

Clinical characterization of asthma with fungal sensitization in a South Indian paediatric cohort

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Key Messages

AFS in our study was characterized by earlier age of onset, higher IgE levels and lower FEV1

We suggest AFS is worth considering in uncontrolled asthma and those with moderate-severe asthma

There is a need to assess anti-fungal drugs as an adjunct to standard therapy in AFS

To the editor,

The biological role of fungi in the pathophysiology of asthma has attracted renewed attention during the last decade. The term severe asthma with fungal sensitization (SAFS) was first introduced in 2006 and has since been recognized as a distinct clinical phenotype in adult asthma. This phenotype includes patients stratified as severe asthma clinically alongside meeting the following immunological criteria: serum total IgE <1000 kU/L, negative serum IgG precipitins to *Aspergillus fumigatus* to exclude allergic bronchopulmonary aspergillosis (ABPA) and demonstrable sensitization to at least one of the following fungal allergens—*Aspergillus fumigatus*, *Cladosporium herbarum*, *Penicillium chrysogenum* (*notatum*),

Candida albicans, *Trichophyton mentagrophytes*, *Alternaria alternate* and *Botrytis cinerea*.¹

Adults with SAFS are more likely to be polysensitized, have uncontrolled symptoms, have higher serum total IgE and more likely to have been admitted to intensive care unit requiring mechanical ventilation.^{2, 3} Data regarding SAFS in children are, however, sparse and it has been suggested that there may be some overlap between fungal bronchitis, combined fungal bronchitis and SAFS and SAFS *per se*.⁴ At least in children, it remains unclear at present whether fungal sensitization is merely a part of atopic diathesis or if it is a significant driver of underlying airway inflammation.

The main objective of this study was to characterize asthma with fungal sensitization (AFS) regardless of underlying severity in a paediatric cohort presenting to a large secondary care teaching hospital (JSS Medical College Hospital, Mysore, Karnataka) in South India.

A retrospective chart review was carried out between 01 July 2020 and 31 March 2021. This study was approved by the Institutional Ethics Committee of JSS Medical College, Mysore, Karnataka, India (JSSMC/IEC/09721/30NCT/2021-22). The study included paediatric asthma patients stratified into well controlled, partly controlled and uncontrolled asthma as per Global Initiative of Asthma (GINA) 2020 guidelines.⁵ Basic demographic, clinical and laboratory data were systematically extracted from medical records. The control status of asthma was determined using the Asthma Control Test (ACT). Assessment of sensitization to aero-allergens including fungal allergens was performed by the skin prick tests using allergen kits by Hollister Stier Allergy (Jubilant Pharma LLC, USA).

Serum total IgE level was measured using a commercial assay (Cobas Electrochemiluminescence Kit; Roche Diagnostics) with appropriate quality assurance measures in place. Spirometry was conducted using the EasyOne NDD (NDD Medical Technologies, MA, USA). Statistical analysis was performed employing Jamovi (v1.6, The Jamovi project, Sydney, Australia). Statistical significance was assessed by Chi-square test for categorical variables and by Student's *T* test or Wilcoxon matched paired sign rank test for continuous variables depending on the distribution of data. Tests for normality were conducted using the Shapiro–Wilk test. A *p*-value of <0.05 was considered statistically significant.

Four hundred and seventeen sequential patients (68.5% males) with asthma were enrolled in the study. The median age of children in the study group with AFS was significantly higher than non-AFS group [median (interquartile range); 11.0 (9.0–14.0) vs. 10.0 (7.0–13.0); *p* = 0.003]. The median age of onset of asthma was significantly lower in the AFS group compared to non-AFS group [4.0 (3.0–7.0) vs. 6.0 (4.0–8.0); *p* = 0.002; Table 1 and Figure 1A]. The AFS group had a significantly lower proportion of patients with coexisting allergic rhinitis as compared to the non-AFS group (21.4% vs. 46.9%; *p* = 0.032).

TABLE 1. Demographic features of the population (*n* = 417)

Variable	Measure	Non-Fungal (n = 349)	Fungal (n = 68)	p-value
Age (years)	Median (IQR)	10.0 (7.0–13.0)	11.0 (9.0–14.0)	0.003 ¹
Sex	Female	110 (31.5)	15 (22.1)	0.158 ²
	Male	239 (68.5)	53 (77.9)	
Age at onset	Median (IQR)	6.0 (4.0–8.0)	4.0 (3.0–7.0)	0.002 ¹
BMI	Underweight	98 (28.1)	23 (33.8)	0.671 ²
	Normal	225 (64.5)	42 (61.8)	
	Overweight	25 (7.2)	3 (4.4)	
	Obese	1 (0.3)	0 (0.0)	
Asthma severity	Well controlled	179 (51.3)	28 (41.2)	0.001 ²
	Partly controlled	110 (31.5)	15 (22.1)	
	Uncontrolled	60 (17.2)	25 (36.8)	
Allergic Rhinitis	Absent	185 (53.1)	53 (77.9)	0.032 ²
	Present	164 (46.9)	15 (21.4)	
Eczema	Absent	332 (95.1)	62 (91.2)	0.622 ²
	Present	17 (4.9)	6 (8.8)	

'n' is the number of non-missing values.

- ¹ Wilcoxon.
- ² Pearson Chi sq.
- ³ Student's *t*.

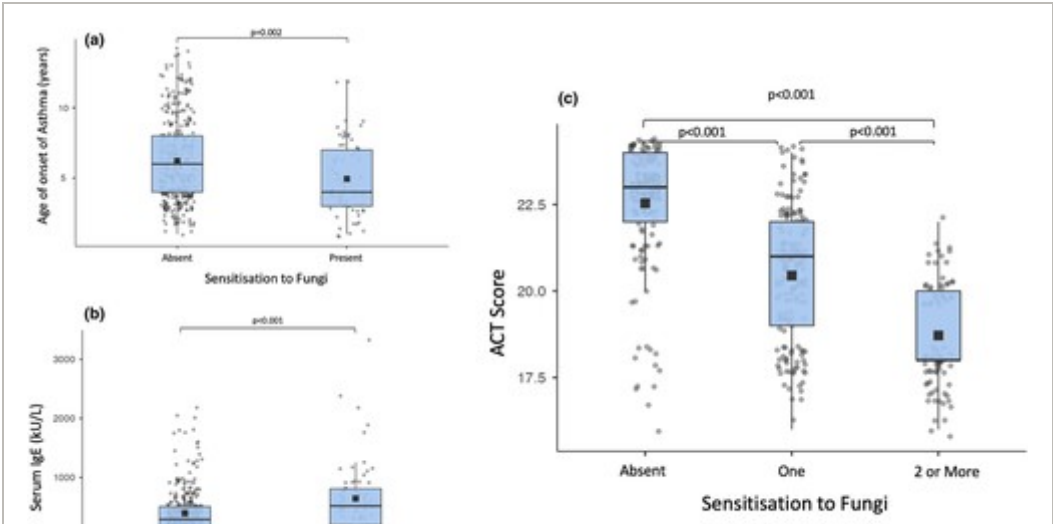


**FIGURE 1**
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(A) Box plot illustrating age of onset of asthma (in years) between AFS and non-AFS groups. The plot illustrates that patients in the AFS group had a lower age of asthma onset than the non-AFS group. The lower and upper borders of the box plot illustrate the Q1 and Q3 quartile. The median is represented by the line that divides the box. The solid square in the box illustrates the mean. Individual data points are plotted as dots. (B) Box plot illustrating serum total IgE between AFS and non-AFS groups: This plot illustrates that the AFS group had significantly higher serum total IgE than the non-AFS group. The lower and upper borders of the box plot illustrate the Q1 and Q3 quartile. The median is represented by the line that divides the box. The solid square in the box illustrates the mean. Individual data points are plotted as dots. (C) Box plot illustrating the relationship between ACT scores and sensitization to none, 1 or ≥ 2 fungal allergens: The plot illustrates that sensitization to ≥ 2 fungal allergens was associated with poorer asthma control. The lower and upper borders of the box plot illustrate quartiles 1 and 3 respectively. The line dividing the box represents the median. The solid square within the box illustrates the mean. Individual data points are plotted as dots. Test of significance was calculated between the two groups in Figures 1 A-C using the Wilcoxon method as data were not normally distributed

Sixty-eight patients (16.3%) showed sensitization to at least one fungal allergen. The most common fungal allergens involved in sensitization in our cohort were *Alternaria* (43.5%), *Helminthosporium* (24.2%) and *Penicillium* mix (24.2%) followed by *Candida albicans* (22.6%). The most common non-fungal allergens in our cohort were house dust mites (62.1%) followed by cockroaches (49.6%). The proportion of children with uncontrolled asthma was higher in the AFS group compared to non-AFS group (36.8% vs. 17.2%; $p = 0.001$). Serum total IgE was significantly higher in the AFS group [517.0 (190.0–808.8) kU/L vs. 290.0 (134.0 to 506.0) kU/L; $p < 0.001$] (Figure 1B), although no significant differences were detected in absolute eosinophil counts in peripheral blood. Asthma control test (ACT) scores ($p = 0.037$), FEV1 ($p = 0.028$) and FEV1/FVC ($p < 0.001$) were significantly lower in the AFS group compared to non-AFS group. Patients with multiple fungal sensitizations had poorer ACT scores in comparison to those with sensitization to a single fungal allergen ($p < 0.001$), that is the median ACT scores in subjects with no fungal allergen was 23.0 (22.0–24.0); with sensitization to one fungal allergen was 21.0 (19.0–22.0) and with sensitization to ≥ 2 fungal allergens was 18.0 (18.0–20.0) (Figure 1C).

These findings are largely in keeping with cohort studies from the UK and Germany which reported an association of AFS with an earlier age of onset, uncontrolled or difficult to control asthma, with polysensitization to other aero-allergens and lung function. Furthermore, *Alternaria* was also the most common fungal allergen implicated in sensitization.^{3, 6, 7} Male predominance and lower proportion of allergic rhinitis as a co-morbidity in AFS has not been reported previously and would require confirmation in multi-

centre prospective studies.

Chest X-ray was performed in all patients and a HRCT thorax was requested only if deemed clinically indicated (e.g. suspicion of bronchiectasis, tuberculosis or post-tuberculosis sequelae). Stool examination for parasites was not performed as these children were regularly dewormed by their general paediatrician, a common clinical practice in India.

This is the largest cohort study characterizing AFS in a paediatric asthma cohort from a Low-Middle Income Country (LMIC). We systematically characterized and stratified patients as per GINA guidelines and used a comprehensive panel of aero-allergens to assess sensitization. This study, however, has limitations. First, it was single-centre retrospective study. Second, other indoor and outdoor environmental confounders such as cigarette smoke exposure, air pollution, socio-economic status, and exposure to animal dander were not factored into analysis. Third, we did not investigate for presence fungi in the airway lining fluid or tissue to exclude concomitant infection. Fourth, aspergillus precipitins were not analysed, although allergic bronchopulmonary aspergillosis is exceedingly rare in children. Fifth, patients were not screened for an underlying parasitic infestation, although they were dewormed prior.

Fungi are abundant and ubiquitous in both indoor and outdoor environments globally. This makes it the largest organic contributor to air particulate matter. Studies on airway mycobiota have identified more than 200 taxa in the sputum and lower airway specimens and asthmatic mycobiota are different from mycobiota in health. Thermotolerant fungi such as *Aspergillus tubingensis* and *Cryptococcus pseudolongus* have been detected in protected brush specimens obtained from the lower airways of asthmatics and are likely to contribute to persistent epithelial activation as evidenced by higher levels of alarmins such as thymic stromal lymphopoietin (TSLP) and IL-33 and chronic airway T2 inflammation reported previously.⁷

Fungal exposure induces inflammation of the airways due to numerous pattern recognition receptors (PRRs) which trigger epithelial cells to release cytokines to recruit and activate innate leucocytes.⁸ Additionally, dendritic cells facilitate a fungal-specific T-cell response. The fungal antigen-specific T cells accumulate at the respiratory barrier to induce resident and recruited leucocytes and structural cells to become activated. Collectively, it is plausible that these immunological events augment physiologic changes contributing to asthma severity.⁸

Fungal allergens are among the most potent aero-allergens due to their multifaceted immunological properties. Fungal proteases and glycosidases damage epithelial cells to allow greater allergen access to subepithelial tissue. Due to the similarity of fungal proteins with human proteins such as heat shock protein, cyclophilin, and manganese superoxide dismutase (MnSOD), peroxiredoxin and thioredoxin, it is plausible that molecular mimicry might lead to autoreactivity and severe inflammation.⁹

In summary, AFS in this paediatric Indian cohort was characterized by an earlier age of

onset, higher serum total IgE, poor symptom control, lower FEV1 and greater disease severity in comparison to the non-AFS group. Based on our clinical experience and current study, we suggest fungal sensitization is worth considering in uncontrolled asthma and those with moderate-severe asthma. Also, it is worth considering in patients living in a damp indoor environment where there is a higher likelihood of exposure to fungi.

Further prospective multi-centre studies are needed to investigate AFS to shed light on the role of fungi in disease pathogenesis, specifically to assess the place for anti-fungal drugs as an adjunct to anti-inflammatory therapies and biological agents in asthma.

CONFLICT OF INTEREST

MTK received funds from ALK Abello to attend an international conference. His department has received educational grants from ALK Abello, MEDA, Allergy Therapeutics and other pharmaceutical companies for the annual PracticAllergy course. MTK has received grants from MRC CiC, GCRF, NIHR and FSA for research not directly related to this manuscript. The other authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

The authors confirm contributions to the paper as follows:

1. *Ashwaghosha Parthasarathi*

Acquisition of data, analysis, interpretation of the data

Verified the underlying data.

Drafting the manuscript for intellectual contents

Managing Submission Process: Responding and making changes to reviewers' feedback

The author approved the final version of the manuscript

2. *Sunag Padukudru*

Acquisition of data, analysis of the data

Verified the underlying data.

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The author approved the final version of the manuscript

3. *Padukudru Anand Mahesh*

Conceptualizing a research idea and creating a research design

Drafting the manuscript for intellectual contents

Critical revision of the manuscript for intellectual content

Managing Submission Process: Responding and making changes to reviewers' feedback

The author approved the final version of the manuscript

4. *Mamidipudi Thirumala Krishna*

Interpretation of the data

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Critical revision of the manuscript for intellectual content

Managing Submission Process: Responding and making changes to reviewers' feedback

The author approved the final version of the manuscript

All the authors had had full access to all the data in the study. They take responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICAL APPROVAL

This study was approved by the Institutional Ethics Committee of JSS Medical College, Mysuru (Approval number: JSSMC/IEC/09721/30NCT/2021-22)

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the base of this research. All human procedures were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

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DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article and are available with the corresponding author upon reasonable request.

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