.5%) were male and 27 (35.5%) were female, resulting in a male-to-female ratio of 1.8:1. Out of the 76 patients, 17 (22.4%) presented in the OPD with clinical signs and symptoms of asthma and were managed as per standard guidelines. A total of 35 (46.1%) were admitted to the paediatric ward with mild to moderate exacerbations of asthma. They responded well to standard treatment for asthma exacerbation. Additionally, 24 (31.5%) patients were admitted to the PICU with severe asthma exacerbations and received treatment for the same. These 24 patients were enrolled in the study.

The mean age of the study participants was 9.55±3.87 years with a male predilection (2.4:1). Among all 24 study participants, 6 out of 24 (25%) had more than three exacerbations per year, thereby labeled as poorly controlled asthma, while 18 out of 24 (75%) patients were well controlled on their medications. Most of the children were on low-dose steroids with short-acting beta-agonists. The total duration of medications was variable, ranging from three months to two years among study participants at the time of presentation [Table/Fig-1].

| Parameters | | Value |
|---|---|---|
| Age (years) | | 9.55±3.87 |
| Gender | Male | 17 (70.8%) |
| | Female | 7 (29.2%) |
| | Male: Female | 2.4:1 |
| Co- morbidities | Allergic Rhinitis | 8 (33.3%) |
| | Adeno-tonsillar hypertrophy | 3 (12.5%) |
| Anthropometric parameters | Weight (Kg) | 31.25±15.84 |
| | Height (Cm) | 132.87±23.37 |
| | BMI (Kg/cm$^2$) | 16.52±3.53 |
| Medications | Low dose ICS+ SABA | 19 (79.16%) |
| | High dose ICS+ LABA | 4 (16.6%) |
| | Oral steroids (> 3-month-ago) | 1 (4.1%) |
| Asthma control | Well controlled | 18 (75%) |
| | Poorly controlled | 6 (25%) |

**[Table/Fig-1]:** Baseline characteristics of study participants.
ICS: Inhaled corticosteroids; SABA: Short acting beta agonists; LABA: Long-acting beta agonists

All patients were screened for eosinophil counts and radiological findings. Out of the total 24 study patients, 13 (54.16%) patients had only eosinophilia, one (4.16%) patient had positive chest X-ray findings [Table/Fig-2], while one (4.16%) patient had both eosinophilia and positive chest X-ray findings. A total of 15 out of 24 (62.5%) patients fulfilled the subcategory criteria (categorised as subgroup A) and were further assessed for biochemical evidence of *Aspergillus* sensitivity. Patients with serum total IgE levels >500 IU/mL (9 out of 15; 60%) were further tested for *Aspergillus*-specific antibody levels and all were found to be positive for *Aspergillus*-specific IgE and IgG [Table/Fig-3].



**[Table/Fig-2]:** Radiological findings of the study participants.

| S. no. | Investigations | | Subgroup A (n=15) | Subgroup B (n=9) | Total (n=24) |
|---|---|---|---|---|---|
| 1. | Absolute eosinophil counts >500 cells/mm$^3$ | | 13 (86.66%) | 00 | 13 (54.16%) |
| 2. | Mean eosinophil counts | | 813.8±154.78 | 252.33±126.01 | 603.5±311.77 |
| 3. | Positive Chest X-ray findings | | 1 (6.67%) | None | 01 (4.17%) |
| 4. | Both AEC >500 cells/mm$^3$ and positive Chest X-ray findings | | 1 (6.67%) | None | 01 (4.17%) |
| 5. | Positive Chest CT findings | | None | None | None |
| 6. | Serum total IgE | >1000 IU/mL | 6 (40%) | ND | 6 (25%) |
| | | 500-1000 IU/mL | 3 (20%) | ND | 3 (12.5%) |
| | | <500 IU/mL | 6 (40%) | ND | 6 (25%) |
| 7. | Mean serum total IgE in ABPA patients (n=6) | | 2181.5±692.44 | ND | - |
| 8. | Mean serum total IgE in SAFS patients (n=3) | | 658.56±115.81 | ND | - |

| | | | | |
|---|---|---|---|---|
| 9. | Mean serum total IgE in all patients of subgroup A (n=15) | 939.60±82.37 | ND | |

**[Table/Fig-3]:** Serological and radiological investigations.
ND: Not done

Out of the 15 patients in subgroup A, 6 out of 15 (40%) children met the ISHAM workgroup criteria for ABPA and were diagnosed accordingly. Since none of them had any CT findings consistent with CB-ABPA, they were diagnosed with S-ABPA (6 out of 24; 25%) [Table/Fig-4].

| | | |
|---|---|---|
| A. | Predisposing condition: Asthma | 24/24 (100%) |
| B. | Obligatory criteria | |
| 1. | Elevated *Aspergillus* specific IgE (>0.35 kUA/L) | 9/24 (37.5%) |
| 2. | Elevated Total Serum IgE (>1000 IU/ml) | 6/24 (25%) |
| C. | Other criteria (two out of three) | |
| 1. | Presence of *Aspergillus* specific IgG | 7/24 (29.1%) |
| 2. | Radiographic pulmonary opacities consistent with ABPA | 2/24 (8.3%) |
| 3. | Total eosinophil counts (>500 cells/ $mm^3$) | 14/24 (58.33%) |

**[Table/Fig-4]:** ISHAM work group criteria for ABPA of the patients.

Three out of 15 patients with serum total IgE levels between 500-1000 IU/mL did not meet the criteria for ABPA (as per ISHAM working group), but all three were positive for *Aspergillus* sensitivity along with a history of recurrent episodes of asthma exacerbations severe enough to be classified as poorly controlled asthma as per GINA guidelines [1]. These three patients (3 out of 24; 12.5%) were diagnosed with SAFS (severe asthma with *Aspergillus* sensitivity) [Table/Fig-5].

| | | |
|---|---|---|
| 1. | Severe (Poorly controlled) Asthma | 6/24 (25%) |
| 2. | Positive for *Aspergillus* specific IgE (>0.4 kU/L) with total serum IgE <1000 IU/mL | 3/24 (12.5%) |

**[Table/Fig-5]:** SAFS criteria for the patients.

## DISCUSSION

The prevalence of aspergillosis is well-defined in cystic fibrosis patients, but it can also affect asthmatic patients in many ways. The spectrum of clinical manifestations varies from allergic symptoms to invasive aspergillosis. Genetically susceptible individuals are more prone to acquire it [17]. The inhaled spores germinate into hyphae within the respiratory tract. These fungal hyphae release various antigens that alter the mucociliary system and breach the respiratory epithelial barrier. They provoke the innate immune system, resulting in hypersensitivity reactions [18]. IgE mediated hypersensitivity reaction is responsible for the majority of the pathogenesis, but IgG-mediated Type-III and cell-mediated Type-IV reactions are also contributory. These reactions lead to a storm of cytokines and chemokines, along with an influx of inflammatory cells. Additionally, these antigens get processed by the antigen-presenting cells and elicit a T-helper cell 2 (Th2) CD4+ T cell response. All these inflammatory reactions result in eosinophilic lung infiltrates, raised total and *Aspergillus*-specific IgE levels, and airway hyper-responsiveness. Upon repeated exposure, permanent tissue damage and airway remodeling occur [18].

Pathologic changes correspond to the extent of airway remodeling and the stage of ABPA. The disease is divided into five stages: acute, remission, exacerbation, steroid-dependent, and end-stage (fibrotic) ABPA [19]. These stages occur over the years in an individual and are well-defined in adult patients, but the data is not available for paediatric patients. Clinically, patients may present with signs and symptoms mimicking asthma exacerbations or with severe pulmonary dysfunction or respiratory failure [19]. Present study retrospectively reviewed 24 paediatric patients presenting with acute severe asthma at a tertiary healthcare centre over one year. In present study it was found that 6 out of the total 24 asthmatic patients (25%) fulfilled the ISHAM workgroup criteria for S-ABPA. Additionally, three asthmatic patients (12.5%) meeting the criteria for SAFS were identified.

The prevalence of AS among adult patients with asthma ranged from 5.5 to 38.5%, and the prevalence of ABPA in asthma varied between 2.5 and 22.3%, with a pooled prevalence of 8.4% [8]. Only a few case reports and two recently published studies have provided data for the Indian paediatric population. The first Indian paediatric case report was published by Chetty A et al., in 1982, who further studied the incidence of aspergillosis in 107 Indian paediatric patients with perennial asthma, reported 15% cases of ABPA [5]. Banerjee B et al., reported a case series of 10 paediatric patients aged 5-13 years. They found raised serum total IgE and positive *Aspergillus*-specific IgE/IgG in these asthmatic patients and diagnosed them with ABPA [20].

Recently, a prospective study was done by Singh M et al., in which they included 100 children aged 5-15 years with poorly controlled asthma and reported an incidence of 26% for ABPA [14]. In a retrospective study by Shah A and Kunal S, a total of 349 patients of all ages were diagnosed with ABPA over 31 years (1985-2016) in their pulmonary unit, with 42 patients in the paediatric age group (3.5-18 years). In their retrospective study of 42 paediatric patients with ABPA, they highlighted the importance of evaluating asthmatic children for ABPA [5]. The findings of both of these studies are compared with our study and shown in [Table/Fig-6].

| Parameters | Shah A and Kunal S [5] | Singh M et al., [14] | Present study |
|---|---|---|---|
| Publication year | Vallabhbhai Patel Chest Institute, Delhi, India | Post Graduate Institute of Medical Education and Research, Chandigarh, India | Shree Guru Gobind Singh Tricentenary University, Gurugram, Haryana, India |
| Year of the study | 2017 | 2015 | 2024 |
| Age group | 3.5-18 years | 5-15 years | 2-18 years |
| Mean age | 12.97±4.02 | 9.56±2.23 | 9.55±3.87 years |
| Age of youngest child | 3.5 years | 5.5 years | SAFS: 3 years ABPA: 9 years |
| M:F ratio | 1.62:1 | 4:1 | 2.4:1 |
| Prevalence of ABPA | 42 out of 349 ABPA Indian patients (adults+ children) | 26 out of 100 Indian asthmatic children | 6 out of 24 Indian children with asthma exacerbation |
| Prevalence of SAFS | ND | ND | 3 out of 24 Indian children with asthma exacerbation |
| *Aspergillus* specific IgE positivity among *Aspergillus* sensitive patients | 96.7% | 96.2% | 100% |

**[Table/Fig-6]:** Comparison with other studies [5,14].
ND: Not done

The diagnosis of ABPA depends on clinical, laboratory, and radiological parameters. Laboratory tests include total and *Aspergillus*-specific serological tests. Raised serum *Aspergillus*-specific IgE and IgG levels are consistent with the diagnosis of ABPA. Moreover, absolute eosinophil counts and positive *Aspergillus* skin tests contribute to the diagnosis. Asthmatic patients with fungal sensitisation can be categorised into four clinical categories: Asthma Associated with Fungal Sensitisation (AAFS), SAFS, serologic ABPA (ABPA S), and central bronchiectasis ABPA (ABPA CB) [10].

The asthmatic patients with mild to moderate asthma, positive fungal skin test (or elevated specific IgE), and total IgE <1000 IU/L are labeled as AAFS, while those with severe asthma, evidence of fungal sensitisation, and total IgE <1000 IU/L are labeled as SAFS [10]. Asthmatic patients with evidence of fungal sensitisation and total IgE >1000 IU/mL are categorised into serologic ABPA (without radiological findings), ABPA-CB (with central bronchiectasis), and ABPA-CB-HAM (with central bronchiectasis and HAM) [21]. The radiological findings of ABPA vary from non specific pulmonary infiltrates, parallel lines (tram lines), ring shadows to consolidation

and fibrosis. The most common finding is fleeting lung opacities on chest X-ray. The CT finding of central bronchiectasis is considered pathognomonic for ABPA [16]. HAM plugs have also recently been added as a characteristic CT finding of ABPA [4]. Regular monitoring with pulmonary function tests helps assess the severity and stage of the disease but does not have any diagnostic value.

In present study, six cases (25%) were identified of S-ABPA and three cases (12.5%) of SAFS based on the criteria given by the ISHAM workgroup in 2013. The cut-off for serum total IgE was set at more than 1000 IU/mL as suggested by the ISHAM workgroup. Singh M et al., proposed a new cut-off of more than 1200 IU/mL with 88.5% sensitivity and 70.5% specificity [14]. All six of the S-ABPA cases also fulfilling this new cut-off value, with a mean serum total IgE of 2181.5 ±692.44 IU/mL. The category of AAFS was not evaluated in present study but is planned for a prospective trial. *Aspergillus*-specific IgE antibody levels of >0.35kUA/L are considered diagnostic for ABPA. In present study, all 9 out of 9 patients (6 with ABPA and 3 with SAFS) tested positive for *Aspergillus*-specific IgE and also had elevated *Aspergillus*-specific IgG antibodies. In present study, only two cases (8.33%) with positive radiological findings in the form of fleeting lung opacities were found, who were further evaluated with CT imaging.

### Limitation(s)

The facility for a chest CT scan is available in-house, but the patients belonged to the poor rural population of peripheral Gurugram and could not afford the cost of a CT scan. Hence, all suspected ABPA could not undergo, limiting the study in terms of radiological evidence for ABPA. Another limitation of present study was the small sample size, as it was a time-lined retrospective study. However, a high sensitivity to aspergillosis was noted, which warrants further evaluation through a planned prospective study. Due to financial constraints, only suspected asthmatic children were evaluated for AS.

## CONCLUSION(S)

Aspergillosis was found to be a prevalent disease entity that complicates the course of illness in paediatric severe asthmatic patients. *Aspergillus* sensitivity in these patients can lead to poorly controlled asthma, and repeated exposures can result in permanent changes in lung parenchyma. Timely recognition of symptomatology and appropriate investigations are important for better management. Moreover, well-defined diagnostic criteria for the paediatric population and knowledge about the treatment of this clinical entity are required to decrease the disease burden and improve the quality of life of affected patients.

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**PLAGIARISM CHECKING METHODS:** [Jain H et al.]

- Plagiarism X-checker: Sep 12, 2023
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- iThenticate Software: Jan 20, 2024 (8%)

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