# INDIAN GUIDELINES FOR DIAGNOSIS OF RESPIRATORY ALLERGY

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# **Introduction and Methodology**

### Introduction

Allergy is defined as an immediate type I hypersensitivity reaction to an allergen. It may affect various organs of the body, particularly respiratory system. Common respiratory allergic diseases are asthma and allergic rhinitis. Estimated prevalence of rhinitis in general population is 10%-30% worldwide and 20%-30% of the Indian population suffers from allergic rhinitis. The allergic reaction is triggered by environmental allergens which are substances that cause allergic reaction. Allergens are mainly grouped into inhalant allergens, ingestant allergens, injectant allergens and contactant allergens. Airborne allergens are the main cause of respiratory allergy. The most common airborne allergens causing respiratory allergy are pollen grains, fungal spores, house dust mites, animal allergens and insect allergens. Allergic diseases have significant impact on the quality-of-life, social life, and economy. Limited diagnostic facilities and inadequate knowledge about allergic testing further add on to the burden of the disease. Patient history and clinical examination are primary modalities for identifying an allergic disease and its likely causative allergens. This is necessary because many other non-allergic causes like viral infections, irritants etc may have similar symptoms. The clinical suspicion of allergic sensitization can be confirmed by demonstrating the presence of allergen specific immunoglobulin-E (IgE) antibodies in vivo (skin tests) or in vitro methods. There is a lack of well-defined protocols and guidelines for the diagnosis of respiratory allergy testing in India.

Therefore, the evidence-based guidelines for the diagnosis of allergic respiratory diseases were framed in a scientific manner to guide/help the clinicians or practicing physicians all over the country. In addition to the extensive review of the literature, including the previously published relevant national and international guidelines, in particular the Indian studies were reviewed to make consensus, easy to understand and simple recommendations by the Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute and duly endorsed by the Indian College of Allergy, Asthma and Applied Immunology (ICAAAI), South Asia Association of Allergy, Asthma and Clinical Immunology (SAAAACI), and National Centre of Respiratory Allergy, Asthma and Immunology (NCRAAI).

#### Methodology

The initiative of development of guidelines for diagnosis of respiratory allergy in India was undertaken by the Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute, Delhi and was duly endorsed by Indian College of Allergy, Asthma and Applied Immunology (ICAAI), South Asia Association of Allergy, Asthma and Clinical Immunology (SAAAACI), and National Centre of Respiratory Allergy, Asthma and Immunology (NCRAAI). For the development of these guidelines, an extensive initial review was done by the experts in the field from all over the country which was followed by a joint virtual meeting. The review of the literature was done by searching the electronic databases PubMed, Medline, Google scholar, Science direct and Cochrane. More than 3000 National and International relevant articles were selected, and 999 articles were studied in-detail.

The major international guidelines, including the ones available from The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI), European Academy of Allergy and Clinical Immunology (EAACI), Australacian Society of Clinical Immunology and Allergy, Allergy Society of South Africa and National Guidelines for practice of allergen immunotherapy in India were also reviewed.

The search was conducted under three subgroups: (a) history taking and examination, (b) allergens in respiratory allergy, and (c) diagnostic testing (in vivo and in vitro). Relevant questions were framed on the basis of discussions with reference to the Indian context. Review of the literature and meetings were organised by the conveners, co-ordinated by the chair and recorded by the rapporteurs. Individual group meetings were conducted before the joint group discussion. The analysis of evidence and discussions regarding level of evidence and recommendations were held in individual group sessions. Thereafter, joint meeting of all the groups was organized for review and discussions. Final decisions were based on a consensus approach. The modified GRADE system was used for classifying the quality of evidence (Table 1). The strength of recommendation was graded as A or B depending upon the level of evidence (Table 1).<sup>1,2</sup> Grade A recommendations in the guidelines should be interpreted as "recommended" and the grade B recommendations as "suggested".

 Table 1. Classification of level of evidence and grading of recommendation

Classification of Level of Evidence					
Level 1	High-quality evidence backed by consistent results from well-performed randomized controlled trials or overwhelming evidence from well-executed observational studies with strong effects				
Level 2	Moderate-quality evidence from randomized trials (that suffer from flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or other limitations)				
Level 3	Low-quality evidence from observational evidence or from controlled trials with several serious limitations				
Useful Practice Point	Not backed by sufficient evidence; however, a consensus reached by working group, based on clinical experience and expertise				
Grading of Recommendation-based on the Quality of Evidence					
Grade A	Strong recommendation to do (or not to do) where the benefits clearly out-weight the risk (or <i>vice versa</i> ) for most, if not all patients				
Grade B	Weak recommendation where benefits and risk are more closely balanced or are more uncertain				

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# **Executive Summary**

Allergy is defined as an immediate type I hypersensitivity reaction to the allergen. Allergy can have an impact on various organs, particularly respiratory system. Allergic diseases are a major health concern worldwide.

### A: History Taking and Examination

#### 1. Common respiratory allergic diseases

- Common respiratory allergic diseases are asthma and allergic rhinitis although the concept of one airway one disease considers them as a single disease.
- Both these diseases have significant impact on the quality-of-life (QoL), social life and economy.
- In a significant proportion of patients these diseases coexist, and the coexistence of both is associated with increased emergency room visits and health care utilization.

#### 2. What are the symptoms of respiratory allergy?

- Symptoms of asthma are typically paroxysmal and include wheezing, cough, breathlessness, and chest tightness.
- No single symptom is specific or more significant for asthma, although nonasthmatics rarely report frequent wheezing.
- Typical symptoms of allergic rhinitis are nasal obstruction, post-nasal drip, sneezing, rhinorrhoea (clear watery secretions), and itchy nose.

#### 3. What are the signs of respiratory allergy?

- Physical examination in asthmatics can be completely normal.
- Wheezing is the most typical sign of asthma and it may be heard only on expiration or on both inspiration and expiration.
- Wheezing is classically polyphonic and usually heard throughout the chest. Children with allergic rhinitis usually exhibit mouth breathing, allergic salute, allergic nasal crease, facial grimacing, nasal snorting, and allergic shiners on general appearance.

Typical signs of allergic rhinitis on nasal and naso-pharygeal examination are clear, watery rhinorrhea, pale or bluish and boggy inferior turbinates.

# 4. Is age at onset of symptoms significant for diagnosis of respiratory allergy?

- The age of onset of symptoms is important for respiratory allergic diseases as these diseases have different risk factors, clinical presentation, impact on QoL and prognosis in various age groups.
- Childhood onset asthma has been demonstrated to have a stronger association with family history and genetics compared to adult onset asthma.
- Childhood onset asthma patients also have better lung functions, prognosis, and higher chances of going into remission or resolve altogether.
- On the other hand, adult onset asthma symptoms are more associated with occupational exposures and smoking. Obesity related phenotypes are also more common in adults.
- Onset of respiratory allergic diseases in the elderly age group is associated with significant comorbidities, polypharmacy, and more severe deterioration in QoL.
- 5.

# Does family history have significance in diagnosis of respiratory allergy?

- Family history of allergic disorders is a significant risk factor for the development of respiratory allergic diseases.
- Both childhood onset as well as adult onset asthma have strong association with the family history of asthma.
- Although association is stronger for childhood onset asthma.
- Family history of allergies is also associated with an increased risk of allergic rhinitis.
- Risk is more if there is a family history of allergic rhinitis.

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# 6. What is the importance of area of residence with regards to respiratory allergy?

- India is a vast country with varied geographical profile.
- From the Himalayas to coastal regions of southern states and from arid Rajasthan to far north-eastern states different allergens predominate.
- Thus, the allergen predominant in one region may lose its significance in another region.
- Additionally, the dominance pattern of allergen also varies according to rural and urban area of residence.
- Hence, knowledge of area-wise allergen predominance helps in identification of allergens, subsequently followed by appropriate testing and treatment.

# 7. What is the relevance of indoor and outdoor symptoms with regard to the respiratory allergy?

• A broader knowledge of indoor and outdoor allergens with detailed history taking of allergic patients can help in selecting appropriate allergen for testing either by skin prick test (SPT) or specific immunoglobulin-E (IgE) against a particular allergen, which in turn, will help in allergen avoidance and designing allergen specific immunotherapy.

# 8. What is the importance of seasonal variation in respiratory allergy?

• The knowledge about season-wise variation in allergen pattern helps a physician in relating to a typical history of seasonal symptom pattern or season-wise variation in symptom pattern of an allergic patient, which in turn, helps in appropriate testing and further treatment.

# 9. What is the significance of work/occupational exposure in respiratory allergy?

• The exposure assessment, including work-place allergen determination, is a cornerstone in identification of allergen type in a patient suspected to be suffering from occupation related allergies because it helps in establishing preventive measures which includes total allergen exposure avoidance or a reduction in exposure (second best option) along with its treatment.

- 10. What is the significance of recurrence of symptoms on repeat exposure(s) to a particular agent/antigen?
  - The importance of elucidating the history of recurrence of symptoms after exposure to a specific environmental condition underlies the fact that one or more allergen(s) predominate in a particular type of environment, and hence, its knowledge helps a physician in narrowing down the possibility of a particular type of allergen which is followed by appropriate testing and adequate treatment of a patient who is suspected to be suffering from repeated allergen exposure.

# 11. What is the relationship of food and skin allergy with respiratory allergy?

- Variety of respiratory symptoms occurs on exposure to food allergens.
- Very rarely patients may have asthma symptoms in response to inhalation of food particles.
- Symptoms on exposure to food additives can infrequently involve lower respiratory tract symptoms, specifically in asthmatic patients.
- In contrast, the perception of food-induced asthma is more common.
- Previous history of presence of a food allergy increases the risk for the development of asthma, as well as life threatening asthma.
- When food-allergy reactions involve the lower respiratory tract, the reactions tend to be more severe.
- In addition, patients with underlying asthma may experience more severe and potentially life-threatening allergic food reactions.

# 12. What is the relationship of food and skin allergy with respiratory allergy?

Allergic dermatitis (AD) is a prerequisite for the development of allergic rhinitis and asthma and specific sensitization.

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- Whether AD in the atopic march is necessary for the progression to other atopic disorders remains to be defined.
- It is also important to identify infants at risk for developing lifelong chronic atopic diseases and utilize the critical window of opportunity early in the life for therapeutic intervention.
- 13 What is the relevance of treatment history in diagnosis of respiratory allergy?
  - Asthma is seen in nearly 35% to 40% of patients with treatment history of eczema and/or atopic dermatitis.
  - History of skin allergy in childhood is important for the diagnosis of respiratory allergy.
  - History of treatment with aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), angiotensin converting enzyme (ACE) inhibitors, beta-blockers and antibiotics play a major role in some individuals for making the diagnosis of respiratory allergy.

#### **B:** Allergens in Respiratory Allergy

- 1. What are the source/location, risk factors and clinical significance of pollen in causation of respiratory allergy?
  - Allergic rhinitis and asthma are most common pollen-associated allergic respiratory diseases.
  - Pollen sensitization in India varies across different parts because of varied geoclimatic conditions.
- 2. Why is pollen calendar important in respiratory allergic diseases? Is there any standardized pollen calendar for India with reference to various geographic areas?
  - Pollen calendar is important in respiratory allergic diseases for taking personal preventive measures and diagnostic and therapeutic considerations.
  - It also helps public health officials to assess the impact of exposure and to develop early warning systems.
- 3. What is the importance of pollen count in respiratory allergic diseases?
  - Increase in pollen count is associated with an increased risk of allergic and asthmatic symptoms.

- A rise in asthma related admissions may be seen during peak pollen season.
- 4. What are the source/location, risk factors and clinical significance of house dust mite in causation of respiratory allergy?
  - Allergic rhinitis and asthma are most common house dust mites associated allergic respiratory diseases.
  - House dust mites sensitization on SPT in India varies from 11% to 88%.
  - The dominant genus found in India is *Dermatophagoides* spp.
  - What is the source/location, risk factors and clinical significance of fungal allergens in causation of respiratory allergy?
    - Most common mold associated allergic respiratory diseases are allergic rhinitis and asthma. *Aspergillus, Penicillium* and *Cladosporium* are the most common indoor fungal allergens.
    - The common fungal allergens to which sensitivity has been elicited included Aspergillus fumigatus, A. flavus, A. niger, A. tamari, Altenaria, Rhizopus, Cladosporium, Curvularia, Fusarium, Helminthosporium, Mucor, Epicoccum and Trichoderma.
  - What are the source/location, risk factors and clinical significance of insect allergens in causation of respiratory allergy?
    - Naso-bronchial allergy and asthma are most common allergic respiratory diseases associated with insects.
    - Prevalence of insect allergy is variable across India ranging from 6% to 64%.
    - Moth, cockroach, housefly and mosquito are common among insect allergens in India.
- 7. What is the source/location, risk factors and clinical significance of other aeroallergens (Animal/Inhalant food allergens/Occupational allergens) in causation of respiratory allergy?
  - Dander allergen sensitivity is commonly seen due to cat, cow and dog dander.
  - Increasing evidence suggests that allergic reactions to foods can occur following inhalation.

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- Occupational allergens responsible for **3**. respiratory allergy mainly include biocides, latex, flour, animals and metals.
- 8. How will one choose the allergens for screening of allergic diseases in adults and pediatric age group?
  - Clinical history along with the knowledge about regional allergens combined with clinical correlation can help in formulating allergen panel for an individual patient.
  - Additional factors, such as exposure to foods and school environment should be considered in clinical history while choosing allergen for pediatric age group.
  - Indian studies suggest house dust mites to be the common allergen in children.

### C: Diagnostic Testing (In Vivo and In Vitro)

- 1. What are the *in vivo* tests for diagnosis of respiratory allergic diseases?
  - *In vivo* tests for the diagnosis of respiratory allergic diseases are
    - 1. Skin prick test
    - 2. Intradermal test (IDT)
    - 3. Patch test
    - 4. Allergen provocation tests
      - (a) Nasal allergen provocation test
      - (b) Bronchial allergen provocation test
      - (c) Conjunctival allergen provocation test
      - (d) Food allergen provocation test

2. What are the *in vitro* tests for diagnosis of respiratory allergic diseases?

- *In vitro* tests for the diagnosis of respiratory allergic diseases are
  - 1. Serum immunoglobulim–E assays
    - (a) Serum total IgE
    - (b) Serum specific IgE
      - (i) Single-plex
      - (ii) Multiplex
  - 2. Cell-based assay

Basophil activation test

- Which tests are better for diagnosis of respiratory allergy: *in vivo* or *in vitro*? Is comparative sensitivity and specificity of various *in vivo* and *in vitro* tests available?
  - Both the type of tests has certain advantages and disadvantages over each other.
    - 1. SPT is simple, inexpensive, reliable and reproducible test and can be performed with virtually any allergen. It provides quick results, but requires a certain amount of co-operation from the patient.
    - 2. SPT in collaboration with clinical history is the most accurate diagnostic test for the diagnosis of respiratory allergy. (2A)
    - 3. IDT has higher sensitivity, but its diagnostic accuracy is limited. (2A)
    - 4. *In vitro* test, *i.e* serum specific IgE is both less sensitive and less specific compared to SPT for the diagnosis of respiratory allergy. (3A)
- Which test is considered as the gold standard test for diagnosis of respiratory allergic diseases?
  - SPT is considered as the gold standard for the diagnosis of respiratory allergy.
- 5. What are the qualifications required for performing *in vivo* (SPT) allergy testing?
  - An allergy specialist/physician or pediatrician formally trained in allergy testing should perform *in vivo* allergy testing. (3A)
  - A nurse/technician trained in allergy testing can also perform *in vivo* allergy testing under the supervision of an experienced physician. (3A)
  - However, an experienced physician well versed in the management of anaphylactic reactions along with all the necessary requirements for the same, should be present, whenever *in vivo* allergy testing is being performed. (UPP)
- 6. What is the appropriate time for performing allergy testing? Can it be performed during acute phase of the disease?
  - SPT should not be performed during acute phase of the disease/uncontrolled asthma. (3A)

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SPT should be done after at least a gap of 3–4 1 weeks from systemic allergic reactions. (3A)

#### 7. What are the indications for SPT?

- SPT should be performed in the following indications:
  - 1. For diagnosis of respiratory allergy by inhalant allergens (1A), food allergens (1A) and drugs. (2A)
  - 2. As reference standard for *in vitro* tests for the diagnosis of respiratory allergy. (1A)
  - 3. For determining bioequivalent potency of allergen extracts. (1A)

### 8. What are the contraindications for SPT?

- SPT is contraindicated in the following conditions:
  - 1. Pregnancy and lactation (3A)
  - 2. Dermatographism (2A)
  - 3. Absence of normal skin (1A)
  - 4. Un-cooperative patient (UPP)
  - 5. Patients who are taking drugs may hinder the action of epinephrine (if needed for anaphylaxis), *e.g.* betablockers and ACE-inhibtors. (1A)
  - 6. Patients who are taking medications (which interfere with test results) which can not be stopped before test, *e.g.* anti-histamines, trycyclic anti-depressants (TCA) and steroids. (3A)
  - 7. Relative contraindication. It should not be performed in young children and when needed, should be performed under the supervision of pediatrician trained in allergy. (3B)

# 9. What is the lower limit of age for performing SPT?

- Based on the literature review and the experience of the expert panel it is recommended that
  - 1. SPT should preferably be done in children >5 years of age. (2A)
  - 2. With strong clinical indications, SPT may be done in children <5 years under the supervision of a pediatrician trained in allergy testing. (3B)

- **10.** How to choose antigens?
  - This has already been discussed in answers to question number 7 and 8 of Part B.
- 11. What is the maximum number of allergens that can be tested at one time?
  - The maximum permissible number of allergens that can be used for SPT in one sitting in an adult could be up to 60. (2A)
  - In pediatric age group, maximum number of permissible allergens that can be tested in one sitting should be <12. (2A)</li>
  - However, a minimum number of allergens on the individualized basis – as per the clinical history, age, prevalence of aeroallergens, exposure factors and pollen calendar – should be used for SPT. (2A)

# 12. How should the patient be prepared for allergy testing?

- The steps of patient preparation before SPT include:
  - 1. The testing procedure and the risk of complications should be explained to the patient before-hand. Informed written consent should also be obtained for the same. (*Consent proforma given in the detailed guidelines*).
  - 2. The test should be deferred if any contraindication to SPT is present.
  - 3. The patient should have a light breakfast at least 2 hours before the test.
  - Someone should accompany the patient to help in case if the patient develops any adverse reaction, like anaphylaxis.
  - 5. In case of male patients with hairy arms, it is required to shave the arms at least 48 hours before the procedure.
  - 6. The medications which may interfere with the SPT results and the duration for which these drugs should be withheld before performing SPT is given in the box.

Drugs	Withholding Period	
Long-acting anti-histamines	7 days	
Short-acting anti-histamines	72 hours	
Tricyclic anti-depressants	2 weeks	
Long-term systemic steroids	2-3 weeks	
Long-term topical steroids	2-3 weeks	
Omalizumab	4 weeks	

### 13. What is the procedure of performing SPT?

- Before beginning to perform SPT, it should be ensured that emergency kit to manage anaphylaxis (if it happens) has been prepared and ready.
- It should contain pre-filled adrenaline syringe, hydrocortisone, injection atropine, anti-histamine and equipment for intubation.
- Also, oxygen supply should be available.
  - 1. Reassure the patient and explain the test procedure.
  - 2. Site: The test can be performed on volar aspect of forearm, outer upper arm and back. The allergen should be applied at a site 5cm from the wrist and 3cm from antecubital fossa. The most commonly used site is volar surface of forearm.
  - 3. Clean the skin site with alcohol prior to SPT.
  - 4. Mark the positions (where allergen has to be applied) with pen. The allergens should be applied 2cm apart to avoid overlapping and false positive results.
  - 5. Apply the drop of allergen on skin with dropper without touching the dropper tip with the skin.
  - 6. A sharp instrument (lancet) is passed through the drop at an angle of 45°–60° or alternatively at 90° upto a depth of 0.9mm to 1mm. Lancet with a point length of 1 mm is the preferred device as evidenced by the literature reviewed.
  - 7. After 15–20 minutes read the test results.
  - 8. Patient (particularly those with multiple positive results and history

of anaphylaxis) should be observed for 20 minutes after the test for any discomfort.

### 14. How to interpret SPT?

- A standardized approach for reading of SPT is lacking.
- It is recommended that allergen be left at the test site should be blotted immediately after skin test.
- Histamine control should be read after 15 minutes of application.
- Allergen prick test should be read after 15–20 minutes.
- As evidenced by the literature, still mean wheal diameter is the most widely used method in practice. *Format for reporting of SPT results is given in the detailed guidelines.*
- A mean wheal diameter of >3mm more than simultaneously performed diluent control (*i.e.*, negative control) is taken as positive response to an allergen on SPT. (2A)

### **15.** What are the complications of SPT?

SPT is considered a relatively safe procedure, except for a few minimal complications. The various complications which can occur during SPT include:

### Local

- 1. Local skin swelling is seen rarely in some patients due to late phase response of IgE. It is more common in IDT. It usually resolves within 36 hours.
- 2. Localised wheal or flare.

### Systemic

Systemic reactions usually begin within 15–30 minutes

- 1. Anaphylaxis
- 2. Vaso-vagal syncope

### Non-allergic complications

- 1. Risk of transmission of infection. This has never been documented, although theoretically possible.
- 2. Headache
- 3. Malaise

- 16. What are indications for IDT in respiratory allergy?
  - The IDT can be done in the following indications:
    - 1. Patients with strong suspicion for allergy to specific allergens and negative SPTs. (3B)
    - 2. Venom allergy. (2A)
    - 3. Drug allergy (beta-lactams, insulin, opiates, anesthetics, neuromuscular relaxants, proton-pump inhibitors, enzymes, chemotherapeutic agents, vaccines). (2A)

# 17. What is the relevance of serum total IgE in diagnosis of respiratory allergy?

- Serum IgE levels usually higher in atopic disorders. Its relevance in respiratory allergy is summarized as:
  - Sensitivity and specificity of serum total IgE is very low for the diagnosis of respiratory allergy and it should not be considered as a reliable marker of allergy status. (2A)
  - 2. Serum total IgE is one of the reliable markers for following disease severity and therapeutic response in allergic bronchopulmonary aspergillosis (ABPA). (1A)
  - 3. Serum total IgE values have significance in omalizumab therapy. (1A)

# 18. What are the indications for serum specific IgE testing?

- The indications for serum specific IgE testing are as follows:
  - 1. In cases with inconclusive SPTs and high suspicion of allergy based on the history.
  - 2. Inability to temporarily discontinue skin test suppressive medication

therapy (*e.g.*, anti-histamines, anti-depressants or beta-blockers).

- 3. Presence of extensive skin disease (*e.g.*, dermatographism or generalized eczema).
- 4. Un-cooperative patient.
- 5. Clinical history suggestive of high risk of anaphylaxis from skin testing.

# 19. What is the role of nasal provocation test in diagnosing respiratory allergy?

- Nasal allergen provocation test (NAPT) is of limited clinical value and is mainly indicated for research purposes. (2A)
- Under the current conditions in India, NAPT is advised in tertiary care centres only (2A).
- Unavailability of standardized allergens specific to Indian conditions further limits the utility of this test.

# 20. What is the role of fractional exhaled nitric oxide (FeNO) and pulmonary function test (PFT) in diagnosing respiratory allergy?

- FeNO is not necessary for making a diagnosis of allergic asthma. (1A)
- High FeNO levels are suggestive of eosinophilic/allergic asthma. (2A)
- In adults: FeNO >50ppb (parts per billion) and in children FeNO >35 ppb signifies eosinophilic inflammation and likelihood of corticosteroids responsiveness in symptomatic asthma patients. (2A)
- FeNO may be a useful tool for follow-up and assessment of the treatment response in allergic asthma. (3A)
- Spirometry is an essential diagnostic modality for the diagnosis and follow-up of allergic asthma. (1A)

# A: History Taking and Examination

# Q1. What are the common respiratory allergic diseases?

Allergic respiratory diseases (ARDs) can be defined as an altered state of health caused by the generation of immunoglobulin-E (IgE) antibodies to airborne allergens leading to various clinical manifestations in the upper and/or lower airways.<sup>3</sup> Although allergic inflammation is present in both the upper and the lower airways; its intensity varies locally in a patient with ARDs.<sup>4,5</sup> This variability in the local inflammation of airways is responsible for varied clinical presentation among the patients. The common respiratory allergic diseases are:

- 1. Bronchial asthma
- 2. Allergic rhinitis/rhinosinusitis

The "one airway, one disease" concept has been firmly established within the medical fraternity.<sup>6</sup> There is abundant evidence supporting this concept that considers allergic rhinitis/ rhinosinusitis and asthma, a single disease entity. This concept of one airway, one disease has become the basis of management for the patients with ARDs. Clinical manifestations of upper and lower respiratory tract involvement may or may not occur simultaneously in patients with ARDs; however, these patients are predisposed to develop other clinical manifestations of ARDs in the future.<sup>7</sup> Rhinitis and asthma are currently classified, treated, and evaluated using different guidelines. A holistic approach to patients with ARDs, also considering its variable clinical expression at different levels is the need of the hour.

**Bronchial asthma.** Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Airflow limitation may later become persistent.

Prevalence of asthma is on a rising trend in several high- as well as low- and middle-income countries.The International Study of Asthma and Allergy in Children (ISAAC) has reported an overall prevalence of 7% of current wheeze among Indian children aged 6-7 years and aged 13-14 years. Notably, the study has reported a higher prevalence of up to 10% to 20% in some areas and 50% or more of this cohort had severe uncontrolled asthma.8 The Indian study on the epidemiology of asthma, respiratory symptoms and chronic bronchitis in adults (INSEARCH) reported that the prevalence of asthma among adults aged more than 15 years, in India was 2.1%. This prevalence rate corresponds to nearly 17.2 million people, aged more than 15 years, having asthma in India.9 The burden of asthma in India exceeds the number of people living with human immunodeficiency virus (HIV) infection or tuberculosis. There are approximately 38 million people affected by asthma in India, which corresponds to 55% of the total population of the United Kingdom (UK).<sup>10</sup>

The burden of prevalent allergic diseases in India has been on an uprising trend. It has been estimated that approximately 20% to 30 % of the total Indian population suffers from at least one allergic disease. A study carried over 50 years ago in Delhi reported prevalence of asthma to be 1% in 1964.<sup>11</sup> Another Indian study<sup>12</sup> documented the prevalence of asthma in 1979 to be 9%. The authors further noted that this prevalence rose over a period of 20 years to 29.5% in the year 1999.<sup>12</sup>

Allergic asthma is a type of asthma where environmental allergies trigger asthma.<sup>13</sup> A substantial number of asthmatic patients have concurrent allergic rhinitis, with allergic rhinitis commonly preceding the onset of asthma.<sup>14,15</sup> Also allergic rhinitis serves as an independent risk factor for the future development of asthma due to similar type 2 helper T (Th2) cell involvement. Coexistence of asthma and allergic rhinitis have been linked to increased emergency room visits and asthma attacks in comparison to individuals with asthma alone.<sup>16</sup>

Allergic rhinitis. Allergic rhinitis is also a global health problem with the considerable economic and social burden. About 40% of the world's population is atopic, with allergic rhinitis as the commonest presentation. Allergic rhinitis, often considered to be an insignificant health problem, affects up to 20% of the world population.<sup>15</sup> In India, the reported prevalence of allergic rhinitis was 11% in children aged 6-7 years, and 24% aged 13-14 years.<sup>17</sup> Similar to asthma, the burden of allergic rhinitis in India is also on an uprising trend. The prevalence was observed to be 10% in 1964.11 While in a survey by All India Co-ordinated Project on Aeroallergens and Human Health, New Delhi, in 2000, 20% to 30% of the study population was found to be suffering from allergic rhinitis.<sup>18</sup> Allergic rhinitis is an independent risk factor for asthma, and it is considered as a preceding disease. In the Coexistence of Allergic Rhinitis and Asthma (CARAS) survey,<sup>19</sup> the prevalence of coexisting allergic rhinitis in asthmatic patients was found to be 65%, with the highest prevalence (80%) in the southern regions of India. The coexistence of both the diseases is more challenging to treat than either disease alone.

#### Summary

Common respiratory allergic diseases are asthma, allergic rhinitis/rhinosinusitis, although the concept of "one airway - one disease" considers them as a single disease. In a significant proportion of patients, these diseases often coexist, and this coexistence is associated with increased emergency room visits and health-care utilization.

# Q2. What are the symptoms of respiratory allergic diseases?

Symptoms of bronchial asthma. The typical symptoms of asthma are paroxysmal wheezing, cough, breathlessness, and chest tightness. These symptoms may be triggered by specific exposures, exercise, or emotions. The cough may be productive of clear or yellow/green discoloured sputum. Sputum in asthmatics may be tenacious and difficult to expectorate and reflect the underlying airway inflammation rather than a respiratory infection. In some instances, the cough may be the only symptom of an episode of asthma. Breathlessness is believed to occur because of the dynamic lung hyperinflation during acute asthma episodes. Patients usually describe their breathlessness as the sensation of difficulty-getting air in their lungs. Exertional symptoms may not be apparent in elderly patients as they have limited ability to exert themselves due to other coexisting health conditions, such as rheumatologic or cardiac disease. This may lead to under-diagnosis of asthma in the elderly. No single symptom is specific or more significant for asthma, although wheezing is a useful sign, as non-asthmatics rarely report frequent wheezing. In younger patients, the symptom of chest tightness is helpful, since it occurs more often in association with asthma than with any other pulmonary or cardiac disorders. The pattern of symptom occurrence, the precipitating or aggravating factors, and the profile of a typical exacerbation are important elements in the clinical evaluation.<sup>20</sup>

In patients with poorly controlled asthma, symptoms may temporally evolve slowly over days or weeks, or present abruptly. The frequency of symptoms and their severity varies significantly within the asthmatic population. The symptoms of asthma are paroxysmal and recurrent in nature and may improve spontaneously, or with treatment. Adult asthmatic patients typically wake up in the early hours of the morning with symptoms, and this nocturnal variability of symptoms is a characteristic of asthma.<sup>20</sup>

Distinguishing whether nocturnal symptoms are due to asthma, angina, or gastro-oesophageal reflux may be difficult, but early-morning asthma symptoms are usually relieved with the administration of inhaled bronchodilators, in contrast to cardiovascular symptoms which occur at any time during the night and, gastrooesophageal reflux which tends to usually cause symptoms soon after the patient reclines at night. Chest symptoms that vary by season and are accompanied by symptoms of irritation of other mucus membranes, such as conjunctivitis and rhinitis, are typical of allergic asthma. Triggers, such as indoor allergens of house dust mite, cockroach, and animal dander proteins are more likely to result in perennial symptoms, whereas pollens and some mould spores are likely to provoke seasonal symptoms. The presence of rhinosinusitis, nasal polyps, conjunctivitis, or eczema, coupled with a family history of asthma or atopy, may further support the diagnosis of asthma. Symptoms after heavy exertion, especially in the cold air, are highly suggestive of exercise-induced asthma, and typically, patients experience symptoms at the end of the exercise, rather than during its performance. Excessive coughing after exercise in the absence of wheeze may also be a sign of asthma. Special considerations should address symptoms

induced by aspirin or those associated with the patient's occupation.<sup>21</sup>

There are various environmental and genetic factors that modulate the clinical presentation in a patient with ARDs. As shown by several studies, clinical manifestations of ARD in a patient depend on the type of airborne allergen to which that patient is sensitized.<sup>3,4,22,23</sup> Age at sensitization and sensitization to several agents (polysensitization) also substantially alter the clinical features and prognosis of ARD patients.<sup>24</sup> Furthermore, clinical manifestations of ARDs also vary temporally as the patient's life progresses.

Intensity and duration of exposure to an airborne allergen called allergenic pressure, greatly influence the clinical presentation of a patient. Contact with an allergen causes pathophysiological changes that affect the development of symptoms triggered not only by allergens but also by other agents, such as infectious microorganisms.<sup>25</sup>

Impact of symptoms. Asthmatics generally have worse indicators of quality-of-life (QoL) and anxiety, despite having their symptoms of asthma under control.<sup>26</sup> Asthma has been shown to be associated with an increased risk of depression, and anxiety disorders.27 Correlation of asthma with major depressive disorder, panic disorder, generalized anxiety disorder and post-traumatic stress disorder has also been confirmed.28 An important area affecting the QoL that is reduced in asthmatic patients is a daily activity. According to the World Health Organization (WHO), asthma is responsible for approximately 250,000 deaths annually. This estimate of mortality due to asthma does not include asthma of infancy that often goes unrecognized and untreated. The economic costs of asthma is high both in terms of direct and indirect costs, especially in severe or uncontrolled asthma.<sup>29</sup> Paediatric asthma results in 14 million missed days of school each year, in the United States. This, in turn, results in loss of workdays and wages for caregivers.<sup>30</sup> In the global burden of disease study conducted between 1990-2016, the Death and Disability Associated Life Years (DALYs) per case of asthma in India were 2.4-fold higher than the global average.<sup>31</sup>

A probabilistic prevalence-based cost of illness study done in Italy found that the overall total economic burden associated with respiratory allergies and their main co-morbidities is approximately  $\notin$ 7.33 billion (27.5% was associated with indirect costs and 72.5% with direct costs). The study model estimated that an average annual economic burden due to allergic asthma, allergic rhinitis, combined allergic rhinitis and asthma, was  $\notin$ 1,35 billion,  $\notin$ 1,72 billion, and  $\notin$ 1,62 billion respectively.<sup>32</sup> In India, the monthly cost can amount to one-third of an average family's monthly income.<sup>33</sup>

Symptoms of allergic rhinitis. Common symptoms of allergic rhinitis/ presenting rhinosinusitis include sneezing; rhinorrhoea consisting of clear watery secretions; and itchy nose with or without itchy, red, or watery eyes. Increased mucus production presenting as postnasal drip and wheezing (particularly expiratory wheezing) are other potential allergic symptoms. Allergic rhinitis can lead to an increase in symptoms of other disease processes, such as asthma, chronic rhinosinusitis, obstructive sleep apnoea, and otitis media. In such patients, untreated allergic rhinitis can be a reason for uncontrolled symptoms of the underlying disease process. Other, less common symptoms that may indicate allergic rhinitis include complaints of chronic nasal congestion; coughing; frequent sinus infections; change in hearing, ear pressure, or pain; itchy throat; hoarseness; snoring; and tiredness or fatigue.34,35 An illustrated description of a symptom of allergic respiratory disorder must contain three essential components: duration, timing, and location.

Impact of symptoms. Allergic rhinitis is often considered as an insignificant clinical illness and is thought to have an only trivial impact on the health of the patient. Although the symptoms of allergic rhinitis do not lead to dangerous deterioration to health, these can be uncomfortable and reduces QoL, school, and work performance.36 Numerous clinical studies, focusing on the patient's perspective, have highlighted that it negatively affects sleep, concentration, performance at work, and school.37,38 Social life and emotional status of the patient are also significantly deteriorated by the symptom burden of the disease.<sup>39</sup> In a large survey, of 3052 patients with rhinitis were found to have impaired health-related QoL (HRQoL) compared with healthy controls of similar age.<sup>40</sup> The impact of severity of rhinitis was more significant compared to the effects of duration of illness on HRQoL. Allergic rhinitis also leads to substantial sleep disturbances and practical problems like the repeated blowing of nose.41,42 Adolescents face issues with concentration which adversely affects their learning and school performance. Children with allergic rhinitis are frequently troubled by nasal and eye symptoms, and other symptoms, such as irritability, thirstiness, sleep, and concentration disturbances. However, they generally do not experience emotional distress and tend to have less interference in their daily activities.43 Children were more troubled by having to take medications and carrying tissues.<sup>44</sup> Associated chronic rhinosinusitis and nasal polyposis lead to further impairment in QoL and sleep.45,46 Sleep disturbances (somnolence, apnoea snoring) tend to increase during pollen season in patients with seasonal allergic rhinitis. There are reports, which show the relationship between allergic rhinitis and mood disorders, anxiety disorders and suicidal ideation.<sup>47</sup> The economic impact of allergic rhinitis is also significant. In a study done in the Swedish population, the costs of allergic rhinitis were appraised. Total cost was estimated at €1.3 billion annually, and individual cost estimates were €961.1 per year.48

#### Summary

## *Symptoms of asthma are typically paroxysmal and include wheezing, cough, breathlessness, and chest tightness.*

No single symptom is specific or more significant for asthma, although non-asthmatics rarely report frequent wheezing. Typical symptoms of allergic rhinitis are nasal obstruction, postnasal drip, sneezing, rhinorrhea (clear watery secretions), and itchy nose.

#### Q3. What are the signs of respiratory allergy?

Clinical signs observed on a careful and thorough physical examination, are an important aid, in making the diagnosis of inhalant allergic diseases. A strong presumptive diagnosis can be made based on history alone.<sup>49</sup> Physical examination findings provide further evidence of allergic disease, and on the basis of history and physical examination, medical therapy can be started unless further testing is warranted.<sup>50</sup> Clinical findings on physical examination of a respiratory allergy patient may be characteristics of a particular disease. Table 2 lists common findings associated with allergic diseases, separated by the area of examination. Although the physical examination is tailored to the chief complaints, it is important that it is complete enough to allow the clinician to evaluate the possible contribution of other diagnoses. The physical examination needs to be evaluated for united airway concept from nose, sinus, throat to chest examination.<sup>51</sup> Skin should also be examined for atopic features. Overall, the physical examination should focus on the head and neck, chest, and skin.

#### Table 2. Signs on physical examination

### Nose and nasopharyngeal findings Clear, watery rhinorrhea

Pale or bluish and boggy inferior turbinates Nasal polyps or polypoid mucosal changes Adenoid hypertrophy

## Oral cavity and oropharyngeal findings

Tonsillar hypertrophy Posterior pharyngeal wall cobblestoning Laryngeal findings Mild vocal fold oedema Pale arytenoids with mild oedema Thick bridging mucus

#### **Ocular findings**

Conjunctivitis Allergic shiner Dennie-Morgan lines Lower eyelid oedema

#### Ear findings

Serous otitis media External auditory canal dermatitis Scarred or perforated tympanic membranes

### Skin findings

Urticarial lesions Eczema or atopic dermatitis

> **General appearance.** Children with longstanding allergic rhinitis typically have a facial appearance characterized by mouth breathing, dark rings under the eyes called allergic shiners (Figure 1A) and performance of an allergic salute (Figure 1B).<sup>48,51</sup> The allergic salute refers to a characteristic manoeuvre done by the patients to manage rhinorrhea that involves wiping their nose with the palm of their hand or tissue in a

vertical direction that displaces the nasal tip superiorly (Figure 1B).<sup>52</sup> Chronic performance of the allergic salute eventually creates a dark crease above the nasal tip (supra-tip), also known as the —allergic nasal crease (Figure 1C).<sup>52</sup> Facial grimacing is a compensatory measure used by patients to relieve nasal itchiness without using a hand or finger.



**Figure 1. Photograph of the patient showing (A) Allergic shiners, (B) Allergic salute, (C) Allergic nasal crease.** *Courtesy: Prof. (Major) K. Nagaraju* 

Other such manoeuvres exhibited by patients to relieve pharyngeal itchiness are nasal snorting or palatal–clicking. Long-standing, early onset allergic rhinitis in children due to chronic nasal obstruction, can also be associated with anatomic changes, such as a high arched palate, widening of the bridge of the nose, and dental malocclusion. The characteristic appearance of children with chronic allergic rhinitis (with or without the palate and dental changes) is sometimes termed the allergic facies.<sup>52</sup>

A patient in acute anaphylaxis is often uncomfortable and has a flushed look. Asthmatic in acute exacerbation usually present with shortness of breath and audible wheezing. Sometimes a patient may present with respiratory distress along with the use of accessory muscles. A patient may cough during the examination, in that case, try to hear the cough to identify the location of origin of the cough.<sup>54</sup>

**Vital signs.** The vital signs are part of any complete physical examination, but these are typically normal except in asthma or severe allergic reactions where increased respiratory rate, tachycardia, and hypotension can be observed.<sup>51</sup> During an acute exacerbation of asthma, physical signs of increased ventilation

may be observed with the use of accessory muscles of respiration and tachypnea.<sup>55</sup> *Pulsus paradoxus* can be observed, which is a sign of severe airway obstruction, and is documented by an exaggerated decrease in systolic blood pressure during inspiration by >10mmHg. As ventilatory effort gets diminished with respiratory muscle fatigue, pulsus paradoxus may be absent, but its absence does not preclude severe airway obstruction.<sup>55</sup>

Nose and nasopharyngeal findings. External nasal findings, as described above, include the presence of an allergic crease indicating longstanding allergic rhinitis.<sup>52</sup> Specific internal nasal findings often depend on whether the rhinitis is acute or chronic. Internally, acute allergic rhinitis is typically manifested by enlarged inferior nasal turbinates that are pale and sometimes described as being blue.51 Venous congestion in the inferior turbinates typically results in oedema (boggy oedema) with a pale bluish or purplish discolouration.56 Nasal mucosa is moist, and it is usually coated by thin and clear mucus. The inferior nasal turbinates in chronic allergic rhinitis can also be swollen, but tend to be erythematous rather than pale and less moist. More longstanding chronic rhinitis is often associated with crusted mucus and patchy epistaxis. Nasal polyps are glistening enlargements protruding from the turbinates and are often associated with allergic rhinitis or asthma.<sup>57</sup> Large nasal polyps can be easily visualized on anterior rhinoscopy. Irritation or bleeding of the nasal septum can indicate the incorrect application of nasal steroid or sinusitis. Sinusitis is sometimes associated with an odour of infection from the mouth and nose.<sup>51</sup> Large polypoid changes at the posterior aspect of the inferior turbinate are referred to as "mulberry turbinate". Adenoid hypertrophy may result from inflammatory mediators present in nasal secretions and is more commonly seen in children, but it does occur in adults. This enlargement can contribute to nasal obstruction and lead to mouth breathing in children.58

**Oral cavity and oropharyngeal findings.** Inflammatory mediators in nasal drainage flowing posteriorly also affect lymphatic tissue in the oropharyngeal region. Tonsillar hypertrophy and hypertrophy of submucosal pharyngeal lymphoid tissue which presents as cobblestoning of oropharynx may occur in the allergic patients.<sup>59</sup> **Laryngeal examination findings.** Allergic involvement of larynx is less recognized likely because its signs and symptoms are similar to laryngopharyngeal reflux. However, certain findings on mirror examination or flexible laryngoscopy suggest allergic disease particularly thick, viscous mucoid secretions that tend to span from one vocal fold to the other ("bridging mucus").<sup>60</sup>

Occular examination findings. Signs of associated allergic conjunctivitis can be observed most often in patients of allergic rhinitis.<sup>51</sup> Typical signs include a periorbital, lid, and conjunctival erythema/hyperemia, chemosis, and watery discharge or excessive tearing.<sup>61</sup> Most cases of allergic rhinitis-associated conjunctivitis tend to be mild and non-purulent. However, in some patients, typically young boys, allergic conjunctivitis can be fairly severe with a purulent discharge and is often associated with a cobblestone appearance of the conjunctiva.<sup>52</sup> Venous congestion in the periorbital region resulting from nasal congestion can lead to the appearance of lower eyelid oedema and dark discolouration below the lower eyelid, termed as "allergic shiner".48 In some cases, hemosiderin leakage from the congested vessels may cause permanent discolouration. Local hypoxia resulting from this congestion may cause spasms of Muller's muscle, which manifest as Dennie-Morgan lines (Figure 2).53



**Figure 2. Photograph of the patient (Dennie-Morgan lines).** *Courtesy: Prof. (Major) K.Nagaraju* 

**Ear examination findings:** Nasopharyngeal oedema around the eustachian tube from inhalant allergies can result in eustachian tube dysfunction, which further leads to the development of serous, non-infected fluid in the middle ear space.<sup>36</sup> The allergic inflammation of middle ear mucosa is also thought to contribute

to the development of serous effusions.<sup>35</sup> Tympanic membranes can be scarred or perforated from chronic recurrent otitis media associated with allergy. Atopic dermatitis in the external auditory canal is important to recognize. The build up of chronic debris and breaches in the skin from digital trauma or instrumentation to relieve itching may lead to repeated bouts of otitis externa.<sup>62</sup>

**Skin examination findings.** Eczema or atopic dermatitis present as a scaly rash of variable appearance with a tendency to involve flexural surfaces.<sup>63</sup> Although urticaria, or hives, can occur anywhere on the body,<sup>64</sup> it is important to describe the rash as generalized or localized (with location), macular, popular, erythematous, vesicular, bullous, etc.<sup>51</sup> In some cases, timing or duration of the rash helps determine the aetiology, as some patients with a respiratory allergy will develop skin symptoms after exposure to offending allergens or during pollen seasons. Patients may exhibit minimal itching usually limited to the skin lesion or generalized pruritus.<sup>52</sup>

Chest examination/findings. There may be no abnormal physical findings when asthma is under control. The most typical physical finding in asthma is wheezing on auscultation, which is usually caused by turbulent airflow through narrowed airways.55 Rhonchi or wheezing in asthma may be heard only on expiration or on both inspiration and expiration but is not always present in severe acute asthma or cough-variant asthma.55 Wheezing may be heard throughout the chest and is classically polyphonic. The quality and character of wheezing are not specific to asthma or to the severity of the underlying disease. In cases of very severe airway obstruction, breath sounds and wheezing may be absent.<sup>51</sup> A prolonged expiratory phase may also suggest asthma. A manoeuvre to enhance wheezing, forced exhalation, can be assessed in asthmatics.65 In chronic, long-standing asthma, barrel chest can be seen due to chronic hyperinflation, and onper cussion, the chest is typically resonant to hyperresonant.51

#### Summary

1. Children with allergic rhinitis usually exhibit mouth breathing, allergic salute, allergic nasal crease, facial grimacing, nasal snorting, and allergic shiners on general appearance.

- 2. Typical signs of allergic rhinitis on nasal and nasopharyngeal examination include clear, watery rhinorrhea, pale or bluish and boggy inferior turbinates.
- 3. The physical examination in asthmatics can be completely normal.
- 4. Wheezing is the most typical sign of asthma, and it may be heard only on expiration or on both inspiration and expiration.
- 5. Wheezing is classically polyphonic and usually heard throughout the chest.

# Q4. Is age at onset of symptoms significant for respiratory allergy?

Asthma and allergic rhinitis vary considerably across the course of life and has different clinical implications according to the age of onset. Childhood asthma is known for its overall high prevalence with a male predominance prior to puberty, common remission and rare mortality. Adult asthma is known for its female predominance, uncommon remission and unusual mortality. Allergic rhinitis also has notably different clinical presentation among children and adults, which are described herein.

#### Childhood-onset asthma

*Risk factors.* Childhood asthma is a uniquely diverse and heterogeneous disorder with variable clinical presentation. It affects 7% of the children in India and is one of the most common chronic diseases of the childhood.<sup>8</sup> Multiple risk factors for the development of asthma in offsprings have been identified that include genetic as well as environmental risk factors.

Genetic risk factors. Both maternal and paternal histories of asthma are associated with an increased risk of asthma in the offsprings. Interestingly, maternal asthma history is more strongly associated with asthma development in the child.<sup>66</sup> Genetically boys are more likely to develop childhood asthma until the point of puberty. This has been explained by smaller airway size in boys compared with girls under the age of 10 years, which predisposes them to worsened airway reactivity, as compared with girls of the same age, height, and weight.67 History of other atopic diseases, such as atopic dermatitis, food allergy and allergic rhinitis in early childhood is strongly associated with the childhood asthma.68 A typical pattern called atopic march had been described clinically in

individuals with atopic disease. This atopic march begins as atopic dermatitis (or eczema) in infancy, develops on to allergic rhinitis (or hay-fever) and then asthma later in childhood.<sup>69</sup> Sensitization to house dust mite (HDM), *Alternaria* mould, and cockroach allergens have been associated with the increased risk of asthma,<sup>70,71</sup> whereas early life exposure to cat and dog allergens have been associated with both increased and decreased risk of asthma in different studies.<sup>72,73</sup>

Environmental risk factors. Maternal tobacco smoking and diet have been implicated as childhood asthma risk factors.74-77 Maternal diet higher in vitamin E, zinc, and polyunsaturated fatty acids has been found to be protective against the development of childhood asthma. In contrast, high sugar intake during pregnancy has been associated withan increased risk of asthma in offspring.<sup>78</sup> Peri-natal risk factors which have been reported to be associated with a higher risk of childhood asthma development include neonatal jaundice, maternal preeclampsia, chronic lung disease of prematurity and cesarean section delivery.79-83 Exposures to antibiotics and antipyretics in infancy have also been described to be associated with increased risk of developing childhood asthma.<sup>84,85</sup> Although their role has not been validated and the studies supporting it have been found to have an uncontrolled confounding bias. Therefore, further studies are warranted before any firm conclusion can be made about these associations. Ultimately gene-environment interactions are also thought to play a critical role in the development of asthma in a child.<sup>86</sup>

### Presentation of Childhood Asthma

*Presentation of asthma: early childhood (0–6 years).* Almost 80% of asthma cases have onset during the first six years of life.<sup>87</sup> The symptoms of asthma during this period are varied and not specific to asthma, making the diagnosis challenging. The primary symptoms of asthma in infancy and early childhood include cough, both dry and productive (although young children rarely expectorate), wheeze, shortness of breath, and work of breathing. As these symptoms can also be present in many other pediatric diseases, it poses a significant diagnostic challenge leading to frequent under-diagnosis and undertreatment.<sup>88,89</sup> In view of the difficulty faced in diagnosing asthma in this age group, the Asthma

Predictive Index was developed.<sup>90</sup> The asthma predictive index guides the physician in the diagnosis of childhood asthma, and under the age of three years, it has limited sensitivity but reasonable specificity. Often in this age group, particularly over 0–3 years, symptoms are virally triggered rather than allergically triggered. Infants will often have very few symptoms until they experience an upper respiratory infection, which can trigger significant and severe inflammatory cascade. In childhood asthma, physician visits and hospitalizations have been observed to be peaked at three years after the diagnosis and then stabilized.<sup>91</sup> This suggests that it takes approximately three years to control and stabilize asthma episodes in childhood.91

Presentation of asthma: late childhood (7–11 years). By this age, children can more reliably perform spirometry and are able to describe their symptoms. Reversible airway obstruction on spirometry can be a helpful diagnostic tool; however, it can be normal despite significant disease and morbidity.92 Therefore, in children, spirometry is often used as a monitoring tool for asthma symptoms after the diagnosis has been established through other assessments.93 Symptoms during this age group transition from discrete episodes of wheezing in response to viral infections to allergen triggered exacerbations. Exercise-induced symptoms manifest more clearly in this age group due to sports-related exertion. Care-takers are also able to appreciate the symptoms of dyspnea or cough with exertion. In children who avoid or develop a loss of interest in exercise or physical activities, underlying asthma should be considered. Some children in this age group will have few day-today symptoms but have severe asthma attacks in response to specific triggers such as cold weather, cigarette smoke, or seasonal allergies. Virally triggered asthma exacerbations occur in this age group also but are observed less often and may contribute to the lower rates of healthcare utilization in this age group as compared with younger years of 0-4years.94

*Presentation of asthma: adolescence (12–18 years).* Prior to puberty, asthma risk is higher among male children while at the time of puberty, the risk is approximately equal between males and females, and after puberty, girls have a higher risk of asthma.<sup>95</sup> Asthma symptoms in this age group are predominantly shortness of breath with exertion, wheezing in response to triggers, chest pain, chest tightness, and cough. Asthma symptoms significantly impact sleep, school, sports, and social engagements in this age group. Adolescents are more aware of symptoms and often feel more embarrassment or stigma around using an inhaler, and in particular, a spacer. This often leads to under-treatment of asthma symptoms.<sup>96</sup> Remission is common in adolescence, with reported remission rates ranging from 16% to 60%.<sup>97–99</sup> Factors linked with an increased probability of asthma remission includes mild disease and minor airway inflammation before adolescence, male sex, and the absence of allergic sensitization.<sup>100,101</sup>

#### Remission and mortality in childhood asthma

Asthma remission usually occurs between the ages of 14-21 years.98 However, extensive longitudinal studies had shown that 50% of the children out of those who started wheezing before the age of 3 years, had stopped wheezing by 12 years of the age.<sup>91,99</sup> The wide variation in reported remission rates is likely due to diverse study designs, and different study populations. The following characteristics of childhood asthma have been found to be associated with higher remission rates: episodic asthma (rather than persistent asthma), milder initial asthma severity, less allergic sensitization, less allergic rhinitis, less atopic dermatitis, and male sex.91,98 Although the morbidity of childhood asthma is significant, mortality is rare with an estimated 28 deaths per million children.<sup>66</sup> There are grave racial disparities in childhood asthma mortality, black, and Hispanic children have shown higher mortality rates.94

#### Adult-onset asthma

Asthma is generally considered as a childhoodonset disease, but longitudinal studies have shown that approximately half of middleaged patients with asthma have had onset in adulthood rather than childhood.<sup>102-104</sup> This proportion of adult-onset asthma increases with age.<sup>103</sup> The annual incidence of asthma amongst adults is estimated to be 0.5%, which is similar to the incidence of childhood asthma.<sup>105</sup> The natural history of asthma occurring in adulthood is complex, and it appears to run a different course to that of childhood-onset disease, wherein the majority of cases the disease is mild, and remission is common.<sup>106</sup> In adults with asthma remission is uncommon, and the disease is often more severe and progressive.<sup>107</sup>

### Phenotypes of adult-onset asthma

Recently different clinical phenotypes of adult-onset asthma have been identified by unbiased cluster analysis of cohorts of asthma patients.<sup>108,109</sup> These phenotypes have been further refined with the addition of biological markers to five groups; early-onset allergic, late-onset eosinophilic, exercise-induced, obesity-related and neutrophilic.<sup>110</sup> There are, however, a number of other clinical phenotypes amongst adults with asthma (Figure 3) that are distinct, including those with occupational asthma, aspirin-associated asthma, and asthma associated with other conditions, such as allergic bronchopulmonary aspergillosis and chronic obstructive airways disease.<sup>111–113</sup>

Eosinophilic asthma. phenotype This is characterized by female predominance, elevated sputum and serum eosinophils, a severe disease associated with sinusitis and less allergic sensitization compared to early-onset disease. Despite a high prevalence of positive skin prick tests (SPTs), this form of asthma appears to be less allergic but is often associated with sinusitis, nasal polyps, and aspirin-exacerbated respiratory disease. A family history of asthma is seen less frequently than those with early-onset asthma.<sup>114</sup> This phenotype of asthma is relatively steroid-resistant but highly responsive to biologic therapies targeting T2 pathways.<sup>115-118</sup>

Obesity-related asthma. Obesity-related asthma is not a well-understood phenotype, and it is unclear whether it is comorbidity common in asthma that confers greater likelihood of breathing pattern disorder or it promotes a pro-inflammatory state that results in asthma.<sup>119-122</sup> Higher body mass index (BMI) is associated with increased levels of inflammatory markers, such as, tumour necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), and leptins and fewer eosinophils, fractional exhaled nitric oxide (FeNO) and corticosteroid responsiveness.<sup>121,122</sup> Clinically, this phenotype comprises of a group of older non-allergic, obese females who have significant symptoms but minimal health-care utilization.<sup>106,107</sup> Neutrophilic asthma. Neutrophilic asthma does not have a widely accepted definition, and the consensus about the characterization of this entity is also lacking. In addition, corticosteroid treatment commonly suppresses eosinophils and causes neutrophilia, which further creates confusion in identifying this phenotype.123-125 Although the clinical phenotype remains poorly described, it has been suggested to be that of adult-onset, associated with severe obstruction and high health-care utilization.<sup>109,126</sup> Smoking is also thought to play a role in the pathogenesis of this phenotype. These patients tend to be less corticosteroid-responsive, and other treatment strategies, such as macrolide antibiotics, have been tried with variable success.127

Aspirin-associated asthma. It tends to occur in adulthood at an average age of 34 years and is more common amongst females.<sup>111</sup> This is a subset of late-onset eosinophilic asthma and is associated with sinusitis, nasal polyps and sensitivity to cyclooxygenase-1 inhibitors including aspirin. Biologically it is characterized by the upregulation of the cysteinyl leukotriene pathway and elevated eosinophils.114 These patients are often relatively corticosteroid resistant, requiring high doses for control, but can be responsive to leukotriene antagonists.<sup>128,129</sup> More recently biologic therapies that target T2 pathways including IL-4, IL-13, and IL-5 have been shown to be effective in patients with asthma and nasal polyps.130-132

Allergic bronchopulmonary aspergillosis. It occurs in 1%-2% of asthma patients, although it has been detected in up to 13% of the population in asthma clinics. ABPA predominantly affects adults, causes asthma exacerbations, deterioration of pulmonary function, mucous plugging, central bronchiectasis, and transient infiltrates with characteristic pulmonary biologic features including elevated total and Aspergillus-specific IgE as well as peripheral eosinophilia.<sup>113,133,134</sup> The diagnosis is based on the presence of asthma, proximal bronchiectasis, sensitization to Aspergillus, and an elevated total IgE.<sup>134</sup> It is important to diagnose ABPA because of the progressive nature of the bronchiectasis in the absence of treatment. The mainstay of the treatment for ABPA is systemic corticosteroids and, in some cases, antifungal agents. Figure 3 shows the importance of age and onset of asthma and asthma phenotypes.



### **Eosinophilic Asthma**

Overweight females High eosinophils Moderate-to-severe Medium-to-high-dose ICS Frequent exacerbations Airflow obstruction

### **Obesity-related Asthma**

Obese older women Different levels of severity Less atopic Low eosinophils and FeNO High-dose inhaled ICS Often associated sinus disease, Gastro-oesophageal reflux

### Neutrophilic Asthma

Neutrophilia Severe obstruction High health-care utilization Smoking is thought to play a role Less corticosteroid responsive

### Aspirin-associated Asthma

Severe obstruction Lower lung function High healthcare utilization Poor quality of life Aspirin sensitivity Often sinus disease High use of oral corticosteroid

Figure 3. Importance of the age of onset of asthma and asthma phenotypes.

#### Natural History

The natural history of asthma in adults is different from that of asthma in children, as it is associated with fewer remissions than asthma occurring in childhood. Risk factors of adultonset asthma also appear to be different than that of childhood-onset disease. Compared to childhood asthma, major associations with adultonset disease are female sex, current smoking, obesity, and low socio-economic status. On the other hand, childhood-onset asthma is associated more frequently with atopy or a family history of asthma.104 Other risk factors of adult-onset asthma include the history of allergic rhinitis, higher BMI, nocturnal gastroesophageal reflux disease; and low physical activity amongst men.<sup>105,120,135-139</sup> The evidence for smoking as a risk factor is mixed with two large cohort studies from Australia and Sweden showing that this is a risk factor for adult-onset asthma and other studies in contrast showing that it is not a risk factor.<sup>104,105,136,139</sup> There is emerging evidence of the association between female hormonal changes and asthma that may partially explain the female predominance of asthma after puberty.<sup>140,141</sup> Some factors that appear to be risk factors for adult-onset asthma include the level of education, atopy (either baseline or newly positive SPTs), occupational exposures or maternal asthma. Despite the differences in risk factors, the prevalence of asthma amongst adults as well as children was shown to be increasing in the second half of the twentieth century.<sup>103,142</sup>

In those who develop asthma as young adults, the natural history appears to be more similar to that of childhood asthma with atopy an important risk factor and more chances of remissions.143 Many patients are diagnosed with asthma in middle age, and this predominantly affects women.<sup>103</sup> The proportion of adult-onset asthma was even higher in women who were obese, non-atopic, and had lower socio-economic status.<sup>103,104</sup> In contrast for men by 50 years, only one-third of asthma is adult-onset asthma.<sup>103</sup> Overall, those with adult-onset asthma are more likely to experience symptoms, including wheeze, new rhinitis, snoring, and weight gain.<sup>138</sup> Adult-onset asthma patients are also more likely to have a decline in lung functions compared to those with the childhood-onset disease. For those who first experience asthma in elderly

age, atopy does not appear to be a risk factor.<sup>143</sup> Older adults who develop asthma have a similar incidence as younger people of approximately 100 case per 100,000. However, disease severity is worse amongst older adults developing asthma compared to younger people and is also more progressive with poor lung function and more fixed airflow obstruction.144 Older adults with asthma are also less likely to experience remission than their younger counterparts.<sup>144</sup> Majority of the elderly population have moderate asthma, and only about 20% of the patients have severe asthma. Decreased perception of dyspnea may result in delayed diagnosis. Long-standing asthmatic may develop a progressive decline in the pulmonary functions.

### Mortality

Asthma deaths are more common amongst adolescents and young adults, those with low socio-economic status, black race, those with substance abuse, and are uncommon in young children and older adults.<sup>145</sup> Elderly patients die more frequently from respiratory diseases and are at more risk of complications of medications.<sup>143</sup> The poor prognosis and higher death rates are due to chronic systemic inflammation and recurrent exacerbations.

#### Allergic rhinitis in children

The prevalence of allergic rhinitis has increased over several decades. It affects 10% to 30% of the global population, with the greatest frequency found in children and adolescents.58 Allergic rhinitis is a part of the "allergic march" during childhood, and, it usually presents after two years of age.<sup>146</sup> Typical symptoms of allergic rhinitis in children include rhinorrhoea, nasal itching, sneezing, and nasal obstruction. The presence of two or more of these symptoms usually confirms a diagnosis of allergic rhinitis. Atypical presentation of allergic rhinitis in children includes disrupted sleep, persistent cough, lethargy, poor appetite, and stunted growth. Children with moderate/severe allergic rhinitis may develop noisy-breathing, repeated throat clearing, snoring, and a reduction in the sense of smell.

Allergic rhinitis in children is usually associated with a family and personal history of atopy. Presence of allergic rhinitis in childhood is also a risk factor for the development of asthma in future. Children presenting with moderate to severe allergic rhinitis may have coexisting asthma and should be routinely screened for asthma. Increased severity of allergic rhinitis symptoms correlates poorly with asthma control. Allergy testing (SPT or specific IgE blood testing) also helps in the diagnosis

### Allergic rhinitis in adults

There are clear similarities, as well as differences between allergic rhinitis in children and adults. A real-life, large-scale, prospective study conducted in Spain concluded that allergic rhinitis in children was more intermittent, had fewer symptoms, and more comorbidities (asthma, conjunctivitis, and atopic dermatitis) than in adults. Adults reported more severe nasal symptoms of allergic rhinitis compared to children.<sup>147</sup> Allergic rhinitis is a risk factor for asthma both in adults and in children.<sup>148-150</sup>

### Summary

- 1. The age of onset of symptoms is important for respiratory allergic diseases as these diseases have different risk factors, clinical presentation, impact on the QoL and prognosis in various age groups.
- 2. Childhood-onset asthma has been demonstrated to have a stronger association with family history and genetics compared to adult-onset asthma.
- 3. Childhood-onset asthma patients also have better lung functions, prognosis, and higher chances of going into remission or resolve altogether. On the other hand, adultonset asthma symptoms have more association with occupational exposures and smoking.
- 4. Obesity-related phenotypes are also more common in adults. The onset of respiratory allergic diseases in the elderly age group is associated with significant comorbidities, polypharmacy, and more severe deterioration in the QoL.
- 5. Importance of the age of onset of asthma and asthmaphenotypes are summarized in figure 3.

# Q5. Does family history has any significance for the respiratory allergy?

Family history of asthma, allergic diseases, and risk of asthma. Familial aggregation of asthma and atopic disease has frequently been noted, suggesting that positive family history might be used to identify offsprings at risk.<sup>151</sup> A family history of asthma is a strong predictor of asthma risk, with most odds ratios falling between 2 and 4 when a first-degree relative has asthma.<sup>152</sup> Studies have shown that a family history of asthma is

a strong determinant for the development of childhood- as well as adult-onset asthma.153 Heredity has shown to influence adult-onset asthma,<sup>154</sup> although childhood-onset asthma has a stronger association with the family history of asthma than adult-onset asthma. Family history of allergic diseases other than asthma was also found to be linked to the risk of childhood-onset asthma; however, it is an inconsistent and less reliable indicator of adult-onset asthma risk.152 Maternal asthma, as well as paternal asthma, has been linked to the risk of asthma.76,155 However, the effect related to paternal asthma seemed to remain more constant over time as that of maternal asthma.<sup>156</sup> History of maternal asthma, although strongly associated with the risk of childhoodonset asthma, does not have a significant association with the development of adult-onset asthma in the offspring. A Finnish populationbased, case-control study<sup>154</sup> of adult-onset asthma also showed that paternal asthma has a stronger effect of adult-onset asthma compared with maternal asthma. Interestingly, paternal allergic diseases did not seem to follow this pattern and showed a small, non-significant risk of asthma.<sup>156</sup> The risk of allergies (asthma, allergic rhinitis/ rhinoconjunctivitis, atopic dermatitis) increases with the number of atopic first-degree relatives.<sup>152</sup> The risk also varies with a population under study among certain populations, family history might prove to have a stronger effect on the risk of asthma in the offspring.<sup>157</sup>

Childhood-onset asthma has a stronger association with family history than lateonset asthma. In a review, the greatest risk for developing early-onset asthma was detected in the hereditary group having both parents with asthma where the adjusted relative risk (RR) was 9.6. In the same review, the RR of early-onset asthma associated with a maternal history of asthma was more (3.9 *versus* 3.3) compared to that of paternal asthma.<sup>156</sup> Children with a family history of asthma are suggested to have a more severe course.<sup>158,159</sup>

Although the association of adult-onset asthma with family history is weak than that of childhood-onset asthma, however, it is still a significant risk factor for adult-onset asthma. As discussed above, increased risk related to paternal asthma extended to adult-onset asthma (adjusted RR-2.0) while the effect related to maternal

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asthma diminished with age (adjusted RR 0.88). The positive predictive value of a family history of asthma is less than 50%.<sup>152,156</sup> Thus, although a family history of asthma clearly predicts an increased likelihood of developing the disease, it fails to identify the majority of children at risk.

Family history of allergic disease other than asthma and risk of asthma. In a 20- year follow-up analysis of Espoo cohort significance of the family history of allergic rhinitis, allergic conjunctivitis and atopic dermatitis was evaluated.<sup>156</sup> In case of family history of allergic disease, the risk for developing childhood-onset asthma increased with number first degree relative with allergic disease.<sup>152</sup> History of either paternal or maternal allergic disease, is shown to have some effect on childhood-onset asthma but it is found to have no significant effect on adult-onset asthma.<sup>152</sup>

**Family history of allergies and allergic rhinitis.** Family history of atopy is also a risk factor for allergic rhinitis in the child, and the association was even stronger if the parent also had allergic rhinitis. Risk increased with the number of first-degree relatives having atopy. In a study, allergic rhinitis was seen in 16% of the children with one allergic parent, 25% if both parents had an allergy and 28% when more than two family members had an allergy.<sup>160</sup> Table 3 shows the significance of family history of allergens and allergic rhinitis.

Authors <sup>Ref</sup>	Study Population	Odds Ratio	95% Confidence Interval
Chhabra <i>et al</i> <sup>161</sup>	Delhi	3.7	2.8-4.7
Davoodi <i>et al</i> <sup>162</sup>	Mysore	13.3	8.8 - 20.1
Cheraghi et al <sup>163</sup>	Pune	6.6	4.6–9.4
Aggarwal <i>et al</i> <sup>164</sup>	Chandigarh, Delhi, Kanpur and Bangalore	6.1	5.4-6.9
Pokharel <i>et al</i> <sup>165</sup>	Haryana	3.0	0.6-14.4

#### Table 3. Family history of allergies and allergic rhinitis

#### Summary

- 1. Family history of allergic disorders is a significant risk factor for the development of respiratory allergic diseases.
- 2. Both childhood-onset and adult-onset asthma have a strong association with the family history of asthma. However, the association is stronger for childhood-onset asthma.
- 3. Family history of allergies is also associated with increased risk of allergic rhinitis. Risk is more if there is a family history of allergic rhinitis.

- Knowledge of asthma risk might help to motivate behavioural efforts on the part of parents of children at risk (e.g., increased use of mattress covers, removal of rugs, avoidance of humidifiers, and efforts to spare children exposure to cigarette smoke). However, all family members affected by atopic diseases would potentially benefit from these efforts.
- . A positive family history of asthma or other allergic diseases might also help health-care providers and parents to identify early signs of respiratory allergy and to be more proactive about treatment.

# Q 6. What is the importance of the area of residence with regards to respiratory allergy?

The growing prevalence of allergy and asthma in India is a cause of major concern, as it is a vast country with varied geographical profiles, climatic conditions, agriculture and food habits. Hence, there is a wide range of areaspecific allergen predominance. The allergen which may be of importance in one region may lose its relevance in some other parts of the country. At present, more than 25% of the total population of India is sensitized with different forms of allergens,<sup>166</sup> and the major sources of allergens identified are the pollen grains, fungal spores, dust mites, insects and food.<sup>167</sup> Also, the dominance pattern of allergen varies according to the rural and urban area of the residence.

Rural and urban. Many studies have found an increased prevalence of allergic sensitization in urban dwellers when compared with rural dwellers.<sup>168</sup> This difference can be explained on the basis of the hygiene hypothesis which suggests that with improving standards of living, decreased exposure to infective factors may facilitate the development of sensitization in urban population.<sup>169</sup> Also, several other factors present in the urban environment including children exposure to diesel exhaust particles, treatment with antibiotics or even maternal supplements of progesterone might contribute to the increased allergen sensitisation.<sup>170</sup> While the rural population is also allergic and to a large number of allergens, though they less commonly report to the health-care system. This may be due to the fact that in rural areas there are more animals, insects, dusty environment, more prevalence of microbiological flora and fauna and more of the trees and weeds. Also, they are more commonly involved in animal and plants/vegetation related occupation. In a study done by Mahesh et al171 it was found that there

was a lower risk of sensitization to cockroach allergens for the subjects less than 21 years old living in sub-urban (odds ratio [OR], 0.32; 95% confidence interval [CI], 0.12-0.81) and rural environments (OR, 0.33; 95% CI, 0.11-0.96) compared with subjects less than 21 years old living in urban areas. There was a higher-risk of sensitization to fungi in subjects less than 21 years old living in sub-urban areas (OR, 1.51; 95% CI, 0.60–3.77) and rural environments (OR, 2.71; 95% CI, 0.98-7.48) compared with subjects less than 21 years old living in the urban areas.<sup>171</sup> According to Gupta et al<sup>172</sup>, in rural population, 20.2% of SPT were positive in contrast to 7.5% in the urban population. They noted that common rural area allergens are pollens from grasses, like Cenchrus ciliaris and Pennisetum; pollens from weed, like Chenopodium and pollens from trees, like Cassia. Other more common allergens in the rural areas were insect allergens from cockroach, honey-bee, house fly, mosquito, dust allergens from grains like bajra and wheat, animal allergens like buffalo, cow and horse dander and fungal allergen like Curvularia. While in urban population different allergens predominated, like HDM, cat epithelia, dog dander, pollens from trees like Ricinus, silk, cotton allergen and funguslike Aspergillus although cockroaches were found common to both urban and rural areas.<sup>172</sup>

Various researchers have described the area-wise allergen distribution of few common allergens as:

Pollen. An All India Coordinated Project (AICP) on Aeroallergens and Human Health sponsored by the Ministry of Environment and forests of the Government of India studied pollens and fungal allergen from 18 different places.<sup>18</sup> Then in view of the climate, topographical, and ecological diversities, the country was divided into five bio-zones, namely Eastern, Western, Northern, Southern and Central regions and different varieties of allergenic pollens were identified in each region. The increased load of pollen in the air is seen at places with heavy monsoons like coastal regions of southern India due to elevated temperatures, humidity and the possibility of osmotic rupture of the pollen and subsequent release of the respirable allergenic particles, popularly known as thunderstorm asthma.<sup>173</sup>

*Fungus.* It is considered that the tropical and sub-tropical climatic conditions of India along with

the high humidity, are most favourable for the growth and propagation of moulds.<sup>17</sup> Most of the allergy-eliciting indoor moulds reported from different Indian mega-cities are filamentous and present in the air around the year, *e.g.*, *Aspergillus*, which are a major contributor of asthma as these discharge a huge number of allergen-containing spores.<sup>174</sup> *Alternaria* and *Pencilli*, has frequently been reported as a fungal sensitizer from north Indian cities like Delhi while *Cladosporium* is unique as it is known to grow in cool erregions.<sup>175</sup>

*Insects and house dust mite.* Allergy to insects are prevalent in areas with poor sanitation systems. In India, cockroach allergens are considered as one of the most important triggering factors for the development of atopic asthma.<sup>4</sup> While HDM is a perennial allergen common in the urban areas and occupies – pillows, mattresses, carpets, soft toys, upholstered materials, and clothing.<sup>176</sup>

#### Summary

Knowledge of area-wise allergen predominance helps in the identification of the allergens, subsequently followed by appropriate testing and treatment.

### Q7. What is the relevance of indoor and outdoor symptoms with regard to the respiratory allergy?

The atopic individuals are known to mount a response to the presence of allergens in his/her environment, either indoor or outdoor. It can occur either in the form of allergic symptoms appearing de novo or an exacerbation of the underlying allergic condition, like rhinitis, asthma, atopic dermatitis, conjunctivitis etc.177 The severity of the respiratory reactions can vary from mild irritation to severe anaphylaxis.178 Stephen et al have demonstrated that the asthmatic patients who are exposed in their homes to the allergens (dust mite, cat, dog) to which they are sensitized have a more severe form of the disease, as measured on the basis of forced expiratory volume in one second (FEV<sub>1</sub>), peak expiratory flow rate (PEFR), bronchial reactivity, SPT and FeNO.179

In case of indoor allergens, the typical history would include perennial (especially, in HDM and cockroaches), early morning and nocturnal symptom pattern with history of aggravation of symptoms while being indoors, and doing household work, like dusting, blooming and opening old dusty books, etc.<sup>180-183</sup>

The indoor allergens of importance to humanity are fungus, HDM, cockroaches and animal dander.<sup>175</sup> Among fungus Aspergillus, *Penicilli* and *smut* spores are significant contributors to the indoor air fungal spores.<sup>176</sup> Other than the household environment, schools/ libraries and occupational areas involving agriculture and raw material are other common sources of exposure to indoor fungal allergens, such as granary, bakery, sugarcane factory, etc. In 1964 HDM were reported as the actual source of house dust allergens.<sup>177</sup> Their specific biology makes them an important allergen source thriving in indoor domestic conditions.<sup>178</sup> These live in close contact with living persons. The ambient temperature and relative humidity required for HDM to thrive is 25 to 30 °C and 55% to 75%, respectively, which matches the average household/office place ambient condition.<sup>184</sup> These thrive on human or pet skin scales, which are colonized by fungi, yeasts, and bacteria. These factors along with the fact that these are light-sensitive and photophobic, explain their distribution on pillows, mattresses, carpets, soft toys, upholstered materials, and clothing.<sup>176</sup> The typical history includes perennial, early morning and indoor symptoms substantiated by a positive SPT to the HDM allergen. Similarly, insects like cockroaches are also apart of important indoor allergen. Previous asthma studies have shown that exposure and sensitization to cockroach allergens is associated with increased asthma morbidity in children.<sup>185</sup> Other animal allergen of importance are mouse and rat allergens. The sensitization is associated with allergic rhinitis in urban children, pharmaceutical workers and laboratory workers with comorbid asthma. Urine is the main source of allergenic proteins in both mice and rats.186

Then there are some individuals who typically report symptoms while being outdoors. In them, the pollen allergens from trees, weeds, grasses and fungal allergens are the common and important cause. The pattern and prevalence of pollen allergens change mainly according to the area and the season as depicted in questions 6 and 8. Amongst fungus, *Alternaria* and *Cladosporium* species produce important outdoor allergens. The sensitization and exposure to species of these genera are associated with the development of asthma and rhinitis, as well as epidemics of asthma exacerbations, some of which are life-threatening.<sup>175</sup>

#### Summary

A broader knowledge of indoor and outdoor allergens with detailed history taking can help guide in appropriate allergen testing either by skin prick test or specific IgE testing to a particular allergen, which will help in allergen avoidance and designing allergen-specific immunotherapy.

# Q8. What is the importance of seasonal variation in respiratory allergy?

The knowledge of season-wise variation in respiratory allergy dates back to as the fifth Century BC when Hippocrates first noted the seasonal variation in exacerbations of asthma.<sup>187</sup> Since then, seasonal patterns have been described for asthma mortality, hospital admissions and emergency department visits.<sup>188</sup> These variations are ascribed to seasonal variation in exposure to the ambient allergens, respiratory infections and meteorological changes.<sup>189</sup> We will discuss the seasonal changes in allergic diseases under three headings, *i.e.* the season-wise symptom pattern, sensitization pattern and the cause of all these, *i.e.* the season-wise prevalence of allergens.

Symptom pattern. These weather-related factors leading to variations in the allergic symptoms are due to changes in wind patterns which may increase episodes of long-distance transport of pollutants and pollen grains, winters induce an increased concentration of all healthrelated air pollutants and allergenic pollen while changes in the temperature and precipitation patterns can also increase the frequency and severity of forest fires. All of these lead to a greater likelihood of developing an allergic respiratory disease in sensitized patients, and aggravation in patients already symptomatic.<sup>190</sup> The nasal symptoms occur maximum in summer and rainy seasons, whereas pulmonary symptoms occur maximum during harsh winters. This shows a correlation between pulmonary symptoms and dust mite and mould allergies and between nasal symptoms and pollen and pine allergies.<sup>190</sup> Other studies have also reported dust mite to be a common allergen for asthma and pollens to be the main cause for rhinitis.<sup>191,192</sup> In older adults, asthma mortality and hospital admissions are more common during the winter months, and in the younger adult population, these are more common in periods of high ambient allergen load.<sup>193</sup> Cold temperatures are related to acute exacerbations of asthma symptoms, whereas warm temperatures are associated with increased asthma prevalence, perhaps due to the higher levels of exposure to the allergens.<sup>194</sup> The relative risk of asthma hospital admissions associated with cold temperatures has been found to be 1.20 (95% CI, 1.01-1.41).<sup>195</sup> Epidemics of asthma has been noted during thunderstorm seasons. In a recent thunderstorm event in Melbourne, Australia on November 21–22, 2016, as more than 9,900 patients presented to hospitals with asthma attacks. In excess of 2,300 emergency calls were received and despite valiant efforts of emergency services, 10 deaths have been attributed to this tragic crisis. They found that the majority (57%) did not have the previous diagnosis of asthma, although most (51%) of these had symptoms suggestive of latent asthma; rhinitis was highly prevalent in 88% of subjects with 71% of these being moderate to severe; 46% of cases were born outside Australia with a mean duration of 16.0±11.9 years living in Australia; and among them, 16% were Indians.<sup>196</sup>

Sensitization Pattern. According to Nanda and Devi<sup>197</sup>, there is a pattern of sensitization to the allergens according to the seasons, as dust mite sensitization is maximum during winter months and rainy season and minimum during summer months. In contrast, pine mix sensitization is maximum during months of March to June. Grass pollen sensitization is maximum during the rainy season and mould is maximum during winters. Peanut and cockroach sensitization is present throughout the year. Additionally, the sensitization to allergens is most common in summer months as compared to winters.<sup>197</sup> Regarding seasonal variation, the maximum number of patients, sensitized is in summer months. In winters, many of the patients are of non-allergic rhinitis with the most common trigger being the cold climate.<sup>191,192</sup> Choi et al<sup>198</sup> found that the skin sensitization rates to D. pteronyssinus (23.2% versus 32.1%, P=0.004) and D. farina (22.2% versus 30.2%, P=0.009) were significantly lower in the summer and higher in the fall (38.3% versus 26.6% and 35.6% versus 25.3%; P=0.001 respectively). The sensitization rates to weed pollens is maximum in fall (13.9% versus 8.3%, P=0.006) and to Aspergillus fumigatus in the winter (2.9% versus 0.7%, P=0.005).198 Also, the increased level of pollutants during winter months alter the sensitization pattern as pollen

from birch trees exposed to higher Ozone (O<sub>3</sub>) levels induces larger wheals and flares in SPT compared to lower O<sub>3</sub>-exposed pollen suggesting an allergenicity increasing effect of O<sub>3</sub>.<sup>199</sup>

Allergen Prevalence. The weather pattern in India is divided into three seasons, such as spring, summer and winter. All India Coordinated Project on Aeroallergens and Human Health" sponsored by The Ministry of Environment and Forests, Government of India has been successfully completed by Singh and Kumar.<sup>200</sup> It has demonstrated a month-seasonwise pollen load in the ambient air, Holoptelea contributed 22.2% pollen in the air in spring and summer season (March to May).<sup>195</sup> Poaceae (grass) pollen (11.8%) were recorded with maximum concentration in summers and rain (April to June) followed by Asteraceae pollens. While Chandrika and Anantha Raju<sup>201</sup> reported that Casurina and Parthenium are predominant during the spring, Eucalyptus and Ricinus are common during autumn, and Cedrus and Argemone are predominant in winter season. The pollens disperse in the air with tree pollens from March to June and grass from May to October.<sup>202</sup> Hence, during summer and rainy season, grass pollen are common allergens. As during rainy season there may be more thunderstorms, which are known to cause sudden peaks in the grass and mould allergen levels and epidemic asthma in those who are sensitised.<sup>203</sup> In insect allergy according to Jyothirmayi and Kumar<sup>204</sup> although HDMs are perennial but increase during the winter season, cockroaches are perennial but increase during summers and rainy seasons, and other insects allergies are also more common during the rainy season. Perennial allergic rhinitis is usually caused by HDMs, fungi, insects (cockroaches), and animal feathers. Like-wise, fungus although a seasonal allergen behaves as perennial because of the prevalence of different fungi during a different season. Hence, a person can have a perennial symptoms if he is allergic to two-three different fungus. For example, mould allergy is more common in winters and Alternaria in summer, and rains.<sup>205</sup> Aspergilli/Penicilli have a maximum concentration in October. Smut spores are the second highest from February to April.<sup>206</sup> Candida does not have a definite season while Cladosporium showed seasonal predilection to winters (November to February).<sup>207</sup>

#### Summary

The knowledge about season-wise allergen pattern helps a physician in relating to a history of seasonal symptom pattern of an allergic patient, which in turn, helps in appropriate testing and further treatment.

# Q9. What is the significance of work/occupational exposure in respiratory allergy?

The exposure to allergens at the work-place has contributed significantly in enhancing the problems of patients suffering from respiratory disorders as the quality of air is poor due to the presence of a large number of allergens.<sup>18</sup> At present, about 200 agents have been implicated in causing occupational asthma in the work-place. Exposure-specific studies about occupational asthma have focused on substances, of high and low molecular-weight. These agents can be divided into two categories by their mechanism of action: immunological and non-immunological. Immunological causes can be further divided into those that induce asthma through an IgE-dependent mechanism, and those that induce asthma through a non-IgE dependent mechanism.208

In an international population-based study (ECRHS-II),<sup>209</sup> exposure to substances in the work-place and new-onset asthma, the authors studied 18 substances which were characterised as being high-risk. Seven of the substances were of high molecular-weight (e.g., latex, flour) and contained proteins that caused IgE-mediated sensitisation. Six substances were low molecularweight (e.g., isocyanates, anhydrides, and sensitizing drugs) that are linked to work-related asthma but have not been consistently associated with IgE-mediated allergy. It also included bioaerosols (moulds, endotoxins) and four mixed environments (metal-work fluids, irritant gases or fumes, textiles, and agriculture with exposure organic particles). The allergen-specific to RR of asthma was calculated as mites (4.9), bioaerosols (4.1), cleaning products (3.7), latex (3.5), agricultural products (3.4) and reactive chemicals (3.4) in the decreasing order. At the same time, occupation-specific risks in the decreasing order were highest for nursing (4.8), woodworking (3.9), printing (3.6), cleaning and caretaking (3.4), agriculture and forestry (3.1) and electrical processors (2.6). Hence, they concluded that the highest risks were recorded for high-molecular-weight agents, but exposure to low-molecular-weight agents and irritants, such as isocyanates, latex, and cleaning products, also contribute substantially to the occurrence of occupational asthma. Cleaning, nursing, farming and forestry were identified as a highrisk occupation. Participants who had atopy at ECRHS-II and parental history of asthma were at the highest risk of occupational asthma.<sup>209</sup>

Epidemiological surveys for respiratory diseases in India were carried out by Singh<sup>210</sup> among agricultural and industrial workers, such as bakeries, poultry, granaries, sugar industry, etc. About 40% to 59% of workers in different work environments suffered from one or more respiratory ailments, while the incidence of occupational asthma was reported to be between 15% to 20%.17 The major allergens present at occupational sites employing organic raw materials, e.g. cattle-shed, granary, poultry, flour mills, bakery, sugar factory etc were fungal. Amongst fungal allergens, Aspergillus, Pencilli, Smut spores were found to be the major contributors.<sup>210,211</sup> Other occupations associated with indoor allergen exposure were identified as people working in food industries, laboratories, and libraries.<sup>18,212</sup> Hence, the work done by several researchers have led to the identification of various allergen according to the occupations. These are described briefly here.

**Bakery.** *Aspergilli/Penicilli* were the dominant type (69.2%) with maximum concentration in October. Smut spores were the second-highest contributor in the packing section (28.5%) from February to April.<sup>206</sup>

**Poultry.** In the poultry environment, 130 fungal forms were isolated from the air survey. Predominant fungi observed were *Candida albicans, Scopulariopsis brevicaulis, Penicillium nigricans, P. frequentens.* In the hatchery section, *Aspergilli/Penicilli* spores were abundant. As far as seasonality of the fungi is concerned, *Candida* did not have a definite season. *Cladosporium* showed seasonal prevalence from November to February. *A. flavus* had seasonal exacerbation from July to October.<sup>207</sup>

**Granary.** Aspergillus was the most common fungus (68.9%) followed by *Cladosporium*. Aspergillus flavus had two distinct seasons; from September to November and May to August, whereas, *Cladosporium* was prevalent in winter months. Other important contributors to granary environment were *Rhizopus*, *Curvularia*, *A. versicolor*, *A. fumigates* and *Epicoccum nigrum*. The spores of *Alternaria* were present throughout with seasonal exacerbation from March to June.<sup>213</sup>

**Sugar Industry.** *Cladosporium* was recorded in the highest concentration (60%) in both cane cutting and bagasse storage regions of the sugar industry which is almost parallel to its outside concentration and was prevalent from November to March. This period also coincides with the crushing sugarcane season of the sugar industry. Other major contributors were *A. fumigatus, Epicoccum, Saccharomyces* and smut spores. *Epicoccum* was prevalent from Novemberto May.<sup>214</sup>

Library. Lot of work has been done on the aeromycoflora of libraries. High concentration of Cladosporium, Penicillium, Paeciliomyces and Aspergillus species were reported to be dominant in the library environment. After agitation of books, the concentration of A. niger, Penicillium sp. and Cladosporium was found to increase several-folds.<sup>215</sup> Nadimuthu and Vittal<sup>216</sup> reported airborne fungi to be present in low concentration in air-conditioned libraries when compared with conventionally ventilated libraries. Mycoflora of library dust in Jalgaon (Maharashtra) was studied with reference to deterioration of books, and Deuteromycotina members were found to be very common and showed luxuriant growth in the dust from the stored books.<sup>215</sup>

**Cattle-shed.** Two sections of a large rural indoor cattle-shed were surveyed. Altogether 35 fungal types were identified. *A. niger, A. flavus* and *Cladosporium cladosporioides* were found to be dominant fungal types recorded.<sup>217</sup>

**Crop fields.** Aerobiological studies with respect to plant diseases of different crops have been carried out by various investigators. Aerial dissemination of uredinospore of ground-nut rust was studied by Mallarah and Rao.<sup>218</sup> In the maize crop, spores of pathogenic fungi were reported to be abundant inthe air 4-5 weeks prior to the appearance of the disease.<sup>219</sup> *Alternaria alternata* was reported to be the causal organism of leaf and stem spot disease of sunflower. The conidia we retrapped from the air when

the crop was in flowering stage.<sup>220</sup> Day-to-day variations in the concentration of Alternaria over onion field infected with purple blotch was studied by Chawla and Rajasab.221 The conidia were present in high concentration in the air when the crop was at 7-8 leaf stage state.<sup>221</sup> The uredospores of Periodispora mori causing mulberry rust appeared in the air from August onwards, and spore concentration gradually increased upto December corresponding with the disease severity.<sup>222</sup> Aerophyllo-mycoflora of some solanaceous crop plants in Bhilai (Madhya Pradesh) showed the fungal population to exhibit wide variation at different stages of crop development. Maximum number of microorganisms were recorded during a nascent stage, and the minimum number was observed during the seedling stage.<sup>223</sup>

**Food processing industry.** According to Upadhyay *et al*,<sup>224</sup> persons involved in the agriculture and food industries may experience an allergy, long-term and short-term respiratory disorders including occupational asthma and dermatitis, etc. Jeebhay *et al*<sup>212</sup>, reported that animal and vegetable high molecular weight proteins present in aerosolized foods during food processing plus colouring agents, preservatives, antioxidants, and food contaminants are the main inhalant allergen sources in exposed workers at these industries.

### Summary

Exposure assessment, including work-place allergen determination, is a cornerstone for the identification of allergen type, and thus, helps in establishing preventive measures such as allergen exposure avoidance or reducing in the amount of allergen in the environment.

# Q10. What is the significance of recurrence of symptoms on repeat exposure(s) to a particular agent/antigen?

**Allergic inflammation.** It is a type of inflammation produced in sensitized subjects after exposure to a specific allergen. On the basis of chronicity, it is divided into acute and chronic reaction.<sup>225</sup>

Acute reaction. A single allergen exposure produces an acute reaction, which is often classified into two temporal phases, early and late phase. In early phase reactions, type-I immediate hypersensitivity reaction is induced within seconds to minutes of allergen challenge, and in many subjects, this is followed by a late phase reaction within several hours. While some people develop a potentially fatal systemic allergic reaction, termed anaphylaxis, within seconds or minutes of the exposure to an allergen to which they were previously sensitized.<sup>178</sup>

Chronic reaction. A persistent or repetitive exposure to allergens results in chronic allergic inflammation. This, in turn, produces longterm changes in the structure of the affected organs and substantial abnormalities in their function. Also, many patients who initially have a single allergic disorder, such as atopic dermatitis, eventually develop others, such as allergic rhinitis and allergic asthma called as the allergic march or atopic march.<sup>226</sup> This process may be driven in part by a vicious circle in which allergic inflammation diminishes the function of the epithelial barrier. This increases the immune system exposure to the original allergens and additional allergens, and hence, existing allergen specific IgE contributes to sensitization to new allergens.<sup>227</sup> Thus, a vicious cycle is set up.

Allergen. There are two main types of allergens. The first type encompasses any non-infectious environmental substance that can induce IgE production (thereby sensitizing the subject) so that later re-exposure to the same substance induces an allergic reaction. Common sources of allergens include grass, weed and tree pollens, animal dander (shedding from skin and fur), HDM, insect allergens, certain foods (notably peanuts, tree nuts, fish, shell-fish, milk and eggs), latex, some medicines and insect venoms. The second type is a non-infectious environmental substance that can induce an adaptive immune response associated with local inflammation but is thought to occur independently of IgE (e.g., allergic contact dermatitis to poison ivy or nickel).<sup>225</sup> The situations associated with repeated allergen exposure can be related to travel to a particular area, seasonal, occupational, food allergy and other indoor allergens (household, libraries, school etc). The detail about these allergens has been given in previous sections. We will discuss it briefly here.

**Area-wise allergens.** The AICP<sup>18</sup> divided the country into five bio-zones, namely Eastern, Western, Northern, Southern and Central regions and different varieties of allergenic pollens were identified in each region. *For example, Holoptelea* 

and *eucalyptus* in north India, *Trema orientalis* and *Areca catechu* in eastern India, *Casuarina equisetifolia* and *Parthenium hysterophorus* in southern India, *Moringa oleifera* and *Prosopis* in western India and *Argemone Mexicana* and *Ricinus communis* in central India.

**Season-wise allergens.** The weather pattern in India is divided into three seasons: spring, summer and winter. Dust mites although perennial but increase during winter season, pollens are more common during summer and spring season and fungi and insects are common during rainy season and insect allergy is common in rainy season.<sup>204</sup>

Occupation-wise allergens. Epidemiological surveys for respiratory diseases among agricultural and industrial workers revealed that the major allergen load is present at occupational sites employing organic raw materials, e.g. cattle-shed, granary, poultry, flour mills, bakery, sugar factory, etc. Fungus is the most common allergen found in these areas, and amongst fungal allergens Aspergillus, Pencilli, Smut spores were found to be the major contributors.200 Another source of main inhalant allergen in industrial area are animal and vegetable proteins, chemicals like metal salts, isocyanates, di-isocyanates, colouring agents, preservatives, and antioxidants.<sup>228</sup> Similarly, common allergens in household area are insects, HDM and cockroaches, cat dander, dog dander, fungus, like Penicillium, Aspergillus and rat urine etc.<sup>229</sup>

### Summary

The importance of elucidating the history of recurrence of symptoms after exposure to a specific environmental condition underlies the fact that one or more allergen(s) predominate in a particular type of environment, and hence, its knowledge helps a physician in narrowing down the possibility of a particular type of allergen which is followed by appropriate testing and adequate treatment of the patient.

# Q11. What is the relationship of food and skin allergy with respiratory allergy?

**Food Allergy.** Food allergy is defined as an adverse immunological reaction that occurs on exposure to a food that re-occurs on repeat exposure.<sup>230</sup> Food allergies and asthma are increasing in children worldwide. Egg, milk, peanut, soy, fish, shell-fish, and tree nuts are the most common food allergens.<sup>231,232</sup> The most frequently observed clinical manifestations

of IgE-mediated food allergies are cutaneous and gastrointestinal symptoms.<sup>233,234</sup> Foods can also induce a wide spectrum of respiratory symptoms that can range from rhinorrhea to lifethreatening anaphylaxis with severe respiratory compromise. Other respiratory symptoms induced by food include sneezing, nasal congestion, throat swelling, coughing, shortness of breath, and wheezing. These symptoms are significantly more likely to occur in patients with the underlying asthma.

Food allergy and asthma. Asthma and food allergy have been commonly shown to coexist with each other, especially as these often share same risk factors (family history of allergy, atopic eczema, and asthma) but the way in which these interact and influence each other is yet to be fully understood. Studies have shown that food allergies can develop in the first year of life and precede the development of asthma.<sup>235,236</sup> Schroeder et al<sup>237</sup> showed that there was a higher prevalence of asthma in children with food allergy, as well as it occurring at an earlier age compared to children without food allergy. Another study<sup>236</sup> showed that compared to children who were not sensitized to common food and aeroallergens, those who were cosensitized had a higher risk of developing respiratory allergic disease. Studies that looked at the timing when food sensitization occurs have shown that food sensitization early in life (within the first 2 years of life) is a strong predictor of allergy by school age and also children with food allergy have approximately double the chance of developing asthma and rhinitis.238,239 There also seems to be an association between asthma and non-IgE-mediated food allergy, although it is less prevalent than that seen in IgEmediated allergy.<sup>240</sup> In a study, approximately one-third of children with non-IgE-mediated food allergy had asthma and allergic rhinitis.<sup>241</sup> Higher rates of asthma (26% to 66%) have also been reported in eosinophilic esophagitis, which is considered a food allergy disease.242-244 Food allergens which trigger asthma symptoms is not fully understood. The respiratory symptoms that occur in food allergic reactions commonly include rhinitis, bronchospasm, cough, and laryngeal edema.<sup>235</sup> One theory is that particles of ingested food are inhaled into the airways, and exposure of these allergenic proteins to mast cells in the lungs causes inflammation, and therefore,

respiratory symptoms.<sup>235</sup> Grain-induced asthma is a frequent occupational allergic disease mainly caused by inhalation of cereal flour or powder and professions mainly affected include bakers, confectioners, pastry factory workers, millers, farmers, and cereal handlers.<sup>245</sup>

Diagnosis is based on a history of work-related asthma symptoms, SPTs, and inhalation challenges to bakery allergens, which is the gold standard test. Aerosolized fish protein allergens have also been detected to cause respiratory related symptoms due to inhalation of fish proteins.<sup>246</sup> Similarly, occupational asthma and allergy has been reported in snow crab-processing workers who on cumulative exposure to snow crab have developed symptoms of asthma and allergy.<sup>247</sup>

Roberts et al<sup>248</sup> performed bronchial challenges in children with proven IgE-mediated food allergy and asthma using aerosolized foods. In this study, despite dietary avoidance of allergens, the children had worse chronic asthma symptoms when there was environmental exposure to the foods. However, when the families stopped cooking the allergenic foods at home, the child's symptoms improved, and they needed less inhaled corticosteroid treatment.248 There has also been research performed on specific food allergens and their association with respiratory symptoms and the development of asthma. For example, in a large birth cohort study,<sup>249</sup> having egg allergy during infancy was predictive of respiratory allergy later in the childhood. In fact, they reported a positive predictive value of 80% if the child also had eczema.249

Rhodes *et al*<sup>233</sup> found that in a study of 100 infants who were deemed to be at high risk of developing asthma and atopy (*i.e.*, had atopic parents), those who were sensitive to egg and milk in the first year of life was found to be predictive of having asthma in adulthood. Another study looking at peanut or tree nut allergies showed that patients with a severe history of asthma was at a greater risk of life-threatening bronchospasm occurring after ingestion of nuts.<sup>250</sup>

**Respiratory allergy due to inhaled food particles.** Respiratory symptoms can occur due to exposure to airborne food particles in foodallergic individuals. Robert *et al*<sup>248</sup> identified 12 children with reported reactions on inhalation of food particles, out of them 9 children and their families allowed a double-blind placebocontrolled challenge with causative food by inhalation and out of that 5 had acute asthma symptoms during the challenges.

Patients with a known fish allergy can present with complaints of wheezing or rhinitis when exposed during cooking or manipulation of the food.<sup>251</sup> These studies indicate that only if a food protein is aerosolized a patient with known sensitivity to that food react to the inhalation.<sup>248</sup>

Food additives and asthma. Food additives have been implicated in respiratory or other allergic reactions. Incidence of allergic reactions to food additives is extremely low but generally over-estimated by the patients.<sup>252</sup> In a large survey done on British population, the authors evaluated more than 15000 patients and reported the prevalence of adverse reactions as 0.01% to 0.23%. The prevalence of allergic reactions to foods (2% to 8% in pediatric population) was higher as compared with the prevalence rate of reactions to additives.<sup>253</sup> The sulphating agents are the most common additives associated with asthmatic reactions. Reactions to sulphites have been reported primarily in patients with underlying asthma.254

**Percept food allergy.** Food-induced asthma is rare, the proportion of patients who perceive that food affects their asthma is relatively high. Kumar et al<sup>255</sup> in their study on 1860 patients, showed that 1097 (58.9%) had a history of food allergy. Of the history positive patients, SPT was done on 470, and it was found that 138 (29.3%) showed a marked positive reaction to the food extracts. Rice elicited positive SPT reaction in maximum number of cases 29 (6.2%) followed by black-gram 28 (5.9%), lentil 26 (5.5%), citrus fruits 25 (5.3%), pea 18 (3.8%), maize 18 (3.8%) and banana 17 (3.6%). The SPT positive patients showed elevated specific IgE levels (range: 0.8-79 IU/mL) against respective food allergens than normal controls (0.73 IU/mL, mean±SD). Food allergy was confirmed in 21 out of 45 (46.6%) of the patients by blinded controlled food challenges.<sup>256</sup> The prevalence of food allergy was estimated to be 4.5% (2.6% to 6.34%) at 95% CI in test population (n=470). Sensitization to food was significantly associated with asthmawhile aeroallergens were strongly related to rhinitis. Food allergy is estimated to be 4.5% in adolescents and adults with asthma, rhinitis or both. Rice, citrus fruits, black-gram and banana are identified as major allergens for inducing allergic symptoms.

In India, many asthma patients have perception of having food allergy, as reported by 90% through a case series.<sup>257</sup> As in many other studies, not one but several food items were perceived by the patients as allergens; 22 commonly consumed food items were identified in this study. Of these, 16 food items were significantly associated with demographic profile, family history, duration of asthma, and smoking. Reported food allergy was mostly atopic as confirmed by serum total IgE levels.257 Food challenge, diet elimination, and food-specific atopic serum markers remain to be elucidated by further study of these data, by conducting food-specific IgE to find out the specificity of food items as food allergens in asthmatic individuals, if this type of diet elimination can be done.

Asthma and food reactions. Patients having respiratory symptoms are more likely to have a fatal or near-fatal reaction after accidental ingestion of food to which they are allergic. The foods responsible for these serious reactions were peanut, tree nuts, egg, and cow milk.<sup>258</sup> Patients with asthma are at greater risk of severe and fatal food induced anaphylaxis compared with patients without history of asthma, allergic rhinitis, or atopic dermatitis.

In a US Physician Reported Registry, 31 of 32 patients with food-related fatalities had diagnosis of asthma. Similarly, in a study done in UK, where 8 out of 8 patients with fatal anaphylaxis had a history of asthma. Patients with asthma or patients who experience respiratory symptoms as part of a food reaction are at a greater risk for a life-threatening allergic reaction to foods.<sup>259</sup>

Legumes are important causative agents of type I hypersensitivity in south Asia and Europe, but such studies are lacking in Indian population. In a study done on 816 patients to investigate black-gram sensitization in asthma and rhinitis patients and to identify IgE-binding proteins, 35 gave history of black-gram hypersensitivity. From these, 16 were SPT positive and 14 had elevated specific IgE (three times of negative controls) to black-gram. Another double-blind, placebo-controlled food challenge established black-gram sensitivity in 4 of 14 patients. Blackgram induces IgE-mediated reactions in 1.7% of asthma and rhinitis patients and contains 8 major IgE-binding components, of which 6 retained IgE reactivity after roasting. Black-gram shares allergenicity with lentil and limabean.<sup>260</sup> Rice is a major food consumed worldwide and needs evaluation for IgE mediated reactions. A study identify rice allergy in patients with rhinitis and asthma identified the allergens in proteins in raw and cooked rice. Kumar et al<sup>261</sup> evaluated 1200 patients using a standard questionnaire and observed a history of rice allergy in 165 cases. Of these, 20 (12.1%) patients demonstrated marked positive SPT and 13 showed significantly raised specific IgE to rice compared to normal controls.

**Relationship of skin allergy with respiratory allergy.** The term atopy was first introduced in 1923. Atopy is defined as a personal or familial propensity to produce IgE antibodies and sensitization in response to environmental triggers.<sup>262</sup> It is used to describe asthma and allergic rhinitis. Ten years later, atopic dermatitis was added as part of the definition, giving rise to the atopic triad. Atopic diseases, including allergic rhinitis, atopic dermatitis and asthma have increased in frequency in recent decades and now affect approximately 20% of the population worldwide.<sup>226</sup>

**Atopic dermatitis.** The terms atopic dermatitis and eczema are considered interchangeable. Atopic dermatitis is a highly pruritic chronic inflammatory skin disease that may manifest predominantly during early infancy but may also present during childhood or adulthood.<sup>263</sup>

**Prevalence of atopic dermatitis.** In the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence of atopic dermatitis in children varies significantly from 0.3% to 20.5% among 56 countries, but there are consistent trends of increasing the disease prevalence over time.<sup>264,265</sup> A Polish study<sup>262</sup> determined the prevalence of atopic dermatitis in less than 6 months old infants to be 17.3% and an international study found a similar atopic dermatitis prevalence of 17.6% in children aged 1–2 years.<sup>266</sup> A US population-based study illustrates that atopic dermatitis starts early in the first few years of life. Of the affected children aged 3–11 years, 85% suffered from atopic dermatitis before

5 years of age, including 45% who developed the condition during the first 6 months of life and 60% during the first year of life.<sup>267</sup>

Progression of atopic dermatitis to allergic rhinitis and asthma. Atopic dermatitis is a major risk factor for the development of asthma, and children with atopic dermatitis have an increased odds ratio of developing asthma compared to children without atopic dermatitis in several studies.<sup>268-271</sup> Main risk factors for the progression and persistence of asthma are IgE sensitization and early onset and severity of atopic dermatitis. Patients with eczema with specific IgE antibodies to common environmental allergens (extrinsic atopic dermatitis) present by 2 to 4 years of age are at higher risk for progressing in the atopic dermatitis to allergic rhinitis and asthma than those with eczema without IgE sensitization (intrinsic atopic dermatitis).<sup>268</sup> von Kobyletzki et al<sup>269</sup> found that children with eczema have three-fold increased odds of developing the asthma and rhinitis at 5-year follow up compared to children without eczema.266 About one in every three children with eczema develops asthma during later childhood.

Influence of eczema in the development asthma. The Tasmanian Longitudinal of Health (TLH) study<sup>270</sup> investigated the influence of eczema on the development of asthma from childhood to adult life. They found that childhood eczema was significantly associated with newonset asthma in three separate life stages: preadolescence (hazard ratio 1.7), adolescence (2.1), and adult life (1.6) as well as over the life-span from the age of 8 to 44 years (1.7).<sup>270</sup> van der Hulst et al<sup>269</sup> examined 13 prospective extrinsic atopic dermatitis cohort studies and observed that the prevalence of asthma in atopic dermatitis cohorts at the age of six years to be about 30%. Kapoor et *al*<sup>271</sup> evaluated the prevalence of allergic rhinitis and asthma in 2270 children with physicianconfirmed atopic dermatitis and found that by three years of age, nearly 66% of the children reported to have allergic rhinitis, asthma, or both, and the presence of these diseases correlated with poor atopic dermatitis control.

### Summary

- 1. Atopic dermatitis is a prerequisite for the development of allergic rhinitis and asthma and specific sensitization.
- 2. Whether atopic dermatitis in the atopic march is necessary for the progression to other atopic disorders remains to be defined.

3. It is also important to identify infants at risk for developing lifelong chronic atopic diseases and utilize the critical window of opportunity early in life for the therapeutic intervention.

# Q12. What is the relevance of treatment history in the diagnosis of respiratory allergy? Medical history in respiratory allergic diseases

- The physician needs a thorough medical history to make an accurate diagnosis of respiratory allergy. Following points are needed to be enquired from the patients:
  - (a) Is there any family history of allergies or asthma?
  - (b) Is there personal history of any allergic conditions?
  - (c) Under what circumstances do these symptoms occur?
  - (d) If medications have been prescribed previously, what was the response to each of them?
  - (e) Were there any relevant complications at birth, such as respiratory distress?
  - (f) Does the patient have any other medical problems, such as gastrointestinal disorders, skin problems, joint problems, or infectious diseases?

# History of eczema and atopic dermatitis treatment

- Asthma is seen in nearly 35% to 40% of the patients with a treatment history of eczema and/or atopic dermatitis.<sup>269</sup>
- Nearly 33% to 38% of the patients with allergic rhinitis had a history of treatment for eczema or atopic dermatitis.<sup>271</sup>
- Treatment history of skin allergy in childhood is important for the diagnosis of respiratory allergy.

### Treatment history of food allergy

- Asthma and food allergy have been commonly shown to coexist with each other.
- Studies have shown that food sensitization early in life (within the first 2 years of life) approximately double the chance of developing asthma and rhinitis.<sup>238,239</sup>
- Rhodes *et al* in a study of 100 infants found that sensitization to egg and milk in the

first year of life was an independent risk factor for the development of asthma in adulthood.<sup>233</sup>

### **Treatment history of drug allergy**

- Drug hypersensitivity reactions are most common in patients over 50 years of age.
- Allergic reactions to drugs are predominantly observed among women.
- Anaphylactic reactions are most commonly observed after history of administration of aspirin, non-steroidal anti-inflammatory agents, intravenous contrast agents, muscle relaxants and beta-lactam antibiotics.
- Allergic reactions to medications usually resolve themselves after the discontinuation of the drug.

### Treatment history and asthma

- Beta-blockers, used to treat blood pressure, heart disease and migraine headaches, glaucoma (eye drop) can trigger asthma symptoms.<sup>272</sup> Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS), such as ibuprofen and naproxen, may trigger symptoms in some people with asthma. Between 8% to 20% of the adult asthmatics experience bronchospasm to these drugs.<sup>273</sup>
- Incidence of ACE inhibitors induced cough range from 5% to 10% of treated the patients.<sup>274</sup>
- Pre-natal antibiotic exposure is found to be associated with a dose-dependent increase in asthma risk.<sup>275</sup>
- Allergy to drugs is diagnosed based on medical history and a number of specific tests: skin tests, blood tests. In diagnosing the causes of anaphylaxis, the basophil activation test is used to exclude false negative and false positive results of skin tests and specific IgE levels.<sup>276</sup>

### Summary

- 1. Asthma is seen in nearly 35% to 40% of the patients with a treatment history of eczema and/or atopic dermatitis.
- 2. History of skin allergy in childhood is important for the diagnosis of respiratory allergy.
- 3. History of treatment with aspirin, NSAIDS, ACEinhibitors, beta-blockers and antibiotics play a major role in some individuals for making the diagnosis of respiratory allergy.

# **History Taking and Examination: A Glance**

- Common respiratory allergic diseases are asthma, and allergic rhinitis. Both these diseases pose as a substantial burden on the QoL, social life, and economy. A significant proportion of patients have both asthma and allergic rhinitis, and the co-existence of both is associated with increased emergency room visits and health-care utilization.
- Symptoms of asthma are typically paroxysmal and include wheezing, cough, breathlessness, and chest tightness. Typical symptoms of allergic rhinitis are nasal obstruction, post-nasal drip, sneezing, rhinorrhoea (clear watery secretions) and itchy nose.
- On physical examination, an asthmatic can be completely normal. Wheezing is the most typical sign of asthma and it may be heard only on expiration. On the other hand, children with allergic rhinitis usually exhibit a plethora of signs and symptoms, such as, sneezing, rhinorrhoea, nasal blockage with associated mouth breathing, allergic salute, allergic nasal crease, facial grimacing, and nasal snorting.
- Respiratory allergic diseases have different risk factors, clinical presentation, impact on QoL and prognosis according to the age of presentation of the disease. Childhood-onset asthma has been demonstrated to have a stronger association with family history, better lung functions and higher chances of going into remission or resolving as compared to adult onset asthma. On the other hand, adult-onset asthma symptoms have more association with occupational exposures, obesity, and smoking.
- Family history of allergic disorders is a significant risk factor for the development of respiratory allergic diseases. Both childhood-onset as well as adult-onset asthma have strong association with the family history of asthma. Family history of allergies is also associated with an increased risk of allergic rhinitis.
- The growing prevalence of allergy and asthma in India is a cause of major concern as it is a vast country with varied geographical profile, climatic conditions, agriculture and food habits. Hence, there is a wide range of area-specific allergen predominance. The allergen which may be of importance in one region may lose its relevance in some other parts of the country. At present, more than 25% of the total population of India is sensitized with different forms of allergens and the major sources of allergens identified are the pollen grains, fungal spores, dust mites,

insects and food. Also, the dominance pattern of allergen varies according to rural and urban area of residence. Thus, the knowledge of area-wise allergen predominance helps in identification of allergens, subsequently followed by appropriate testing and treatment.

- Similarly, the atopic individuals are known to mount a response to the presence of allergens in his/her environment either indoor or outdoor. It can occur either in the form of allergic symptoms appearing *de novo* or an exacerbation of the underlying allergic condition, like rhinitis, asthma, atopic dermatitis, conjunctivitis, etc. The severity of respiratory reactions can vary from mild irritation to severe anaphylaxis reaction. In case of indoor allergen the typical history would include peremial (especially, in HDM and cockroaches), early morning and nocturnal symptom pattern with history of aggravation of symptoms while being indoors, while doing household work like dusting, blooming, opening old dusty books in home, libraries etc. Previous studies have demonstrated that the asthmatic subjects who are exposed in their homes to allergens (dust mite, cat, dog) to which they are sensitized have a more severe form of the disease, as measured on the basis of FEV<sub>1</sub>, PEFR, bronchial reactivity (PC20), SPT and FeNO. Hence, a broader knowledge of indoor and outdoor allergens with detailed history taking of allergic patients can help in selecting appropriate allergen for testing either by skin prick test or specific IgE against a particular allergen, which will in turn, help in allergen avoidance and designing allergen-specific immunotherapy.
- Like-wise, the knowledge of season-wise variation in respiratory allergy dates back to as as the fifth Century BC when Hippocrates first noted the seasonal variation in exacerbations of asthma, since then the seasonal patterns have been described for asthma mortality, hospital admissions and emergency department visits. These variations are ascribed to seasonal variations in the exposure to ambient allergens, respiratory infections and meteorological changes. The knowledge about season-wise variation in allergen pattern helps a physician in relating to a typical history of seasonal symptom pattern or season-wise variation in symptom pattern of an allergic patient, which in turn, helps in appropriate testing and further treatment.
- Also, the exposure to allergens at work-place has contributed significantly in enhancing the

problems of patients suffering from respiratory disorders as the quality of air is poor due to presence of large number of allergens. At present, about 200 agents have been implicated in causing occupational asthma in the work-place. Exposure-specific studies about occupational asthma have focused on substances, of high- and low-molecular weight. The exposure assessment, including work-place allergen determination, is a cornerstone in the identification of allergen type in a patient suspected to be suffering from occupation-related allergies because it helps in the establishing preventive measures which includes total allergen exposure avoidance or a reduction in the exposure (second best option) along with its treatment.

- The persistent or repetitive exposure to these allergens results in chronic allergic inflammation, which in turn, produces long-term changes in the structure of the affected organs and substantial abnormalities in their function. Also, many patients who initially have a single allergic disorder, such as atopic dermatitis, eventually develop others, such as allergic rhinitis and allergic asthma called as the allergic march or atopic march. This process may be driven in part by a vicious circle in which allergic inflammation diminishes the function of the epithelial barrier. This increases the immune system's exposure to the original allergens and additional allergens, and hence, existing allergen specific IgE contributes to sensitization to new allergens.
- Hence, a vicious cycle is set up and thus, the importance of elucidating the history of recurrence of symptoms after the exposure to a specific environmental condition underlies the fact that one or more allergen(s) predominate in a particular type of environment, and hence, its knowledge helps a physician in narrowing down the possibility of a particular type of allergen which is followed by appropriate testing and adequate treatment of a patient who is suspected to be suffering from repeated allergen exposure.
- Food allergy is defined as an adverse immunological reaction that occurs on exposure to a food that re-occurs on repeat exposures. Food allergies and asthma are increasing in children worldwide. Egg, milk, peanut, soy, fish, shellfish, and tree nuts are the most common food allergens. The most frequently observed clinical manifestations of IgE-mediated food allergies are cutaneous and gastrointestinal symptoms. Foods can also induce a wide spectrum of respiratory symptoms that can range from rhinorrhea to lifethreatening anaphylaxis with severe respiratory compromise. Other respiratory symptoms induced by food include sneezing, nasal congestion, throat swelling, coughing, shortness

of breath, and wheezing. These symptoms are significantly more likely to occur in patients with underlying asthma.

- Atopy is defined as a personal or familial propensity to produce IgE antibodies and sensitization in response to environmental triggers. It is used to describe asthma and allergic rhinitis. Ten years later, atopic dermatitis was added as part of the definition, giving rise to the atopic triad. Atopic dermatitis is a highly pruritic chronic inflammatory skin disease that may manifest predominantly during early infancy but may also present during childhood or adulthood. Atopic diseases, including allergic rhinitis, atopic dermatitis and asthma have increased in frequency in recent decades and now affect approximately 20% of the population worldwide. Atopic dermatitis is a prerequisite for the development of allergic rhinitis and asthma and specific sensitization. Whether atopic dermatitis in the atopic march is necessary for the progression to other atopic disorders remains to be defined. It also is important to identify infants at risk for developing life-long chronic atopic diseases and utilize the critical window of opportunity early in life for therapeutic intervention.
- Medical history in respiratory allergic diseases: the physician needs a thorough medical history to make an accurate diagnosis of respiratory allergy. Following questions are needed to be asked:
  - ✓ Is there any family history of allergies or asthma?
  - ✓ Is there personal history of any allergic conditions?
  - ✓ Under what circumstances do these symptoms occur?
  - ✓ If medications have been prescribed previously, what has been the response to each of them?
  - ✓ Were there any relevant complications at birth, such as respiratory distress?
  - ✓ Does the patient have any other medical problems, such as gastrointestinal disorders, skin problems, joint problems, or infectious diseases?
- Asthma is seen in nearly 35% to 40% of patients with treatment history of eczema and/or atopic dermatitis. Hence, history of skin allergy in childhood is important for the diagnosis of respiratory allergy.
- History of treatment with aspirin, NSAIDS, ACE inhibitors, beta-blockers and antibiotics play major role in some individuals for making the diagnosis of respiratory allergy.
# **B:** Allergens in Respiratory Allergy

# Q1. What are the source/location, risk factors and clinical significance of pollens in causation of respiratory allergy? Discuss pollen allergens in different geographical locations in India.

Air carries a number of particles with varied characteristics. These particles pose a burden on the human respiratory tract.<sup>277–282</sup> Pollen grains constitute one of these particles and are amongst the important known allergens.<sup>280</sup> Pollen grains are produced by a variety of plants, but only some cause allergic diseases. Allergenic pollens are divided into grasses, weeds or trees pollen, as these observe a generalized seasonal flowering pattern.<sup>281,282</sup>

Plants are classified according to their pollination process into anemophilous, entomophilous or amphiphilous.<sup>282,283</sup> Entomophilous flowers are rarely known to cause allergic diseases as these produce sticky and heavy pollen grains in small amounts transported by the insects.<sup>283</sup> However, anemophilons pollen grains are light weight, small and produced in large amounts and are transmitted by the wind. Thus, these are related with allergic diseases, as these characteristics enable these pollen grains to travel distances in the air.<sup>284</sup> Amphiphilous flowers are pollinated both by wind and insects and are also important allergens.

Pollen allergens are known to cause respiratory allergy symptoms in hypersensitive and sensitized individuals.<sup>285</sup> These cause allergic diseases called pollinosis consisting of allergic rhinitis, asthma, allergic conjunctivitis and atopic dermatitis.<sup>285–289</sup> Size of the pollen grains play an important role in inducing allergic symptoms.<sup>283,290,291</sup>

**Risk factors for pollen allergy.** Symptom development differs from person to person and is influenced by various host and environmental factors even with similar exposures (Table 4).<sup>292–295</sup>

**Factors influencing hyperreactivity and pollen threshold.** It is a well-known fact that the same amount of pollen does not cause the same intensity of complaints among individual patients with hay-fever. Different factors or exposures have been implicated in temporary changes in nasal and airway reactivity. Bronchial hyper-reactivity (BHR) may be variable over time because of several reasons.<sup>291</sup>

	Host Factors
Atopy <sup>296</sup>	Atopic individuals are prone to increased BHR
Gender <sup>296</sup>	Boys among children and females among adults have more occurrence of BHR
Lung function <sup>296</sup>	Lower FEV <sub>1</sub> and ratio of FEV <sub>1</sub> /FVC have been shown to be associated with increased occurrence of BHR
Ethinicity <sup>297,298</sup>	Pollen threshold levels for symptoms are differential according to ethnicity
Smoking <sup>299</sup>	Smoking is associated with increased BHR and respiratory infections
Respiratory infection <sup>300-302</sup>	Respiratory tract is infiltrated with inflammatory cells, post infectious state is associated with increased BHR
	Environmental Factors
Seasonal factors <sup>198,305,306</sup>	There is fluctuation in pollen concentration during season
Meteriological factors <sup>303,304</sup>	Environmental temperature, wind speed, thunderstorms have been known to influence pollen allergy
Year-to-year variability <sup>307</sup>	There is difference in amount of pollen from same tree in different years
Regional variability <sup>307</sup>	Regional variability in allergen release is observed from same pollen source
Air pollution <sup>308,309</sup>	Increased environmental temperature and increased environmental CO <sub>2</sub> influences. The pollination process, affecting the pollen threshold
Rural and urban <sup>310</sup>	Difference in biodiversity and exotic plants plays a role
Diurnal variation <sup>311–313</sup>	Allergen release is variable over the day

**Pollen of allergenic significance in India.** India is a country with varied geo-climatic conditions, thus regional pollen distribution is of utmost importance.<sup>311-313</sup> Different eco-geographical regions in India support different allergenic pollen flora and many taxa need to be investigated for their allergenic properties in the local population. It is, therefore, important for the clinicians to select only those pollen antigens which are prevalent in the area where the patient is residing.<sup>312,313</sup>

#### Table 4. Risk factors for pollen allergy

**Prevalence of pollen at various places of India.** Prevalence of various pollens in the four regions

(i.e., North-West, South, East and Central) of India is presented in table 5.

# Table 5. Pollen prevalence at various places of India

Pollen	Local Name	Pollen Type	Season	North - West	South	East	Central
Acanthaceae <sup>314</sup> Adhatoda vasica <sup>315-317</sup>	Malabar nut, Arulsa	Weed		✓			✓
Amaranthaceae Amaranthus spinosus <sup>314–333</sup> Chenopodium album <sup>314–316,322,323,327,331, 334–344</sup> Suaeda fruticosa <sup>315,317</sup>	Shrubby Seablight	Weed	September- October	√ √ √	√ √	✓ ✓	✓ ✓ ✓
Anacardiaceae Mangifera indica <sup>338,344,345</sup>	Mango Tree	Tree	February- March				✓
Aracaceae Borassus flabellifer <sup>318,345–348</sup> Cocos nucifera <sup>173,314,315,318,336,337,344,345,347,349–351</sup> Pheonix sylvestris <sup>173,337,345,347</sup>	Toddy palm Coconut Indian date	Tree Tree Tree	February- March	√	✓ ✓	✓ ✓ ✓	~
Asteraceae Ageratum conyzoides <sup>314,315,317,330, 331,352-355</sup> Parthenium <sup>173,314,315,317,322,323,327,329,330,332,337,</sup> 342-344,345,351,356-359	Goat, Weed Carrot grass	Weed Weed	All the year	✓ ✓	✓ ✓	✓ ✓	√ √
Xanthium strumarium <sup>314–318,324,327,331,332,338,</sup> 343,346–348,360–362	Prickly burweed	Weed	March- April	✓	✓		✓
Bignoniaceae Dolichandron Platycalyx <sup>360,363</sup>	Markhamia, Siala tree	Tree	August- October	~	✓		
Boraginaceae Ehretia laevis <sup>315,355</sup>		Tree	March- April	~			~
<b>Brassicaceae</b> <i>Brassica campestris</i> <sup>315–318,327,330, 353,360,364–366 <i>Brassica nigra</i><sup>315–318,360,364–366</sup></sup>	Pivili Rai, Sarso (mustard) Black mustard		September- January	✓ ✓	√ √		✓ ✓
Cannabaceae Cannabis sativa <sup>315,316,322,327,331,353, 355,356, 364,367</sup>	Charas, Ganja, Bhaang, Marijuana	Weed	February- April	~			~
Caricaceae Carica papaya <sup>327,337,338,345,347</sup>	Рарауа	Shrub	September- October	~	✓	~	~
Cleomaceae Cleome gynandra <sup>315–317,332,355,333,363</sup>		Weed	August- October	✓	✓	✓	✓
Convolvulacea Ipomoea distichim <sup>173,315,353,360,363</sup>	Sadabahar	Weed	All the year	~		~	
Cycadaceae Cycas circinalis <sup>368</sup>	Sago palm	Tree				✓	
<b>Cyperaceae</b> <i>Cyperus rotundus</i> <sup>314–319,322,337,339, 341,344,346,347,355, 358,360</sup>	Nut grass	Grass	All the year	✓		√	~

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# Cont...

Pollen	Local Name	Pollen Type	Season	North - West	South	East	Central
Euphorbiaceae <sup>330,347,360</sup> Trewia nudiflora <sup>173,333,353,3</sup> 64,369           Ricinus communis <sup>173,315–318,322,326–340,343, 344,346,34</sup> 7,352,353,356,361,366,364,366,370	Castor bean Red lotus	Weed	September- October	√ √	√	√ √	√ √
Mallotus philippensis <sup>326,353,3</sup> 64,369 Putranjiva <sup>315,317,321,322,326,357,378</sup>				√ √	✓		✓
Fabaceae Acacia Arabica <sup>173,317,318,330,347</sup> Acacia catechu <sup>317,342,360,371,372</sup>	Babul Kher	Tree Tree	March, September-	✓ ✓	√ √	✓ ✓	✓ ✓
Bauhinia variegate <sup>173,316,323,330</sup>	Kachnar	Tree	October	✓			~
<b>Cassia siamea</b> <sup>315,316,318,327,330,347,354,366,373 <b>Cassia occidentalis</b><sup>315,316,318,326,330, 332,347,352- 355,360,373</sup></sup>	Cassod Kasunda, Bari Kasondi, Kasaunda	Tree Weed		✓ ✓	✓ ✓	✓ ✓	~
Peltophorum <sup>318,322,344–346,361,371, 373,374</sup> Prosopis juliflora <sup>318,319,321,326-328, 330,351,356,360,362</sup> ,363,367,375,376	Copperpod Ganda-babool	Tree Tree			✓ ✓	✓	✓ ✓
Crotalaria juncea <sup>363,373</sup>	Brown hemp, keekar Madras hemp	Tree		✓		✓	
Lamiaceae Cassia fistulosa <sup>91,363</sup>	Wild Bergamo	Tree	April-May			~	
Lythraceae Lawsonia inermis <sup>316,317,332,345</sup>	Henna tree	Tree	October- December	×	~		✓
<b>Meliaceae</b> <i>Azadirachta indica</i> <sup>314–318,325,330,332,337,338,344,347, 353,357,360,364,371,373</sup>	Neem	Tree	February- April	✓	~	✓	✓
<b>Moraceae</b> <i>Morusalba</i> <sup>315,317,322,326,330, 332,346,347, 353,356,360,362,364</sup>	Shahtoot (mulberry)	Tree	February	✓	✓		~
Myrtaceae Eucalyptus spp <sup>315,316,318,321,322,326,329,</sup> 331,335,337,342,345-349,362,366,367,374	Eucalyptus, Safeda	Tree	September- October	✓	~	✓	✓
Pinaceae Cedrus deodara <sup>322,326,353,364,373,377</sup>	Deodar	Tree	November- January	✓	~	✓	✓
Poaceae Cenchrus ciliaris <sup>316,317,332, 353,355,362</sup>	Buffel grass	Grass	September-	✓	✓		~
<i>Cynodon dactylon</i> <sup>315,325,327, 329,330,353,378–382</sup>	Bermuda grass	Grass	October February- March	✓	~		~
Paspalum distichium <sup>353</sup>	Crown grass Bahia	Grass Grass	April March - April	✓			
Imperata cylindrica <sup>362,373,378,379</sup>	Satintails	Grass	February- March	~	~		
<b>Poa annua</b> 314,318,319,322,323,325, 326,337,341,345,347, 353–356, 364–368,370,371,379,380,383	Meadow grass	Grass	April	✓			

#### Cont...

Pollen	Local Name	Pollen Type	Season	North - West	South	East	Central
<b>Pennisetum typhoides</b> 314,315,331,362,37, 8,379,384	Foxtail/Fountain grass	Grass	February- March	~			~
Sorghum vulgare 314,315,317,327,332,3, 48,362,378,384	Jowar		April			✓	
Zeamays <sup>315-317,332,344,348,361</sup>	Corn		September- November	<b>V</b>	✓		~
<b>Polygonaceae</b> <i>Rumex acetosa</i> <sup>315–317,332,369,373</sup> <i>Rumex dentatus</i> <sup>316,321,322,326,357</sup>	Red sorrel, Sour weed	Weed Weed	March- November	✓ ✓	~		✓
Salicaceae Populus deltoids <sup>321,373</sup>	Poplar	Tree	June- August	✓			
<b>Simaroubaceae</b> <i>Ailanthus excelsa</i> <sup>314–316, 353, 357, 362, 373, 380</sup>	Tree of heaven	Tree	January- February	✓			
Solanaceae Solanum xanthocarpum <sup>363,373</sup>		Weed	Annual			✓	
Typhaceae Typha domingensis Tunha angustata <sup>315-318,327,363</sup>	Cumbungi	Weed	Annual	✓	✓		~
Ulmaceae Holoptelea integrifolia <sup>314,315,317, 322-325,</sup> 328,334,339,340,344,346,356, 357,373,379,381, 382,385-387		Tree	February- April	~	√		~

✓ Symbol means prevalence shown only by pollen demonstration in air.

✓ Symbol means prevalence shown as per SPT and aerobiological demonstration.

### Summary

- 1. Allergic rhinitis and asthma are most common pollen associated allergic respiratory diseases.
- 2. Pollen sensitization varies across different parts in India because of varied geo-climatic conditions.
- 3. We recommend that asthma and allergic rhinitis patients in India should be tested for pollen sensitization as per relevant pollen distribution in various areas. (1A)

# Q2. Why is pollen calendar important in respiratory allergic diseases? Is there any standardized pollen calendar for India with reference to various geographic/climatic conditions?

Pollen calendars, defined as graphs narrating the annual dynamics of major airborne pollen types in a given location. These provide readily accessible visual information on the various airborne pollen types occurring in the course of the year.<sup>388</sup> Pollen calendars are commonly used to depict seasonal distribution of pollens in the atmosphere and most of the calendars are produced using Spieksma's model in which daily pollen counts of 10-day periods in a particular season are summed up, averaged over the years and depicted as pictorial calendar of that local area.<sup>389-400</sup>

Pollen calender monitoring. Allergenic content of the atmosphere varies among countries but even in the same country, according to climate (temperature, geography, winds, rains, and humidity), vegetation, and cultural factors.401 The unique aerobiological conditions of an area clearly affect the clinical manifestations of respiratory allergy that may increase the social and economic burden of allergic diseases.<sup>401-404</sup> Pollen concentrations vary within the same country in different ecogeographical and eco-geo-climatic zones.402-404 Although some pollen grains can travel hundreds to thousands of kilometers in the atmosphere. Local pollen emissions are the principal driver of pollen concentrations in a given area. Pollen calendars are, thus, location specific, with pollen concentrations closely linked to the local distribution of flora, meteorology, and climate.<sup>405-408</sup> Thus, pollen monitoring is very important for the management of respiratory allergy.<sup>391</sup>

# Pollen calendars can be useful in many ways

*For clinical warning.* Important preventive measures for sensitized patients is to provide information on the occurrence of different pollen types in order to diminish exposure to pollen allergens when levels are above clinical thresholds in their local regions.<sup>304,409-413</sup>

*To document seasonal characteristics.* Pollen calendars provide readily accessible visual information on the various airborne pollen types occurring in the course of the year, about the pollen content in the air and pollen season characteristics of that area which can be used for future references.<sup>414</sup>

*Prevention of allergy symptoms.* Pollen calendars can be used in allergy clinical facilities for symptoms correlation and subsequent selection of the allergens panel for the diagnosis, also an important preventive tool for sensitized patients in the sense of diminishing exposure to aeroallergens and/or treatment adjustments when levels are above clinical thresholds.<sup>285,409,410,412-417</sup>

*To predict pollen timing.* The emission of allergenic pollen from its source is directly linked to seasonality of the flowering phenophase, which makes pollen calendars the simplest observation-oriented approach for predicting the time of occurrence of airborne pollen in a given area.<sup>418,419</sup>

*To guide officials.* Pollen calendars can also help public health officials to assess exposure, develop early warning systems, improve guidance to limit the exposure, and promote therapy in advance of high pollen loads.<sup>25,286,401,418-429</sup>

*To tour guides.* Local pollen calendar of an area helps in planning tours and administration, as high pollen threshold time or place can be avoided by particular pollen sensitized people.<sup>330,335</sup>

*To guide forensic investigators.* Pollen calendar gives information about the different pollen grains trapped by the corpses, depending on the season which helps in identifying the season or place in which the death happened.<sup>304,409–413,417,430–434</sup>

Pollen calenders have their own limitations as well. Commonly used Spieksma's model overcomes season-specific short-term shifts in pollen occurrence, but hides day-to-day variability in the pollen concentrations and so has limited potential for the management of allergic diseases.400-410 Also, as pollens can travel over a long distance by wind, some pollens may not represent the local pollen calendar.<sup>389,394,410,411,435</sup> Moreover, pollen calendar represents the previous year air pollen dynamics, it may not include the new pollens those entered in the local region in the current time, and hence, cannot be used for diagnosing new pollen allergy.<sup>389,427,428</sup> Finally, the country with varied geo-graphic and geo-climatic areas may have multiple pollen calendars for that local area. 389,399,402,403,405,422,436

In India various studies tried to establish the dominant pollens and their predominant seasons at various periods of time.

From Eastern India. Gauhati and its semi-urban areas had Poaceae, Cheno-Amaranth, Asteraceae, Putranjiva, Mangifera and Eucalyptus were the dominant types of pollens.354,437-442 Eastern Himalayan areas like Darjeeling, Kurseong, Agartala, Bodhgaya, Kalimpong had Acer, Alnus nepalensis, Betula, Bucklandiapopulnea, Eucalyptus and Pinus.443-447 In Berhampore, a total of 31 pollen types were identified in which 18 were highly allergenic, including Acacia auriculiformis, Areca catechu, Azadirachta indica, Barringtonia racemosa, Bombax ceiba, Borassus flabellifer, Carica papaya, Cassia sp., Casuarina equisetifolia, Cheno-Amaranthaceae, Cocos nucifera, Croton bonplandianum, Cyperaceae, Dillenia indica, Eucalyptus sp.448 Greater Kolkata had higher frequency of grass pollen in the air whereas Central Kolkata where Trema orientalis was the dominant pollen type, followed by grasses. Pollens of Acacia auriculiformis, Eucalyptus sp., Borassus flabellifer, Cassia sp., Azadirachta indica, etc were also found in moderate concentration in most places of West Bengal.449 In the Salt Lake City, Kolkata, Areca catechu, Borassus flabellifer and Phoenix sylvestris were recorded frequently.450 In various studies from Kolkata, the most abundant pollen grains were Trema orientalis, followed by Poaceae, Casurina equisetifolia, Cocos nucifera, Azadirachta indica, Carica papaya and Cyperaceae.<sup>337,338,345,347,451–458</sup> One study from Kolkata reported that allergenically significant

pollen types were *Lantana, Cucurbita maxima, Cassia fistula, Cocos nucifera* and *Calophyllum inophyllum*.<sup>459</sup> A survey in West Bengal revealed, 59 types of pollen in the air and their maximum concentration was recorded in May. *Trema oriental* spollen were in high concentration from May to July. Pollen types of family Asteraceae and Chenopodiaceae were maximum in June and other important pollen types were Asteraceae, *Pongamia, Areca catechue, Xanthium, Cocos*.<sup>369</sup>

From Western India. Pune, Jalgaon, Nagpur, Mumbai showed 31 pollen types. It is reported that grass pollen as the most dominant pollen types contributing 33.3% of total pollen load followed by tree and weeds.314,460-463 In Aurangabad with high frequency of grass pollen followed by Azadirechta indica, Parthenium and Moringa, one study showed where Parthenium contributed 12.5% followed by grass pollen.<sup>464</sup> Bikaner showed a total of 35 pollen types from the atmosphere and among them *Poaceae* (26.7%) is more common, followed by Amaranth-Chenopod (11.50%) and Cyperaceae (10.30%).<sup>465</sup> A survey at Pune revealed Parthenium to be the highest contributor to the pollen load with two peak seasons, *i.e.*, from September to November and January to April. Cocos and Cassia were observed throughout the year. Cocos pollen were recorded in high concentration in April to May and November to December.466,467 At Aurangabad, Datura alba was prevalent in the air from August to October with an annual concentration of 8.2%. Cleome contributed 6.8% pollen from June to August. Other important contributors were Alternanthera, Typha, Bougainvellia, etc.<sup>468,469</sup>

From Northern India. In Allahabad, 80 types of pollens were identified, Holoptelea integrifolia being the most common followed by Azadirachta indica, Ailanthus excelsa, Putranjiva roxburghii, Madhuca longifolia, Syzygium cumini, Aegle marmelos.<sup>341</sup> Meerut and Gorakhpur were mostly dominated by the grasses.<sup>363,470</sup> In Delhi, a total number of 112 different pollens were documented and Poaceae, Brassica, Prosopis, Artemisia, Xanthium, Morus, Eucalyptus, Parthenium and others were dominant pollen taxa in the air.<sup>369,471</sup> Dehradun Pinus followed by showed Broussonetia, Rosaceae, Poaceae, Debregeasia, Rumex and Morus as dominant pollens.472 In Srinagar and Uttarakhand, Platanus orientalis, Narcissus, Salix were the major airborne pollens.<sup>357,473,474</sup> In Punjab, Meliaceae, Xanthorrhoeaceae, Amaranthaceae, Brassicaceae, Cannabinaceae, Chenopodiaceae, Myrtaceae, Moraceae, Poaceae and Asteraceae were the common pollens.<sup>357,475</sup>

From Central India. Bhopal, the dominant pollen types were Poaceae, Holopielea, Chenopodium, Amaranthaceae, Cyperaceae, Tamarindus, Xanthium, Eucalyptus, Ailanthus.<sup>476</sup> At Gwalior, prevalence of Poaceae, Artemisia, Apocynaceae, Rosa, Cicer, Ricinus and Carica papaya and others were observed.339 Jabalpur had prevalence of Holoptelea, Parthenium, Ailanthus, Amaranthus as common pollens.477 From Central India surveys, carried out at Bombay, Gwalior, Nagpur, Bhopal and Kolhapur, Poaceae, Asteraceae, Apocynaceae families, Rosa, Cicer, Ricinus, Ailanthus, Holoptelea, Cheno/Amaranth and Cyperus were observed to be the dominant pollen.331,478

From Southern India. At various places, such as Visakhapatnam, Bangalore, Trivandrum, Kodaikanal and Chennai, Casuarina, Parthenium, Spathodia, Cheno/Amaranth, Cocos and Eucalyptus were found to be the dominant pollens.479 At Visakhapatnam, 24 pollen types were recorded and Poaceae, Peltophorum, Cocos, Casuarina, Cyperaceae, Eucalyptus were the dominant types.<sup>479,113</sup> A survey at Trivandrum revealed 15 pollen types and dominant were Poaceae, Cheno/ Amaranth, Aporosa, etc.<sup>480</sup> At Chennai, pollen from Poaceae were the most abundant type and contributed 19.4% to the total pollen load from June to August. Pollen of Acalypha was recorded in the highest concentration in the month of August, followed by the pollen of Casuarina in the months of January and March.374 The airborne pollen of Poaceae, Prosopis, Casuarina, Typha and Palmae were important pollens at Tiruchirapalli.<sup>481,116</sup> At Trivandrum, Amaranthus, Cocos, grass, Cassia, Pinus, Anacardium, Ricinus, *Eucalyptus* and others were observed.<sup>336</sup> Bangalore reported the dominance of the pollen grains of Parthenium hysterophorus, Poaceae, Eucalyptus sp., Casuarina sp., etc.482 The major pollen types identified from the atmosphere of Bangalore were Parthenium hysterophorus, Casuarina equisetifolia, Cheno/ Amaranth, Cocos nucifera, Ricinus communis and grasses.<sup>483</sup> Gulbarga showed the prevalence of Poaceae, Cassia, Parthenium, Xanthhim.484

As various ecological and geo-climatic zones of India have a different pollen pattern which varies with season, there is no well-defined pollen calendar which can be followed throughout India.

# Summary

- 1. Pollen calendar is important in respiratory allergic diseases, for taking personal preventive measure and for diagnostic and therapeutic considerations.
- 2. Pollen calander also helps public health officials assess exposure, develop early warning systems.

# Q3. What is the importance of pollen count in respiratory allergic diseases?

Pollens are important aeroallergens which trigger symptoms in patients with allergic diseases, such as allergic rhinitis and asthma.<sup>364</sup> Pollen grains are deposited in the upper airways as a result of their large particle size. Experimental evidence suggests that rhinitis, but not asthma, is caused by the inhalation of whole pollen in amounts encountered naturally. Pollen debris are small enough to access the bronchial tree and result in causation of pollen asthma.<sup>485</sup>

Another study from Delhi observed that maximum pollen concentration was in the month of September and minimum in the month of December.<sup>486</sup> Another study conducted in Bangalore city reported maximum air-borne pollen concentration in the months of October and November.<sup>487</sup> Allahabad had highest pollen were in the month of March and lowest in the month of July.<sup>357</sup> Another study from Gwalior<sup>325</sup> showed maximum pollen concentration in the month of March followed by April and minimum in the month of July.

A study from Jaipur, demonstrated a significant positive correlation between number of monthly new asthmatics and allergic rhinitis patients reported at clinics with grass pollen count.<sup>325</sup> A study conducted in Kolkata showed that asthma-related health admissions (ARHA) were more than 40% of the annual ARHA during the months of March and September.<sup>488</sup>

The systematic review and meta-analysis done by Kitinoja *et al*<sup>489</sup> provided new evidence that short-term pollen exposure significantly increases the risk of allergic and asthmatic symptoms. This meta-analysis did not show any statistically significant relationship between the pollen exposure and the lung functions. The summary effect estimates for 10 grains/m<sup>3</sup> increase in the pollen exposure indicated a 2% decrease in peak expiratory flow (PEF) values, while no change was observed in relation to FEV<sub>1</sub> values.<sup>489</sup> Another study to look at the effects of birch pollinosis on allergic rhino-conjunctivitis concluded that for an increase of 10 grains/m<sup>3</sup> were associated with increased odds of nasal, ocular, and bronchial symptoms.<sup>490</sup>

A sharp rise in asthma-related health admissions during September has been reported from countries like Australia and Canada, known as the "September epidemic".491 It primarily affects school children. It has been suggested that they may carry the source (namely, rhinoviral inoculum) for asthma exacerbation.492 Studies from around the world observed an association between either aeroallergens or gaseous/particulate air pollutants and asthma exacerbation.493-495 Multiple studies worldwide have found that increase in ragweed pollen is associated with increased symptoms of allergic rhinitis and asthma496-498 along with an increase in the emergency department visits for ocular symptoms among children.499 Grass pollen500, Artemisia, Chenopodium and Humulus scandens<sup>501</sup> is also associated with an increase in symptoms of respiratory allergy.<sup>502</sup> Another study showed deterioration in the QoL in patients with allergic rhinitis and allergic rhinitis along with asthma.<sup>503</sup>

Some studies do not support the hypothesis that high exposure to pollen is a risk factor for developing hay-fever. High pollen exposure has no effect on the risk of acquiring allergic rhino-conjunctivitis, or it may even confer some protection against it. Studies from several countries showed that the prevalence of hayfever and asthma tends to be lower in rural than in urban areas, and lowest among the people living on farms who are presumably exposed to pollen more often and in higher concentrations than others.<sup>168,504,505</sup>

#### Summary

- 1. Increase in pollen count is associated with an increased risk of allergic and asthmatic symptoms.
- 2. A rise in asthma related admissions may be seen during peak pollen season.
- 3. *A rise in pollen count is associated with rise in allergic symptoms and emergency department visits. (2A)*

# Q4. What are the source/location, risk factors and clinical significance of house dust mite in causation of respiratory allergy?

Mites, small sac-like animals which are parasitic in nature are classified as HDM sand storage mites.<sup>506</sup> These are closely linked to humans and their food is human and animal dander.<sup>507</sup> Their shed skins and excreta are the allergenic proteins which cause symptoms.<sup>508,509</sup> Humans may be exposed to mite allergens either by direct contact inhalation or ingestion in a sensitized person.<sup>510</sup> Symptoms caused by mite sensitization are usually respiratory in nature (sneezing, itching, watery eyes, wheezing, etc).<sup>511</sup>

House dust mites constitute an important source of indoor allergens.<sup>510–512</sup> Approximately 1% to 2% of the general population worldwide has allergic sensitization towards HDMs which varies between 20% to 80%.<sup>513</sup> Various factors influence the allergic sensitization to HDMs, such as ethnicity, socio-economic conditions, geographical variations etc.514 HDMs include Dermatophagoiodes pteronyssinus (Dp)and Dermatophagoiodes farina (Df). Storage mites include Lepidoglyphus destructor (Ld), Blomia tropicalis (Bt), Tyrophagus putrescentiae (TP).<sup>515</sup> The dominant genus found in india were Dermatophagoides spp, followed by Blomia spp.<sup>516</sup> Sensitivity prevalence of HDMs varies from 11.5% to 88% in various cities in India.517-519

Humans may be exposed to mite allergens wither by direct contact, inhalation or ingestion.520 Symptoms caused by mite sensitisation are usually respiratory in nature.521 House dust mites has been shown to be associated with allergic asthma, rhinitis, rhino-conjunctivitis, kerato-conjuntivitis and otitis media, atopic eczema and papular urticaria, anaphylaxis, gastrointestinal allergy.522 One study showed allergic rhinitis (71.4%), asthma (59.2%), contact dermatitis (6.1%), conjunctivitis (2.0%) to be associated with HDM allergy.523 HDM allergens are very important risk factors for asthma.428,524-526 These are considered to be the major cause of asthma worldwide, ranged from the 5% to 30% in the general population<sup>524</sup> with approximately 50% of the patients with HDM-induced allergic rhinitis and allergic asthma as well.525 Table 6 shows risk factors for HDMs.

Before 2000, the HDM survey was conducted by sample collection from house dust from various parts of India. At that time the mostly identified species throughout india were *Dp*, *Df*, *Bt*, *TP*, *LD*, *Acarus siro*.<sup>516,534,550,561-568</sup>

In North India,<sup>315,329,382,534,563,564,569-572</sup> mainly Delhi, Uttar Pradesh, Chattisgarh and some parts of Jammu and Kashmir had *Dp*, *Df*, *Bt* as the predominant species. Some areas of Uttar Pradesh and Jammu and Kashmir showed *Bt* as a common HDM isolated. In Punjab *Df* followed by *Dp* were identified as common species.<sup>331</sup> Various studies from north India have shown HDM sensitization on SPT and IDT.<sup>315,329,382,572</sup> HDM sensitization was studied in Delhi and Allahabad during 2008–2011 and SPT was performed on a total of 918 patients for 58 types of aeroallergens and HDM sensitivity was found in 12.4% of

#### Table 6. Risk factors for house dust mites

Risk factors	
Dose <sup>331,524,526–533</sup>	Increased HDM exposure is associated with increased risk of allergic asthma
<b>Source</b> <sup>509,534</sup>	Bed mattress is the major habitat of HDM
Seasonal variation <sup>509,520,535–543</sup>	Pre-monsoon is associated with high HDM count, winter is associated with low HDM count
<b>Temperature</b> <sup>506,519,523,544–552</sup>	Increased temperature is associated with increased HDM concentration
Humidity <sup>544–546,553</sup>	At least 50% relative humidity is needed for HDM survival
High altitude <sup>551,552</sup>	Because of less relative humidity, less count of HDM is seen
House types <sup>520</sup>	Material used for making house and micro-climate inside the house determines the HDM species
Air pollution <sup>554,555</sup>	Air pollution increases HDM related airway reactivity
Helminths <sup>556,557</sup>	Increased helminth infestation is associated with decreased HDM related airway allergy symptoms
Protective allele <sup>555,558</sup>	Polymorphism of IL-4 gene may have decreased reactivity to HDM
Cross-reactivity <sup>559</sup>	Tropomyosin containing sea-food may have cross reactivity with HDM
Probiotics <sup>560</sup>	Probiotics have a significant effect of on rhinitis-related quality-of-life

patients.<sup>382</sup> Another 8-year retrospective study was carried out among 4835 patients from Delhi which revealed HDM sensitization in 12.0% patients.<sup>572</sup> Other aeroallergen sensitization study of childhood asthmatics done in Allahabad city showed 7.8% sensitivity to HDM allergens. One more study from Allahabad in which patients were tested with 60 different allergens found 60% to be SPT positive with *Df* extracts.<sup>329</sup> Aeroallergen sensitivity was studied in 1050 patients from Udaipur during 2002–2016, and 44.2% was reported to be *Df*-sensitive through IDT.<sup>315</sup>

In South India, 342,561,561,569,573-577 Dp, Df, Bt were the common species except some areas of Karnataka where Bt was common. Some studies have shown HDM sensitization from south India.<sup>342,576,577</sup> In 2011, a HDM sensitization study depicted 52.5% and 46.0% SPT reactivity for Dp and Df, respectively, performed on 139 bronchial asthma patients in the Bangalore region. Another Bangalore-based study involving 486 allergic rhinitis patients revealed HDM as the most common allergen, with positive results in 44.7% of cases.<sup>576</sup> From Andhra Pradesh, 73.7% HDM sensitivity was reported among 331 nasobronchial allergic patients.<sup>342</sup> In 2012–2013, a hospital-based study was done in Central Kerala consisting of 139 patients from five districts, namely Alappuzha, Idukki, Ernakulam, Kottayam and Thrissur; 23% HDM sensitivity was reported among asthma and allergic rhinitis patients.577

In Eastern India<sup>521,521,534,548,570,573,578–581</sup> Dp, Df, Bt were the common species. In Assam, Bt was the common house mite whereas in Meghalaya, Ld was idenfied as a common one. A number of studies have shown HDM sensitization from eastern India.521,548,579-582 In a study on 188 asthmatic patients about HDM sensitization from Kolkata, Saha et al<sup>579</sup> reported that 82% reacted to Dermatophagoides mites, 80% to Df, 46% to Dp, and 43% to both species of mites.<sup>579</sup> In 2010, a Kolkatabased study reported Dp (75.1%), Df (63.7%) and Bt (72%) sensitivity, and Bt was reported first time from Kolkata.580 A recent retrospective study from West Bengal reported a sensitivity of 80.3% and 84.9% for *Dp* and *Df*, respectively.<sup>581</sup> These three mites caused 33.0%, 25.2% and 18.8% sensitization in Kolkata population, respectively. The same population was also sensitized for *Dp*, Df and Bt with sensitization rate of 81.2%, 87.9% and 74.2%, respectively.<sup>582</sup>

Studies from central India showed HDM sensitization, with Dp and Df were the most dominant spices.355,562,583-588 However, common HDM species identified from Gujarat were Bt and TP. A Bhopal-based study reported 74.2% sensitization for Df among 89 patients with united airway disease 120 different allergen extracts.355 Study from Nagpur revealed 56.6% Dp sensitization among 143 patients of allergic rhinitis and bronchial asthma.588 Another multicentre study undertaken to evaluate the allergen patterns in patients with severe persistent allergic rhinitis from Central India showed 18% Df sensitivity.587 Study from Mumbai showed signifcant positivity to one or more dust mites in 53.2% patients.586

# Summary

- 1. Allergic rhinitis and asthma are most common HDM associated allergic respiratory diseases.
- 2. HDM sensitization on SPT in India varies from 11% to 88%.
- 3. The dominant genuses found in India are Dermatophagoides spp.
- 4. We recommend that patients with asthma and allergic rhinitis in India should be tested for HDM sensitization. (1A)

Q5. What are the source/location, risk factors and clinical significance of fungal allergens in causation of respiratory allergy? Discuss fungal allergen in different geographical locations in India.

Fungi are eukaryotic organisms completely relying on the external nutrients and living as saprophytes on other animals and plants. Over one lakh species of fungus have been reported but only few are known to cause disease in man and animals.589 Various fungal genera induce type I allergies in susceptible persons.<sup>590</sup> The filamentous fungi constitute a major part of common aeroallergens.<sup>591–593</sup> Fungi belong mainly to three phyla: Zygomycota, Ascomycota and Deuteromycota.594,595 Fungal spores constitute a major health risk. These are not only associated with IgE-mediated type I allergies but also are causative agent for other diseases.596,597 Moulds are found in all parts of India because of the favourable climatic conditions permitting their growth.<sup>217,598</sup> Fungi are found both indoors and outdoors and are prevalent in all geographical areas. Fungal allergy is estimated at 20% to 30% among atopic individuals and upto 6% in the general population.373,599,600 Fungal allergens are known to cause hypersensitivity

and are associated with conditions, such as bronchial asthma, allergic rhinitis, allergic bronchopulmonary mycoses, hypersensitivity pneumonitis, and atopic dermatitis.<sup>277,442,546,601-605</sup>

Microscopic fungi are universal and can colonize any organic substance. The main reservoir for microscopic fungi is soil and plant remains. As these are small in size, these disperse and reach much higher concentration in the air as compared to pollen.<sup>606</sup> Spore concentration in the air is variable and dependent on climatic factors, such as temperature, wind speed and relative humidity. Other factors affecting the growth of fungi include humidity, ventilation, the amount of biodegradable material, and the presence of pets, plants, and carpets, etc.<sup>607,608</sup>

The most common genera in India inducing allergy are *Aspergillus* spp, *Alternaria* spp, *Cladosporium* spp, *Penicillium* spp and *Epicoccum* spp.<sup>609,610</sup>

**Outdoor fungal allergens.** Singh *et al*<sup>363</sup> conducted a coordinated study in various cities of India to study the air born fungus and reported *Cladosporium* as the most dominant fungus.<sup>363</sup> Some workers have also demonstrated the geographical distribution of fungi in various parts of India (Table 7).<sup>386,440,445,457,468,599,605,611-616</sup>

Indoor fungal allergens. Fungi in the indoor environment have not been studied extensively. All India Coordinated Project on aeroallergens included poultry farms, libraries, bakeries and residential houses etc and found Aspergillus, Penicillium and Cladosporium fungi to be the most prevalent in the indoor environment.363 Aspergillius spp and Penicillium spp was the dominant fungal type found in bakeries.<sup>206</sup> Aspergillus spp were the predominant fungi from graneries and poultry.<sup>207,213</sup> Cladosporium spp were the commonest fungi in sugar industries.<sup>214</sup> Cladosporium, Penicillium, Paeciliomyces and Aspergillus spores were reported from library environment.<sup>618</sup> Aspergillus spp and Cladosporium spp were found to be dominant fungal types in cattle sheds.457 Cladosporium and Aspergillus spp were found to be predominant in the residential houses of allergy patients in Bangalore.<sup>620</sup> Study done in Agra showed that *Rizopus spp* followed by Fusarium spp were predominant in the residential houses.363 Studies have demonstrated fungal sensitization on SPT to various fungal species (Table 8).

#### Table 7. Fungal species in different part of India

Name of Fungus	ч	ч			ral
	Nort	Sout	East	West	Cent
Aspergillus spp <sup>319,386,599,601,605,611–614,617</sup>	✓	✓	✓	✓	✓
<i>Alternaria</i> spp <sup>2,386,457,599,601,605,611–613, 615,617</sup>	$\checkmark$	✓	$\checkmark$	$\checkmark$	~
Aureobasidium spp <sup>363</sup>			✓		
<i>Cladosporium</i> spp <sup>363,386,445,468,599,601,605, 612–615,618</sup>	$\checkmark$	✓	$\checkmark$	$\checkmark$	$\checkmark$
Curvularia spp <sup>369,445,468,599,601,605,615,619</sup>	✓	✓	✓	✓	✓
Candida spp <sup>363,601</sup>	✓				
Chaetomium spp <sup>612</sup>		✓			
Drechslera spp <sup>363,615,617</sup>	$\checkmark$		$\checkmark$	✓	
<i>Epicoccum</i> spp <sup>363,601,608,611,612</sup>	✓	✓			
<i>Fusarium</i> spp <sup>363,440,613,614,617,618</sup>	✓		✓		✓
<i>Ganoderma</i> spp <sup>445</sup>			✓		
Helminthosporium spp <sup>445,613,614,618</sup>	✓		✓		✓
<i>Mucor</i> spp <sup>445,457,487</sup>	✓		✓	✓	
Memnoniella spp <sup>617</sup>				✓	
Nigrospora spp <sup>363,599,615–617</sup>	✓	✓	✓	✓	
Neurospora spp <sup>363,612</sup>	✓	✓	✓		
Penicillium spp <sup>363,386,440,605,614,616,617</sup>	✓	✓	$\checkmark$	$\checkmark$	✓
Periconia spp <sup>363</sup>			✓	✓	
Pithomyces spp <sup>617</sup>				✓	
Rhizopus spp <sup>363,605,612</sup>	✓	✓	✓		
Stachybotrys spp <sup>617</sup>				✓	
Trichoderma spp <sup>605</sup>			$\checkmark$	$\checkmark$	
Ulocladium spp <sup>363,601</sup>	~				

#### Summary

- 1. Most common mold associated allergic respiratory diseases are allergic rhinitis and asthma.
- 2. Aspergillus, Penicillium and Cladosporium are the most common indoor fungal allergens.
- 3. The common fungal allergens to which sensitivity was elicited included Aspergillus fumigatus, A. flavus, A. niger, A. tamari, Altenaria, Rhizopus, Cladosporium, Curvularia, Fusarium, Helminthosporium, Mucor, Epicoccum and Trichoderma.
- 4. We recommend that patients with asthma and allergic rhinitis in India should be tested for fungal sensitization.(1A)

# Q 6. What are the source/location, risk factors and clinical significance of insect allergens in causation of respiratory allergy?

Insects are an important member of the phylum *Arthropoda* and are characterized by

 Table 8. SPT-based fungal allergen prevalence in different parts of India

Name of Fungus	th	th	دىد	st	itral
	Nor	Sou	Eas	Wes	Cen
Aspergillus fumigates <sup>315,329,332,348,359, 366,</sup> 378, 380, 382,520,572,576,577,605,615,621		~	~		~
Aspergillus flavus <sup>315,329,332,348,359,378, 380, 520,</sup> 576,577, 605,615,621	✓	~	~		~
Aspergillus niger <sup>315,329,348,359,366,378,520,576,</sup> 577,605,615	✓	~	~		~
Aspergillus japonicus <sup>615</sup>			$\checkmark$		
Aspergillus nidulans <sup>205,378,605</sup>	$\checkmark$		✓		
Aspergillus tamarii <sup>315,359,381,382,572</sup>	$\checkmark$	✓			$\checkmark$
Aspergillus versicolor <sup>315,329,359</sup>	$\checkmark$				✓
Aspergillus sydowii <sup>605,615</sup>					
Alternaria spp <sup>315,332,366,378,381,382,520,572,576,605,615</sup>	$\checkmark$	✓	✓		✓
Acrothecium spp <sup>315</sup>					
<i>Botrytis</i> spp <sup>315</sup>					✓
<i>Cladosporium</i> spp <sup>315,348,366,382,520,572,576,605,615</sup>	$\checkmark$	✓	✓		✓
<i>Curvularia</i> spp <sup>315,332,378,381,382,572,576,605,615,621</sup>	$\checkmark$	✓	✓		✓
Candida spp <sup>315,329,332,348,359,378,382,572,576</sup>	$\checkmark$	$\checkmark$			$\checkmark$
Drechslera spp <sup>615</sup>			✓		
Epicoccum spp <sup>382,572</sup>	$\checkmark$				
<i>Fusarium</i> spp <sup>315,332,366,378,615,621</sup>	$\checkmark$	✓	✓		✓
<i>Helminthosporium</i> spp <sup>315,332,366,382,572,576,621</sup>	$\checkmark$	✓			✓
<i>Mucor</i> spp <sup>205,315,332,382</sup>	$\checkmark$	✓			✓
Nigrospora spp <sup>315,332,615</sup>		$\checkmark$	$\checkmark$		✓
Neurospora spp <sup>378,621</sup>	$\checkmark$				
Penicillium spp <sup>205,315,366,576,605,615,621</sup>	$\checkmark$	✓	$\checkmark$		$\checkmark$
<i>Phoma</i> spp <sup>315,382,572,621</sup>	$\checkmark$				✓
<i>Rhizopus</i> spp <sup>315,332,348,378,382,572,615,621</sup>	$\checkmark$	~	~		✓
<i>Trichoderma</i> spp <sup>205,315,332,378,382,572,576,605</sup>	$\checkmark$	~	$\checkmark$		$\checkmark$

an exoskeleton, a body showing segmentation, bilateral symmetry and jointed appendages.<sup>622</sup> Insects are the largest group among animals and plants in the world and it is believed that insects make 75% to 80% of the total animal species on this planet.<sup>623</sup> Insects constitute two-thirds of the total fauna in India and comprise nearly 10 lakh species. Most of the studies have quoted 750,000 insect species.<sup>624</sup> Important orders in the family insecta include *Coleoptera, Hymenoptera, Diptera* and *Hemiptera*. Butterflies and moths comprise an important group.<sup>625</sup>

Insect allergy is a worldwide health problem. The variety and distribution of insects and the accumulation of debris associated with heavy infestations vary significantly with time and geographic location. Insect inhalant allergens are found indoors, outdoors, homes, and at the work place.626 Class Insecta includes cockroaches, moths, butterflies, bees, mayflies, caddisflies, flies, fleas, midges, ants, and vespids.<sup>627</sup> Insects can broadly be classified as stinging insects, biting insects and non-stinging and non-biting insects. All insect matter, like wings, scales, saliva, dried faecal matter, and venom can cause allergic diseases, such as rhinitis, conjunctivitis, asthma, urticaria and gastric disorders.622 Predominant sources of environment and cockroach allergens include cockroach saliva, fecal matter, spermatophore, shredded skin, and desiccated remains of the insect. Inhalation of these cockroach allergens can cause allergic responses in humans.628 Several studies in recent years have confirmed the association of cockroach exposure and increased asthma morbidity in inner city areas in the United States and also in other countries.647-650 Exposure to low levels of Blag 1 and Blag 2 allergens has been associated with wheezing among infants in the first three months of life and with increased proliferative T-cell responses.<sup>651</sup> Other reports have shown association of cockroach allergen exposure with persistent childhood wheezing652 and severe asthma.653 Table 9 shows the risk factors for insect allergy.

Studies conducted in Delhi have found that insects are most important allergen resulting in nasobronchial allergy. SPT prevalence ranged from 39% to 44%. Moth was the most prevalent, ranged from 30% to 33% of all insects. Mosquito prevalence was around 31%. Prevalence of cockroach varied between 19% to 25%. Prevalence of housefly varied between 26% to 29%. Prevalence of rice weevil varied between 12% to 16%.378,572 Studies conducted in Northern India (cities like Lucknow and Allahabad) concluded that insect prevalence on SPT ranged from 18.7% to 33.3%. Most prevalent insects include cockroach female (16.7% to 30%), cockroach male (14.6% to 31.4%), moth (15% to 35%), cricket (16.7% to 20.45%), locust female (33.3%), locust male (25%), grasshopper (19.3% to 20.2%), housefly (20%) and mosquito (20%).329,366,378,380

SPT reactivity from Western India states (like Gujarat and Rajasthan) concluded that SPT prevalence of insects was approximately 45%. Most prevalent insects among the group were

## Table 9. Risk factors for insect allergy

## Seasonal/Perennial<sup>627</sup>

Seasonal (*e.g.*, vast aquatic insect emergences, such as caddisflies, mayflies, and midges) perennial (*e.g.*, terrestrial pests, such as cockroaches)

## **Socio-ecnomic Groups**

Cockroach allergy is important for the development of asthma in inner cities among lower socio-economic groups<sup>629-631</sup>

### **Indoor and Outdoor Environment**

A study on cockroach allergen Bla g 1 in dust collected from children bedrooms reported that 85.3% had detectable levels and 50.2% had high levels.<sup>185</sup>

Cockroach-induced asthma occurs whenever substandard housing permits cockroach infestation. This includes rural and semi-rural areas, suburbs, and small towns and cities across the world.<sup>632</sup>

Municipal sewage systems and septic tank areas facilitates entry of cockroach into nearby homes through crawl spaces, construction joints, and attic vents  $^{\rm 627}$ 

### **Temperature and Humidity**

German cockroach (*Blattella germanica*) and American cockroach (*Periplaneta americana*) predominate in temperate and tropical areas. German cockroach is commonly found in cool and dry climates whereas the larger American cockroach prefers hot and humid conditions.<sup>633</sup>

### **Occupational Profile**

People whose professional activity is connected with insects, are usually sensitized to them.<sup>311,634-645</sup> Risk factors for common housefly (*Musca domestica*) occurs in closed breeding rooms, livestock stables, barns, pharmaceutical industry and workers.<sup>646</sup> Bee keepers are exposed to honeybees (*Apis mellifera*).<sup>635</sup> Risk factors for silkworm (*Bombyx mori*) includes occupational exposure among silk workers, clothing and bedding.<sup>636</sup>

moth (20.2% to 41.6%), yellow wasp (14.2% to 37.5%), housefly (38%), mosquito (33.2% to 36.2%), butterfly (20.8% to 31.2%), locust female (20.8% to 37.6%), locust male (12.5% to 37.6%), honeybee (29.1% to 35.0%), ant (12.5% to 28.4%), cockroach female (8.3% to 45.0%), cockroach male (44.2%), grasshopper (25% to 26.4%), hornet (16.4% to 25%) and cricket (8.3% to 22.2%).654,655 In another study conducted in central Rajasthan, SPT insect prevalence in rural and urban areas was 25.1% and 24.6%, respectively. Most prevalent insects in rural areas were cockroach female (46.6%), cockroach male (36.6%), honeybee (16.6%), housefly (36.6%) and mosquito (30%), while in urban areas these were cockroach female (40%), cockroach male (28.5%), honeybee (10%), housefly (27.1%), mosquito (30%).<sup>172</sup>

Studies conducted in Southern India (states like Kerala and Karnataka) concluded that SPT prevalence of insects varied between 6.6% to 64.5%. Rice weevil comprised 30.5% of all SPT positivity. Other insects were housefly (5.0% to 29.7%), ant (11.7% to 23.4%), grasshopper (5.8% to 30.5%), wasp (7.2), moth (5.8) and mosquito (10.1% to 22.3%). SPT prevalence of cockroach was 25% in most studies. In one study, female cockroach comprised 25.1% and male cockroach comprised 24%.<sup>343,348,656,657</sup>

In Central India, a study conducted with insect allergy showed SPT prevalence of insects as 10.6% with grasshopper being the most prevalent insect (3.4%).<sup>588</sup>

## Summary

- 1. Naso-bronchial allergy and asthma are the most common allergic respiratory diseases associated with the insects.
- 2. Prevalence of insect allergy is variable across India ranging from 6% to 64%.
- 3. Moth, cockroach, housefly and mosquito are most common among insect allergens in India.
- 4. We recommend that asthma and allergic rhinitis patients in India should be tested for insect sensitization.(1A)

Q7. What are the source/location, risk factors and clinical significance of other aeroallergens (animal/inhalant food allergens/occupational allergens) in causation of respiratory allergy?

> Humans are constantly exposed to animals and various studies have shown the allergenic potential of animal products. Various studies have been done on allergens of cat, horse, cow, pig, dog, rabbit, buffalo and other animals.<sup>329,359,378,654,658</sup> Allergic diseases caused by animals are not uncommon. Allergy to pets can result in significant morbidities and can manifest as asthma, urticaria, angioedema, contact dermatitis and anaphylaxis.<sup>659</sup>

> Animalproducts are one of the important groups of inhalant allergens.<sup>329,359,361,366,378,577,587,654,658,660-663</sup> The source of animal allergens can be domestic or stray animals, laboratory animals and animals in slaughter houses, dairy farms and stables are also important sources. Animal allergens are present indoor and outdoor environments.<sup>664–668</sup> Young age, positive family history of allergic disorders; associated allergic disorders are factors responsible for the increased sensitization to animal allergens.<sup>658</sup>

Prevalence of animal dander allergen was studied between 1996–2019 in different parts of India. A study was done in Delhi in 68 patients with bronchial asthma with or without allergic rhinitis and SPT showed dander allergen sensitivity among different allergens.<sup>658</sup>

Another study was done in Lucknow in 48 patients of nasobronchial allergy and SPT was performed for 60 types of aeroallergens. Dander allergen sensitivity was found in 3.1% of patients and the most common dander was cow dander (6.3%) and dog dander (6.3%).<sup>378</sup> A group of 60 patients with united airway disease from Allahabad was tested with 60 different allergens with SPT and 5% were found to be SPT positive with danders and among the dander group, the most common allergens were cat dander (8.3%), dog dander (6.7)%, cow dander (3.3%) and human dander (1.7%).<sup>329</sup> Another study for aeroallergen sensitivity studied patients of bronchial asthma and allergic rhinitis from Udaipur and 3.4% was found to be SPT positive with dander and the most common danders were cat dander (3%), cow dander (2.2%) and buffalo dander (1.5%).359 Aeroallergen sensitivity was studied in 1050 allergic rhinitis patients from Udaipur and it was found that 52% were positive for dander, 24% for chicken feather through intradermal allergy testing.<sup>654</sup> Another study done on 100 patients of naso-bronchial allergy, SPT positivity for dander was 6% and dog dander (8%) was the most common dander to which sensitivity was elicited and other was buffalo dander (4%). Bangalorebased study involving 486 allergic rhinitis patients revealed sensitivity to dander was 1.9% and the most common dander were dog dander (2.9%) and buffalo dander (1.4%).<sup>576</sup>

A hospital-based study done in Central Kerala from 2012–2013 consisting of 139 patients found that cat dander (22.3%) was the most common followed by cow dander (20.1%) and dog dander (19.4%).<sup>577</sup> Another study from Central Maharashtra in patients with bronchial asthma and allergic rhinitis showed a positive SPT of 29% to animal epithelia.<sup>661</sup>

**Inhalant food allergens.** Food hypersensitivity reactions typically include cutaneous, gastrointestinal, and respiratory symptoms, such as urticaria, atopic dermatitis, nausea, vomiting, diarrhea, coughing, and asthma.<sup>669</sup> Although the

vast majority of published reports have focused on specific allergic symptoms and clinical manifestations following the ingestion of food allergens, an increasing number of investigations have highlighted allergic reactions to foods that have occurred following inhalation. The source mainly is occupational exposure.<sup>670</sup>

# Common animal dander

Cat dander <sup>329,359,576,577,654,658,661</sup>
Cow dander <sup>329,359,378,577,654,658</sup>
Dog dander <sup>329,366,378,576,577,654,658,660,661</sup>
Buffalo dander <sup>359,366,378,654,661</sup>
Human dander <sup>329,654</sup>
Goat dander <sup>658</sup>
Horse dander <sup>378,654,658</sup>
Ox dander <sup>658</sup>
Pigeon epithelia <sup>662</sup>
Chicken feathers <sup>654</sup>
Pigeon feathers <sup>654</sup>

Exposure to food allergens through inhalation can also cause food hypersensitivity reactions. Various foods have been reported to cause such reactions.<sup>670–689</sup> Risk factors include the presence of atopy, the intensity of exposure, duration of exposure and cooking in the confined area.<sup>670,673</sup>

Allergic reactions upon incidental inhalation of fish odors or fumes resulting in clinical manifestation in the form of wheezing have been reported. Occupational asthma due to fish odor inhalation has also been reported.671,672 Seafood, like fish and snow crab are known to cause occupational asthma in seafood processing workers.673-675 Various seeds that have been reported to have allergenic potential after inhalation includes poppy seed, sunflower seeds and lupine seeds.676-679 Occupational exposure to airborne cereal grain dust and soyabean flour has been implicated in occupational asthma.680-683 Egg yolk and egg white proteins can also cause allergic sensitization following inhalation.670,684 Cow milk protein casein has been implicated in occupational asthma.<sup>670</sup> Other foods having allergenic potential after inhalation include carrot, asparagus, chickpea, peanut.670,687-689

**Inhalant occupational allergens.** Occupational exposures to substances in the work-place environment can cause inflammation and allergy.

Exposure to chemicals can cause exacerbation of respiratory diseases.<sup>690</sup> Approximately 9% to 25% of all adult onset asthma cases occour due to occupational exposures.<sup>691,692</sup> These diseases adversely affect human health.<sup>693,694</sup>

Occupational asthma and allergic rhinitis are common respiratory diseases in industrialized countries.695 Occupational allergic diseases can affect workers' productivity and QoL.696 Many occupations are at risk of allergic diseases which include health-care staff, kitchen workers, spray painters, bakers, worker of food processing industry, laboratory technicians, and hairdressers.<sup>203,697</sup> About 250 agents have been identified as causes of occupational allergic diseases.<sup>208</sup> Exposure through inhalation can cause allergic rhinitis, occupational asthma, and hypersensitivity pneumonitis. Various occupational allergens have been reported to cause such reactions. These include both proteins and chemicals, high molecular weight (HMW) and low molecular weight (LMW) compounds, and natural and synthetic products. Some of the most common occupational allergens are wheat and enzymes used in bakeries, latex, antimicrobials, and biocides used by healthcare workers, nickel and cobalt used by metal workers and persulphates used by hair-dressers. Protein allergens are usually HMW, while chemical allergens are LMW. HMW allergens are most commonly associated with IgE-responses.698

Fewer chemical allergens has been identified as causative agents of asthma.<sup>699</sup> Most important LMW allergen is toluene di-isocyanate, which is a potent allergen used in automobile industry and exposure can lead to a variety of diseases, including asthma, rhinitis, and atopic contact dermatitis.<sup>700</sup> Latex allergen, a HMW allergen causes latex allergy in 6% to 17% healthcare workers with rubber gloves lead to the development of urticaria, rhinitis, conjunctivitis, asthma, anaphylaxis, and atopic contact dermatitis.<sup>701</sup> Flour is also a HMW allergen that causes asthma, rhinitis, and atopic contact dermatitis after its exposure.702 Exposure to laboratory animals, such as mice and rats, can causes of occupational allergy to laboratory animals.<sup>703</sup> The source mainly is occupational exposure and occupational groups include health-care staff, kitchen workers, spray painters, bakers, food processing industry worker,

laboratory technicians, and hairdressers.<sup>203,697</sup> Risk factors include presence of atopy, route, duration and source of the exposure, predisposing skin injuries and genetics.698,704 Around thousands of LMW chemical allergens have been identified as causative agents of skin sensitisation, but only fewer chemical allergens have been identified as causative agents of asthma.699 Biocides (formaldehyde, glutaraldehyde, and orthophthaldehyde) commonly used to sterilize medical devices, medical gloves, hand sanitisers and soaps (chloroxylenol), have also been identified as common sources of allergens.705 Majority of allergies induced by HMW allergens are IgE-mediated, detection and quantification of specific IgE is used for the confirmation of allergy.706 Baker's asthma is common and wheat and rye flour proteins are common baker allergens.707 Spices are a particulate matter that is associated with various respiratory problems and the exposure was assessed by the prevalence of incidence rate of all occupations in the particulate matter from spice fields and spice processing units were found to be the nodal cause for the initiation of allergic symptoms.<sup>224,708,709</sup> Animal and vegetable HMW proteins present in aerosolized foods during food processing, additives, preservatives, antioxidants and food contaminants are the main inhalant allergen sources.<sup>212</sup> Exposure to laboratory animals, such as mice and rats can cause occupational allergy and is commonly seen in technicians, animal care-takers, physicians and scientists who work in pharmaceutical industries, university laboratories, and animal breeding facilities.703,710 Rodents, such as mice and rats, most commonly used in animal research and their urine is the main source of the allergenic protein in both mice and rats but allergens can also be found in dander, hair, saliva, and serum.711 Metals are considered to be one of the most common occupational allergens<sup>703</sup> and exposure to metals, such as gold, chromium, cobalt, platinum, nickel, palladium and mercury can cause wide range of allergic diseases, like atopic contact dermatitis, occupational asthma, and anaphylaxis.691,712 Study done by Zug et al<sup>712</sup> showed that following patch testing of 4,454 patients, nickel sulphate (19.0%), cobalt chloride (8.4%), and potassium dichromate (4.8%) were among the most common metal allergens, with nickel being identified as the most frequent positive allergen.

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### Summary

- 1. Dander allergen sensitivity is commonly seen due to cat, cow and dog dander.
- 2. Increasing evidence suggests that allergic reactions to foods can occur following inhalation.
- 3. Occupational allergens responsible for respiratory allergy mainly include biocides, latex, flour, animals and metals.
- 4. We recommend that the asthma and allergic rhinitis patients with relevant exposure history may be tested for dander and occupational allergen sensitization.(1A)

# Q8. How will you choose the allergens for screening of allergic diseases in adults and pediatric age group?

Allergy tests are used to determine whether a patient's symptoms are due to the allergenspecific IgE antibodies.<sup>713</sup> The most important diagnostic test is the clinical history.<sup>714</sup> A patient is unlikely to have allergies if he/she do not have symptoms after exposure to the suspected allergen. The history should focus on whether there is a relationship between exposure to allergens and development of symptoms. When obtaining a history, it is important to be familiar with the common types of aeroallergens including when and where these are likely to be present in the environment as well as specific situations that increases the likelihood of the exposure.715 Important points to be considered in history taking includes.716

- 1. *Seasonality*.<sup>715</sup> Seasonal allergens are pollens and outdoor molds whereas perennial are animal dander, cockroaches, dust mites and indoor molds.
- 2. Environment. Indoor environmental factors, such as presence of cockroaches, water damage, visible mold, dampness on the walls and passive smoking were independently associated with asthma in school children.717,718 Cockroach-produced allergens have been identified as a major cause of childhood asthma in the home environment.<sup>185,719</sup> HDM is another important allergen.381,720
- 3. *Pet or insect exposure.* The timing of the exposure to pets appears critical, with pre-natal or infancy exposure more consistently inversely associated and later exposure sometimes positively associated with allergic outcomes.<sup>721</sup> Numerous studies have reported that pre-natal or early life exposures to mammals, including pets and livestock, are inversely associated with pediatric allergy.

4. *Familial atopy*. Patients of asthma and/or rhinitis has a positive family history of atopy<sup>717,722-724</sup>

While taking patients's history, occupational history, history of travel and number of affected body organs should also be considered. Additional parameters to be considered while choosing allergen for paediatric patients includes the following.

- 1. *Mode of delivery.* Birth by cesarean section may increase the risk of allergic disease.<sup>721,725-729</sup> However, few studies do not support the above hypothesis.<sup>730-732</sup>
- 2. *Maternal smoking.* There was significant relationship between foetal exposure to tobacco smoke via maternal passive smoking and asthma and allergic rhinitis.<sup>717,733-736</sup>

House dust, HDM, relevant pollens (grass, tree or weeds), fungus (Alternaria, Aspergillus), insects (cockroach) and pet animals (dog, cat, buffalo) dander are the commonest aeroallergens prevalent in India, whereas milk, egg, peanut, soya, wheat, tree nut, fish and shell fish contribute to the majority of food allergens.373,737 In infancy, the main symptoms of possible allergic nature are atopic dermatitis, gastrointestinal symptoms, recurrent wheezing, whereas bronchial asthma and allergic rhinitis and conjunctivitis are the main problems later in the childhood. Adverse reactions to foods, mainly cow's milk protein and hen's egg are most common in the first years of life, whereas allergy to inhalant allergens mostly occurs later.738 A common standardized allergen battery is recommended for the clinical use and research across the Europe.739,740 In the United States, according to the third National Health and Nutrition Examination Surveys, 10 allergens were used for skin tests and the most common positive skin tests were dust mite (Dermatophagoides spp), perennial rye (Lolium perenne), short ragweed (Ambrosia eliator), German cockroach (Blatella germanica), Bermuda grass (Cynodondactylon), cat (Felix domesticus), Russian thistle (Salsola kati), white oak (Quercus alba), Alternaria alternata and peanut.741 If the history is consistent with allergy but unclear about the specific allergen, it is reasonable to screen for atopy using a small panel of common aeroallergens (for respiratory conditions) or foods (for atopic dermatitis). These panels should contain representative allergens that are present where the patient lives. Pollen mixtures can be used to screen for a variety of sensitivities. If a mixture is positive, then the individual components can be enumerated.715

Allergen sensitization patterns for children across India have been studied. In a study conducted in a tertiary care centre in Rajasthan including 60 children with respiratory allergic diseases between 5 and 15 years, overall highest percentage of SPT positivity was found among HDM (66.6%), storage mite (41.6%), wheat (33.3%), animal dander (30%), and Kentucky bluegrass (26.6%).722 Another study performed amongst 180 children (5-18 years) in a tertiary care centre in North India demonstrated that 100 children (55.6%) were sensitized to at least one aeroallergen, suggesting atopy.381 A crosssectional, observational study was conducted to study the type of allergic sensitivity in a pediatric population in Hyderabad and 67% of patients were found to be sensitive to aeroallergen but

33% had a negative SPT. Mites were the most common aeroallergen found in patients with allergic diseases in a study.<sup>742</sup> Another study conducted in Delhi concluded that cockroach (male–17.3%, female–14.6%) followed by HDM to be the common allergens in children less than 10 years of age.<sup>572</sup>

### Summary

- 1. Clinical history along with the knowledge about regional allergens combined with clinical correlation can help in formulating allergen panel for individual patient.
- 2. Additional factors like exposure to foods and school environment should be considered in clinical history while choosing allergen for pediatric age group.
- 3. Indian studies suggest HDM to be the common allergens in children.

# **Suggested Allergen Panels**

# Pan India Respiratory Allergen Panel

	Trees	Weeds
Pollen	Cocos nucifera Acacia arabica Acacia catechu Cassia siamea Azadirachta indica	Amaranthus spinosus Chenopodium album Parthenium Ricinus communis Cassia occidentalis
Fungi	Aspergillus fumigates Aspergillus flavus Aspergillus niger Alternaria spp Cladosporium spp Curvularia spp Fusarium spp Rhizopus spp Trichoderma spp	
Insects	Moth Cockroach Mosquito Housefly	
House Dust Mite	Dermatophagoides pteronyssinus Dermatophagoides farinae Blomia spp	
Dander (Relevant exposure history required)	Cat Dog Cow	
Feather	Pigeon Chicken	

# North-West India Respiratory Allergen Panel

	Trees	Weeds	Grasses	Others
Pollen	Ehretia laevis Cocos nucifera Dolichandrone platycalyx Acacia arabica Acacia catechu Bauhinia variegata C. siamea Prosopis juliflora Azadirachta indica Eucalyptus spp Populus deltoides Holoptelea integrifolia	Amaranthus Spinosus Chenopodium album Ageratum conyzoides Parthenium spp Cannabis sativa Gynandropis gyandra Ricinus communis Cassia occidentalis	Cyperus rotundus Cenchrus ciliaris Cynodon dactylon Paspalum Imperata cylindrica Poa annua	Ipomoea distichum Trewia nudiflora Brassica campestris Brassica nigra
Fungi	Aspergillus spp Alternaria spp Cladosporium spp Curvularia spp Drechslera spp Epicoccum spp Fusarium spp Ganoderma leucidium Helminthosporium spp Mucor spp Memnoniella spp Nigrospora spp Neurospora spp Penicillium spp Periconia spp Pithomyces spp Rhizopus spp Stachybotrys spp			

# Eastern India Respiratory Allergen Panel

	Trees	Weeds	Grasses	Others
Pollen	Borassus flabellifer Cocos nucifera Pheonix sylvestris Carica papaya Cycas circinalis Acacia arabica Acacia catechu Cassica siamea Peltophorum Cedrus deodara Azadirachta indica Eucalyptus spp	Amaranthus spinosus Chenopodium album Ageratum conyzoides Parthenium Ricinus communis Cassia occidentalis	Cyperus rotundus Cybnodon dactylon Imperata cylindrical Cenchrus ciliary Sorghum vulgarre Pennisetum typhoides	Ipomoea distichum
Fungi	Aspergillus spp Alternaria spp Aureobasidium spp Cladosporium spp Curvularia spp Drechslera spp Fusarium spp Ganoderma spp Helminthosporium spp Mucor spp Nigrospora spp Neurospora spp Penicillium spp Periconia spp Rhizopus spp Trichoderma spp			

# Southern India Respiratory Allergen Panel

	Trees	Weeds	Grasses
Pollen	Borassus flabellifer Cocos nucifera Acacia arabica Acacia catechu Cassica siamea Peltophorum Prosopis juliflora Cedrus deodara Azadirachta indica Eucalyptus spp Holoptelea integrifolia	Amaranthus spinosus Chenopodium album Ageratum conyzoides Parthenium spp Ricinus communis Cassia occidentalis	
Fungi	Aspergillus spp Alternaria spp Cladosporium spp Curvularia spp Chaetomium spp Epicoccum spp Nigrospora spp Neurospora spp Penicillium spp Rhizopus spp		

# Central India Respiratory Allergen Panel

	Trees	Weeds	Grasses	Others
Pollen	Cocos nucifera Acacia arabica Acacia catechu Cassica siamea Prosopis juliflora Cedrus deodara Azadirachta indica Cenchrus ciliaris Holoptelea integrifolia	Amaranthus spinosus Chenopodium album Parthenium Cannabis sativa Ricinus communis Cassia occidentalis	Cyperus rotundus Cynodon dactylon Pennisetum Cenchrus ciliaris	Brassica campestris Brassica nigra Cleome gynandra Trewia nudiflora
Fungi	Aspergillus spp Alternaria spp Cladosporium spp Curvularia spp Candida spp Epicoccum spp Fusarium spp Helminthosporium spp Nigrospora spp Penicillium spp Periconia spp Ulocladium spp			

# **Allergens in Respiratory Allergy: A Glance**

- Pollen grains are amongst the important known allergens. A variety of host and environmental factors are implicated in the development of pollen allergy. Host factors include history of atopy, gender, ethnicity, smoking, respiratory infection and lung function. Environmental factors include meteorological factors, season, year to year variability, air pollution, rural and urban, regional variability and diurnal variation. Wide spectrum of pollen species are prevalent in various parts of India.
- Pollen calendars, defined as graphs narrating the annual dynamics of major airborne pollen types in a given location. Pollen calendars are commonly used to depict seasonal distribution of pollen in the atmosphere. Pollen calendars can be useful in a variety of ways which includes for clinical warning, to document seasonal characteristics, prevention of allergy symptoms, to predict pollen timing, to guide officials, to tour guides and to guide forensic investigators.
- Increase in pollen count is associated with an increased risk of allergic and asthmatic symptoms. A rise in asthma related admissions and emergency department visits may be seen during peak pollen season.
- HDM constitute an important source of indoor allergens. The dominant genus found in India were *Dermatophagoides* spp, followed by *Blomia* spp Risk factors for HDM include dose, source, seasonal variation, temperature, humidity, cross reactivity, high altitude, house types, air pollution, helminths, protective allele and probiotics.
- Moulds are found in all parts of India because of the favourable climatic conditions permitting their growth. The most common genera in India inducing allergy are *Aspergillus* spp, *Alternaria* spp, *Cladosporium* spp and *Penicillium* spp and *epicoccum*. Fungal allergens are known

to cause hypersensitivity and are associated with conditions like bronchial asthma, allergic rhinitis, allergic bronchopulmonary mycoses, hypersensitivity pneumonitis, and atopic dermatitis.

- Insect inhalant allergens are found indoors, outdoors, homes, and at the work-places. All insect matters like wings, scales, saliva, dried faecal matter, and venom can cause allergic diseases, such as rhinitis, conjunctivitis, asthma, urticaria and gastric disorders. Cockroach exposure is associated with increased asthma morbidity. Moth, cockroach, housefly and mosquito are common among insect allergens in India.
- Animal products are one of the important groups of inhalant allergens which are present in indoor and outdoor environments. Young age, positive family history of allergic disorders, associated allergic disorders are the factors responsible for increased sensitization to animal allergens. Dander allergen sensitivity is commonly seen due to cat, cow and dog.
- Exposure to food allergens through inhalation can also cause food hypersensitivity reactions. Exposure to chemicals can cause exacerbation of respiratory diseases. Approximately 9% to 25% of all adult-onset asthma cases occur due to occupational exposures. Occupational allergens responsible for respiratory allergy mainly include biocides, latex, flour, animals and metals.
- The most important diagnostic test for screening of allergic diseases in adults and pediatric age group is the clinical history. Important points to be considered in history include seasonality, environment, pet or insect exposure, familial atopy, etc. Mode of delivery and maternal smoking needs to consider in paediatric population. A common standardized allergen battery is recommended for clinical use and research across Europe.

# C: Diagnostic Testing (in vivo and in vitro)

# Q1. What are the *in vivo* tests for diagnosis of respiratory allergic diseases?

Allergy tests are used to determine if a patient's symptoms are due to the allergenspecific IgE-antibodies.<sup>713</sup> Patient history and clinical examination are primary modalities for identifying an allergic etiology and identifying the likely causative allergens responsible for the allergic symptoms.<sup>743</sup> This is necessary because many symptoms can also be due to other non-allergic etiology, like viral infections, irritants etc. The clinical suspicion of allergic sensitization is confirmed by demonstrating the presence of allergen-specific IgE antibodies *in vivo* (skin tests) or *in vitro*. The *in vivo* tests for the diagnosis of respiratory allergic diseases are:<sup>744</sup>

- 1. Skin prick test
- 2. Intradermal test
- 3. Patch test
- 4. Allergen provocation test

Skin prick test represents the first-line of investigation for the diagnosis of IgE mediated type I allergic reaction. It is the most commonly used in vivo test for the screening or diagnosis of respiratory allergy. If performed optimally and interpreted correctly, SPT provides reliable confirmation of culprit allergen for the diagnosis of respiratory allergy.<sup>742</sup> It is simple, inexpensive and provides quick results, but requires a certain amount of co-operation from the patient.744 It is considered gold standard and can be performed with virtually any allergen and is more sensitive than in vitro tests.745 Prick-to-prick method is more reliable technique that can be used for certain plant allergens, especially for fresh foods and vegetables.<sup>746</sup> It is because many times it is difficult to develop stable test extracts for these allergens. The procedure is performed by first pricking the fresh food/vegetable with the lancet and then pricking the skin. The technique is utilized when clinically allergy is suspected to foods is suspected, especially in condition like oral allergy syndrome.746 However, the degree of skin test reactivity can be different depending on the variety of a fruit or vegetable.747

**Intradermal test** can be used to evaluate both immediate IgE-mediated allergy and delayed-type hypersensitivity. It carries a higher risk of adverse reactions and requires higher levels of technical and interpretive expertise.<sup>748</sup> In comparison to SPT, IDT has higher sensitivity but lower specificity.<sup>744</sup> IDT is mainly indicated in case of:<sup>749-752</sup>

- 1. Suspected respiratory allergies with negative SPT
- 2. Venom allergy
- 3. Drug allergy

IDT is contraindicated in the following conditions:<sup>748</sup>

- 1. Diffuse dermatologic conditions, like eczema, urticaria and dermographism (absence of normal skin)
- 2. Un-cooperative patient
- 3. When antihistamines or other medications interfering with the test could not be stopped.

Relative contraindications are:748

- 1. Unstable bronchial asthma
- 2. During pregnancy
- 3. Infants or young children.

**Patch test** is the gold standard for the identification of a suspected contact with allergen.<sup>713</sup> Patch tests are especially important in identifying occupational dermatitis. It is indicated in patients with chronic, pruritic, eczematous, or lichenified dermatitis if underlying or secondary allergic contact dermatitis is suspected.<sup>713</sup> It is not relevant to immediate or IgE-mediated allergy.<sup>748</sup> The major limitation of patch test is in the diagnosis of allergic contact dermatitis and lack of standardized interpretation method.<sup>713</sup>

**Allegen provocation tests:** Different methods of allergen provocation tests are:

- 1. Nasal allergen provocation test
- 2. Bronchial allergen provocation test
- 3. Conjunctival allergen provocation test and
- 4. Food allergen provocation test

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Even patch test is essentially a provocation test. Due to safety issues and lack of standardization in conjunction with increased availability of high-quality reagents for skin tests or *in vitro* diagnosis, the allergen challenge was almost abandoned from daily practice and reserved for research purposes.<sup>753</sup> However, currently challenge tests are slowly entering to daily clinical practice mainly due to an improved safety profile and better standardization. The nasal and ocular provocation tests can be easily implemented in clinical practice.<sup>753</sup>

*Nasal allergen provocation test* may be indicated when there is discrepancy between history and results of SPT or sIgE measurement for diagnosis of allergic rhinitis.<sup>754</sup> In clinical setting qualitative measurements via a symptom scale are appropriate, while for research quantitative measurements with high reproducibility are needed.<sup>753</sup> Various responses to nasal allergen provocation test are:<sup>754</sup>

- (a) immediate response (10–20 min),
- (b) late response (after 6–8 hours),
- (c) dual immediate and late response, and
- (d) delayed response (beginning 24–32 hours, maximum at 32–36 hours, and resolving within 56 hours).

During the procedure a doctor should be present with an emergency kit available in view of potential bronchoconstriction or anaphylactic event. The test is generally safe when performed correctly. Major limitation may be the potential bias due to intrinsic non-specific nasal hyperreactivity.<sup>755</sup> Allergen application itself may generate non-specific reactions due to the preservatives.

**Bronchial provocation test** can be performed by challenging the airways with a variety of physical and chemical stimuli. The airway narrowing is measured by changes in FEV<sub>1</sub> after gradually increasing the dose of provoking allergen. Inhalation of the provoking agent is stopped when 20% decline in FEV<sub>1</sub> is achieved. Airway hyper-responsiveness is expressed as the provocative concentration (PC20) or the provocative dose (PD20) of the stimulus that causes a 20% reduction in FEV<sub>1</sub>.<sup>756</sup> Bronchial provocation test is highly reproducible with small within-subject variability. The test is now mostly restricted to specialized centers where experts are available. The magnitude of the bronchoconstriction induced by bronchial provocation test may be more difficult to control than that with direct challenges, which is the major limitation of the test.<sup>753</sup>

*The conjunctival allergen provocation test* involves the instillation of specific concentrations of an allergen solution in the ocular conjunctiva to elicit an IgE-mediated allergic reaction of the ocular surface mucosa in a suspected sensitized patient.<sup>757</sup> Even though procedure is safe, conjunctival non-specific hyper-reactivity is a limitation. The test may be difficult to perform in uncooperative patients. The lack of standardized allergens relevant for a geographical area is another important limitation of the test.<sup>753</sup>

Food allergen provocation test is considered as a gold standard diagnostic for food-related adverse reactions.758 The test is also indicated for follow-up of previously diagnosed food sensitivities.<sup>759</sup> Grading of the risk of a positive reaction, including an anaphylactic reaction, is done by measuring specific-IgE to recombinant allergens. The specific IgE-total IgE ratio is more accurate than specific-IgE alone in predicting the outcomes of challenges performed. The patient is exposed to a specific food in safe environment under a standardised protocol. Immediate reactions usually appear within 2 hours after the last food intake. Urticaria and angioedema are the most frequent objective signs. Major limitation of the test is difficulty in interpretation, especially for subjective symptoms.760

# Summary

In vivo tests for the diagnosis of respiratory allergic diseases are

- Skin prick test
- Intradermal test
  - Patch test
  - *Allergen provocation tests These are of following types:* 
    - (a) Nasal allergen provocation test
    - *(b)* Bronchial allergen provocation test
    - (c) Conjunctival allergen provocation test
    - (*d*) Food allergen provocation test

# Q2. What are the *in vitro* tests for the diagnosis of respiratory allergic diseases?

Prevalence of allergic diseases is increasing worldwide, and hence, there is a need for accurate

diagnosis of these diseases. The main purpose of *in-vitro* testing is that it helps in detecting the presence of IgE antibodies which confirms that sensitization has occurred.<sup>761</sup> The various *in vitro* tests used for the diagnoses of respiratory allergy include.<sup>744</sup>

- 1. Serum IgE assays
  - (a) Serum total IgE
  - (b) Serum specific IgE
- 2. Cell-based assays Basophil activation test (BAT)

Serum total IgE levels. The sensitivity and specificity of serum total IgE levels is very low for diagnosing the allergic disorders. Elevated levels of serum IgE may be seen in situations, like infestations of parasites, primary immunedeficiencies, infections like Epstein-Barr virus (EBV), rheumatoid arthritis and smoking.716 Serum IgE levels varies with age. Initially, serum IgE levels increase progressively up to the age of 15 years, than decline from the 2nd to the 8th decade of life. Earlier, different immunoassays using specific antibodies for human IgE were used to measure total IgE levels in the serum.744 In most of the cases, these antibodies are conjugated on a solid phase, *i.e.*, capture antibody and/or directly labeled with radio-nuclide, enzyme, or fluorophore. Automated platforms have made the tests more accurate, reproducible, sensitive and specific.744 Half-life of free serum/plasma IgE is 2 to 3 days and that of cell bound IgE is several weeks. Clinical detection of IgE is restricted to free serum/plasma IgE which ignores the major contribution of cell-bound IgE.762 These assays, commercially available, have been cross standardized to a common primary human IgE standard (WHO 11/234). Total IgE values are recorded in International Units per unit volume (IU/mL) or kIU/L.<sup>744</sup>

**Serum specific IgE.** IgE molecules produced against specific antigens are referred as serum specific IgE.<sup>716</sup> It is the most frequently used *in-vitro* diagnostic test to detect allergen sensitization in a patient with positive history of exposure to an allergen.<sup>744</sup> The sensitivity of specific serum IgE antibody is comparable to that of SPT for respiratory allergy. Now-a-days, qualitative, semi-quantitative, and/or quantitative IgE immunoassays are also accessible.<sup>744</sup> High levels of total IgE (>300 kIU/L) are associated with false positive results

because of non-specific binding to test allergens.<sup>716</sup> Classic sandwich technique-based assays with minor variation are used to detect specific IgE. Serum specific IgE levels can be measured by a single-plexed, multi-plexed strategy.<sup>744</sup>

*Single-plex.* It detects specific IgE against single allergen.744 The single-plexed strategy is done for a selected panel of allergens. The allergist sees the patient and performs the SPT, followed by serum specific IgE test (if required). But in certain situations, it is difficult to detect specific IgE by single-plexed technique.744 For example, this can be the case in a polysensitized patient with SPT results showing a large number of positive results and making a long list of allergens to be tested in such a case. There are a large number of singleplexed diagnostics systems in the world. The major ones are Radio allergosorbent test (RAST), Phadia, Siemens, Hycor and Euroimmune. All these methods differ in terms of solid phase, allergen extract, amount of serum required, type of anti-IgE antibody, enzyme substrate, stop solution and reading systems used. For example, gamma-counter and photometer are used for reading results in RAST and Phadia, respectively. Now-a-days, enzyme conjugated anti-human IgE antibodies (Immunocap) has replaced RAST.<sup>716</sup> Specific IgE in serum or plasma to many allergen extracts (about >650) and 105 individual molecular allergens can be measured by the fluorescence enzyme immunoassay (FEIA). Newer technologies, like ImmunoCAP gives more benefits in terms of sensitivity and efficiency.763 Newer generations of ImmunoCAP instruments provide better accuracy as well as reproducibility, and are more rapid procedure with higher capacity.761 Sometimes it could be difficult to interpret and/or manage results generated by the different varieties of methods used. So, the specific characteristics of each method should be well known to the allergist.

*Multi-plex assay.* It simultaneously detects specific IgE against many different allergen components (>100).<sup>764</sup> The Immunoblot test is a multi-plex assay which is done on a nitrocellulose membrane coated with 20 selected allergens. Immunoblotting test has high Sensitivity, and hence, may serve as a quick and cost-effective screening test. However, ImmunoCAP is recommended for accurately determining the level of specific IgE for immunotherapy.<sup>765</sup>

Multi-plex micro array-based immunoassay. Immuno Solid-phase Allergen Chip (ISAC) involves the application of proteomic microarray approach in the diagnosis of allergic sensitization. In ISAC 74 there, are 74 different allergenic proteins. Latest version of this allergen chip enables the determination of specific IgE to 112 different single molecules from 51 different plant and animal allergen sources.<sup>763</sup> ISAC 112 multi-plex assay allow the binding of high-affinity sIgE when compared to ImmunoCAP single-plex assay. The ISAC multi-plex test has been found to correlate well with ImmunoCAP single-plex results.744 Another type of microarray based multi-plex assay is MeDALL (The Mechanisms of the Development of Allergies) allergen chip, was developed within the MeDALL European project. It is based on 170 relevant allergens is newer micro array technology.<sup>766</sup>

ALEX (as in Allergen EXplorer) was developed by Macro-ArrayDX in Vienna (Austria). The test is performed using an array of allergens spotted on a solid phase by way of nano-particles. ALEX contains 282 reagents (157 allergen extracts and 125 recombinant or highly purified molecules).<sup>767</sup>

Cellular Assays-Basophil Activation Test (BAT) is a flow-cytometric based assay, which is specific, but complex procedure, and therefore, restricted to certain situations. It can be helpful in case of equivocal and/or negative results obtained with other available in vitro and in vivo tests, and also in case of discordant results.744 Since, it is a flow-cytometric based assay, therefore, it should be performed by the staff well-trained in flow cytometry technique.<sup>768</sup> Various surface-marker combinations, which help to correctly identify the basophils include the combinations CCR3b/CD3, or CD123b/HLA-DR-, or IgEb/CD203cb. The only lineage-specific basophil marker is CD203c. The precise identification of the population of basophils is a must for accurate interpretation of the test results. This is followed by identification of the appearance and/or upregulation of the desired activation/degranulation marker, like CD63 or (lysosomal- associated membrane protein [LAMP-3]) and CD203.744

At present, the best definition of a positive test result is based on the frequency of activated basophils following stimulation. A test result of at least 15% activated basophils is generally taken as a cut-off value and with a stimulation index of at least 2. Both IgE dependant as well as independent pathways are assessed by basophil activation test and this is the main benefit of basophil activation test. The commercially available basophil activation assays are rarely thoroughly validated. A standardized technique for the performance of the test and interpretation of the results is still not available.<sup>744</sup>

## Summary

Following are the in-vitro tests for the diagnosis of respiratory allergic diseases

- 1. Serum IgE assays
  - (a) Serum total IgE
  - (b) Serum specific IgE
    - (i) Single-plex
    - (ii) Multi-plex
- 2. Cell based assay–Basophil activation test
- Q 3. Which tests are better for diagnosis of respiratory allergy: *in vivo* or *in vitro*? Is comparative sensitivity and specificity of various *in vivo* and *in vitro* tests available?

Various *in vivo* and *in vitro* tests for diagnosing respiratory allergy have been discussed in question number 1 and 2. Both the type of tests have certain advantages and disadvantages over each other. Amongst various available *in vivo* and *in vitro* tests for diagnosing respiratory allergy, SPT and serum specific IgE are the most commonly employed tests.

#### Advantages of *in vivo* tests

- Skin tests, especially SPT, are the simple, convenient, reliable, cost-effective, biologically significant, reproducible and time-effective and sensitive tool for the diagnosis and management of IgEmediated diseases.
- *In vivo* assessment offers quick results (within 10 minutes).
- SPT can be performed with virtually any allergen<sup>744</sup> and is considered as the gold standarad test.

### Disadvantages of *in vivo* tests

- Technical errors that can interfere with SPT results are:
  - (a) difficulty in reading overlapping results when tests are applied too close (<2cm),
  - (b) bleeding at test site resulting in misreading it as false positive result

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- (c) insufficient skin penetration resulting in false negative results
- SPT is difficult to perform in children.
- Certain drugs, like anti-histamines can interfere with the results, so need to be stopped before SPT.<sup>713,744,748</sup>
- Serious adverse reactions, like anaphylaxis (although rare) have been reported so, it should be conducted under proper medical supervision.
- A positive SPT does not always mean allergic disease.<sup>744</sup>
- The results of skin test can differ with
  - (a) season (more sensitive in October for seasonal allergens and in February for perennial allergens),
  - (b) the site of application (back is more sensitive than the arm),
  - (c) the instrument used for pricking
  - (d) extract source (standardized *versus* unstandardized)
  - (e) time of day when it is done (more sensitive in morning than evening).
  - (f) age<sup>715,769–771</sup>
- In addition, there is a risk of cross-reactivity, especially with crude antigens.
- The results are difficult to assess when applied on pigmented skin.<sup>744,748</sup>
- Skin sensitivity is decreased in some conditions, like
  - (g) renal failure,
  - (h) malignancy,
  - (i) diabetes,
  - (j) spinal cord injuries
  - (k) long-term steroid use, etc.<sup>716</sup>

# Advantages of in vitro tests744,748

- Serum IgE assays can be performed by any trained laboratory technician. The results are not affected by the operator's experience.
- No risk of systemic reactions during test since the test does not require administration of potentially dangerous allergens to the patient.
- Modern sIgE results can be obtained within a couple of hours.

- These are not affected by anti-histamine drugs.
- Serum specific IgE detection offers quantitative detection of allergic disease as compared to SPT.<sup>716</sup>

# Disadvantages of *in vitro* tests

- The number of allergens which can be tested by *in vitro* tests is limited by the costs.<sup>744,748</sup>
- *In vitro* assays done by chemiluminescence are more specific (especially, if low levels of specific IgE are present) than those done by ELISA or similar techniques.
- The major drawback of sIgE assessment is the occurrence of false positive results with high total IgE levels (>300 kIU/L) due to non-specific binding to test allergens.<sup>716</sup>
- IgE tests are not significant at all for diagnosing various drug allergies.
- Clinical detection of IgE is limited to free serum/plasma IgE (t1/2=2-3 days) which ignores the large contribution of cellbound IgE (t1/2=several weeks).<sup>762</sup>

It is difficult to directly compare the two methods (SPT and sIgE) as these differ profoundly in many aspects.<sup>772,773</sup>

Comparative sensitivity and specificity of various in vivo and in vitro tests. Comparative studies have been conducted to establish sensitivity, specificity of SPT, intradermal test and in vitro test, i.e. sIgE with respect to aeroallergens. These are shown in tables 10-12. Interpretation of these results differs, depending on whether the comparative gold standard is clinical history or controlled provocation challenges. According to a systematic review and meta-analysis, the pooled estimate for sensitivity and specificity for SPT in allergic rhinitis was 85 and 77%, respectively.774 Another comparative study reported that sensitivity and specificity of SPT for allergen extract of timothy grass pollen was 87% and 86%, respectively, keeping positive nasal provocation challenges as a standard.775 Addition of IDT increased the sensitivity further to 93% without changing the specificity. When the IDT has been evaluated as a stand alone tool for diagnosing allergic rhinitis, the estimate for sensitivity was between 60% and 79% and the specificity was 68%.774 Thus, better than SPT.

<b>Author<sup>Ref</sup></b> Year	Study Design	Allergic Disease	Sample Size	Allergens Used	Gold Standard	Sensitivity (%)	Specificity (%)	Comments
Nevis et al <sup>774</sup> 2016	Meta-analysis	AR	Meta- analyisis	Cat, Timothy Alternaria Ragweed HDM etc	NAPT	8	3	SPT is accurate in discriminating the subjects with or without AR
Krouse et al <sup>775</sup> 2004	Cross-sectional	AR	37	Timothy	NAPT	87	86	Epicutaneous testing with the Multi- Test II offers 87% sensitivity and 86% specificity in assessing timothy grass reactivity
Tschopp <i>et a</i> <sup>[76</sup> 1998	Quassi experimental	AR BA	8329	Cat, Dog HDM, Grass Birch Parietaria	Clinical criteria	BA-65 AR-68	BA-78 AR-86	SPT have the best positive predictive value and the best efficiency to diagnose respiratory atopic diseases
Wood et al <sup>778</sup> 1998	Cross-sectional	BA AR	120	Cat	Cat challenge test	93.6	87.2	Although both SPT and RAST values exhibited excellent efficiency in the diagnosis of cat allergy, IDST scores added little to the diagnostic evaluation
Peterson <i>et al</i> <sup>779</sup> 1986	Cross-sectional	AR Conjuctivitis	69	Birch timothy	NAPT	97	70	A high diagnostic precision and a high diagnostic value was found for both SPT and RAST
Pepys et al <sup>780</sup> 1975	Cross-sectional	BA AR	141	Sweet vernal Cocksfoot Meadow fescue, Rye, Timothy	NAPT	33	89	The degree of agreement between NAPT results and RAST on the one hand and provocation tests and SPT on the other hand was of the same order, 76% and 79% respectively, of a total number of 136 subjects tested
Suaad <i>et al</i> <sup>781</sup> 2016	Cross-sectional	AR BA	128	HDM extracts, pollens of trees, Grasses and weeds and extract for mold allergens	Clinical history	87.5	AA	SPT results correlate significantly with elevated total IgE levels and total serum IgE could be a predictor of positive SPT
Contd								

Table 10. Studies reviwed for sensitivity and specificity of SPT

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	minatin mouse and ID' n SPTs j	ts or	ET) metl tt obtain specific nd that h with N	tests in c truly cau nultiple	ng AR ar id specif ap test w ity, and	stinguish gic from	U/mL
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y Co	SP <sup>7</sup> pat alle dia	rep	SKi SF and SP of J	Sta to 1 alle pos	SPJ pos hov rais acc	A 6 ind wh	% The lot the lict the
Specificit (%)	94	64	78.6	20	80	74	Atleast 80 with extra once of 50000 SU/m
itivity							with ct entration 000 SU/mL
Sens (%)	67	42	85.3	8	94.1	100	>80% extra conce of 500
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Alle Use	Mor	Alte	Rag	Graa Mug Birrc Pelli Derr	Mix Poll Cott Hou HDJ	Cat	6-gr Poll HDJ Birc Poll
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<b>Aut</b> Year	Shar et al 2005	Kro et al 2004	Gun et al 2004	Past et al <sup>®</sup> 1988	Han et al <sup>®</sup> 2020	Zare et al <sup>6</sup> 2004	Nicc et al <sup>6</sup> 2015

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The sensitivity of sIgE immunoassays compared with SPT is reported between 50% to 90%, with the average being approximately 70% to 75% in most of the studies.713 Similar sensitivity has also been reported when immunoassays are compared with symptoms induced after natural or controlled organ challenge tests.713 Diagnostic efficiency of IgE, SPT, and Phadiatop in allergic asthma and rhinitis were studied over 8329 well-randomized adults from the Swiss Population Registry.776 The study reported that the sensitivity of Phadiatop was significantly higher than that of SPT to diagnose asthma and allergic rhinitis (72.5% versus 65.4%, 77.1% versus 68.4%, respectively). However, SPT was significantly more specific than Phadiatop to exclude asthma and allergic rhinitis (77.8% versus 71.9% and 85.9% versus 80.5%, respectively).776 Concordance between in vitro sIgE antibody assays and SPT results are between 85% and 95%, depending on the allergen being and the method used to detect sIgE.777

According to the available literature, the sensitivity and specificity of SPT in comparison to nasal allergic provocation test varies from 68.1% to 100% and 70% to 91%, respectively (Table 10).<sup>774–776,778–781</sup> SPT is generally considered less sensitive but less specific than IDT which

Table 11. Studies reviewed for sensitivity and specificity of IDT

is partially explained by the larger volumes of test solutions administered by the intradermal route. However, SPT is more specific than the IDT.<sup>777,782</sup> IDTs are generally used when increased sensitivity is the main goal of testing, especially SPT results are negative despite a significant history of the exposure.<sup>777</sup> There are limited studies on the assessment of diagnostic accuracy of IDT (Table 11).<sup>775,778,782–787</sup> IDT for most allergens exhibit poor efficiency in predicting organ challenge responses and correlating with the presence of detectable sIgE.<sup>713</sup>

According to the available literature, both the sensitivity and specificity of sIgE in relation to SPT for diagnosing respiratory allergic diseases varies from 50 to 100 (Table 12).776,778-780,783,788-807 Sensitivity was less than 90% in most of the studies. Sensitivity and specificity of the specific IgE test differs according to the technique and the allergen extract used. Majority of the studies used SPT as standard test to assess the diagnostic accuracy of specific IgE test.<sup>789–794,798–800,803–805</sup> Although few studies used clinical diagnosis of allergy and nasal allergen provocation test as gold standard to compare sIgE and SPT.778-780,783 Those studies also concluded that the SPT have better diagnostic efficiency for respiratory allergy.

Year	Size	Cut-off (mms)	Anergen Extracts	Standard	(%)	(%)
Sharma <i>et al</i> <sup>783</sup> 2008	69	>6	Mouse-epithelia extract	Mouse challenge	100	35-65
Ahlstedt <i>et al<sup>787</sup></i> 1974	65	NA	Timothy Birch Dog	NAPT	86 agreement with RAST	NPV-96
Krouse <i>et al</i> <sup>775</sup> 2004	37	≥3	Timothy grass	NAPT	50	100
Krouse <i>et al</i> <sup>784</sup> 2004	44	≥3	Alternaria	NAPT	27	69
Gungor <i>et al</i> <sup>785</sup> 2004	62	≥2	Ragweed	NAPT	79.4	67.9
Wood <i>et al</i> <sup>778</sup> 1998	120	≥6	Cat	Cat challenge	<60	32
Escudero <i>et al</i> <sup>786</sup> 1993	65	>5	Alternaria tenius	History plus positive Challenge	94-100	92
Menardo <i>et al</i> <sup>782</sup> 1982	30	NA	HDM	SPT, RAST	IDT more sensitive than SPT	NPV-100

						:
Comments	SPT have the best positive predictive value and the best efficiency to diagnose respiratory atopic diseases	Although both SPT and RAST values exhibited excellent efficiency in the diagnosis of cat allergy, IDST scores added little to the diagnostic evaluation	A high diagnostic precision and a high diagnostic value were found for both SPT and RAST	The degree of agreement between NAPT and RAST results on the one hand and NAPT and prick tests on the other hand was of the same, 76% and 79% respectively, in a total number of 136 subjects tested	SPT perform best in discriminating patients with and without mouse allergy. Mouse-specific LgE and IDTs appear to be less useful than SPT in the diagnosis of mouse allergy	Contd.
Specificity	Phadiatop BA-71.9 AR-80.5 SPT BA-78 AR-86	slgE-90.5 SPT-87.2	SPT Birch-94 Timothy-70 RAST Birch-100 Timothy-70	NA	slgE-91 SPT-94	
Sensitivity	Phadiatop BA-72.5 AR-77.5 SPT BA-65 AR-65 AR-68	slgE-87.2 SPT-93.6	SPT Birch-97 Timothy-97 RAST Birch-82 Timothy-94	NA	slgE-47 SPT-67	
Gold Standard	Clinical criteria	Cat challenge test	NAPT Conjuctival- provaction test	NAPT	NAPT	
Allergens Used	Cat Dog HDM Grass Birch Parietaria	Cat	Birch Timothy	Sweet vernal Cocksfoot Meadow fescue Rye Timothy	Mouse	
Technique	SPT IgE Phadiotop	SPT IDT RAST	SPT RAST	SPT RAST	SPT	
Sample Size	8329	120	69	141	61	
f Allergic Disease	AR BA	BA AR	AR Conjunctivitis	BA AR	AR, Ocular skin symptoms	
<b>Author<sup>Re</sup> Year</b>	Ischop <i>et al<sup>776</sup></i> 1998	Wood et al <sup>778</sup> 1998	Peterson # al <sup>779</sup> 1986	Pepys <i>et al</i> <sup>780</sup> 1975	Sharma # al <sup>783</sup> 2008	

Table 12. Studies reviewed for sensitivity and specificity of Specific IgE

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	Specifi	NA	92–100	NA	66-06	NA	
		nore 1 the ars 1PT in 50 years	91 coat83 t-1gE53 sbas	ilar for 0.79 T-0.76	-67 Grass	assays 1 at the ecificity	
	ivity	owed a 1 e ratio ir of <30 ye sitives 5 oup of ≥⁵	aciaCAF ad Aller ellHamle al Phade 89	ve is sim o-CAP-( yymRAS	87% thelium mix–59	vity of 3 ompared vel of spo differ	
	Sensiti	SPT sh positiw group Few pc age gro	Pharma Kallest Neo Ab Classic RAST-	RO cur Immun Phadez	HDM Cat epi Mould mix-46	Sensitiv when c 95% lev did not	
	dard	story	or nd tests				
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	ğ	Ċ	Q b q	SP	SP	ID SL	
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	Tech	SPT Imum	Phan Systi Kallı Kallı Systi Neo Neo IgE class RAS	Mod Phac Imm	Phan Imm systt	Phan Syst RAS mod	
	e Size						
	Sampl	692	34	48	167	198	
			<u>a</u>				
	Allergi Disease	AR	BA AR Urticar	BA AR	BA AR	BA AR	
:	thor <sup>Ref</sup> r	888 0	agni ***	Ác J	International State	iams	
Cont	Au Yea	Jung et al 2010	Buc et al 1994	Cor et al 1994	Gleo et al 199(	Will et al 1992	

# Indian Guidelines for Diagnosis of Respiratory Allergy

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<b>Author<sup>Ref</sup></b> Year	Allergic Disease	Sample Size	Technique	Allergens Used	Gold Standard	Sensitivity	Specificity	Comments	
Nolte <i>et al</i> <sup>793</sup> 1997	AR	54	HYTEC method PharmaciaCAP system	Cat D. pteronyssinus Birch pollen Timothy grass with equineserum	SPT	Hytec-78-100 CAP-50-100	Hytec-66-93 CAP-70-87	The HYTEC system fulfils the current analytical requirements necessary to measure allergen-sIgE antibody quantitatively and qualitatively, and compares favourably in performance with the CAP system	
Kam <i>et al</i> <sup>794</sup> 1994	BA	96	Phadezym RAST (PhRAST), PharmaciaCAP, and Multiple- chemiluminescen tassay(CLA-MAST)	<i>D. pteronyssinus,</i> <i>Candida albicans</i> <i>Aspergillus</i> Short ragweed Bermuda grass	TGI TCI	With IDT as reference RAST-80 CAP-86 MAST-75 With SPT as reference RAST-60, CAP-79 MAST-NA	With IDT as reference RAST-92, CAP-94 MAST-80 With SPT as reference RAST-95 CAP-90 MAST-81	CAP system is the preferred test and provides a useful guide for prescription of environmental control and immunotherapy in unselected patients	
Wood et al <sup>795</sup> 2007	Food allergy	80	ImmunoCAP Immulite and Turbo RAST	Peanut and soy	ImmunoCAP	NA	NA	Immulite over-estimating and Turbo RAST underestimates IgE compared with ImmunoCAP	
Blanco et al <sup>7%</sup> 1998	BA AR	20	ImmunoCAP Ala STAT	Natural latex extract commercial latex extract Glove latex extract	SPT	ImmunoCAP-84 Ala STAT- 86	NA	SPT with natural latex extracts has shown a diagnostic efficacy close to 100%, significantly higher than that of latex-specific serum IgE determination	
Yang et al <sup>797</sup> 2018	Food allergy	204	ImmunoCAP Immulite	Alternaria alternata Birch-alder mix Cat dander D. farinae, D. pteronyssinus Dog dander, Buckwheat Crab, Egg white, Mackerel Milk, Peach, Peanut Shrimp, Soybean and Wheat flour	Semi quantitative AdvanSure allergy screen-test	Overall concordance rate ranged from 81% to 99% with the cut-off value of 0.35kIUA/L	NA	Immulite 2000 and ImmunoCAP assays demonstrated good concordance and correlation for 16 common allergens, but international standards against each specific allergen for Calibration and harmonization of sIgE tests are still needed	
								Contd	

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Comments	Laboratory testing for sIgE can be successfully accomplished by immulite 2000 immune analyzer at a diagnostic accuracy relative to SPT,	comparable to the results acquired by CAP technology but not fully comparable on the level of an individual patient	The performance of ImmunoCAP compared to SPT vary among 53 inhalant allergens. CAP should be considered complementary, not equivalent, to SPT	SPT and sIgE are two tests that are rather concordant, but with different sensitivity and specificity distinct for each allergen	SPT is more sensitive but less specific than ImmunoCAP	The positive rate of the SPT is higher than CAP when evaluating mold allergy Clinicians should note that a discrepancy may exist between the results of <i>in</i> <i>vitro</i> and <i>in vivo</i> tests when evaluating old allergy Contd
Specificity	NA		20-80	83-93	SPT-94 CAP-100	NA
Sensitivity	NA		50-80	75-93	SPT-100 CAP-69	AN
Gold Standard	SPT		TAS	SPT Clinical history	NA	Clinical history
Allergens Used	D. <i>pteronyssinus</i> Cat dander, Egg white, Milk, Peanut Orchard grass Alternariatenuis Ragweed and insect venoms in selected patients	Birch, cat dander, Ragweed, <i>D. pteronyssitus</i> , Orchardgrass, Egg white, Milk and peanut in non- selected group	53 Allergens	D. pteronyssinus Parietaria officinalis Cypress and Dog	Cat	5 fungal antigens Candida Alternaria Aspergillus Cladosporium Penicillium
Technique	Immulite-2000 Immuno CAP		ImmunoCAP	ImmunoCAP	SPT ImmunoCAP	IDT ImmunoCAP
Sample Size	Selected patient group (N=569; varied sample size for each allergen) Non-selected group (N=100; 8 allergens)		250	793	<del>11</del>	73
Allergic Disease	Food allergy		AR	BA AR	AR	AR
<b>Author<sup>Ref</sup></b> Year	Lokas <i>et al<sup>798</sup></i> 2016		Calabria et al <sup>799</sup> 2009	Bignardi <i>et al</i> <sup>800</sup> 2019	Robertson et al <sup>801</sup> 2012	Liang <i>et al</i> <sup>802</sup> 2006

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<b>Author<sup>Ref</sup></b> Year	Allergic Disease	Sample Size	Technique	Allergens Used	Gold Standard	Sensitivity	Specificity	Comments
Ciprandi et al <sup>803</sup> 2010	AR	610	ImmunoCAP SPT	HDM, Cat, Dog Grasses mix, Compositaemix <i>Parietaria officinalis</i> Birch, Hazel, Olivetree Alternariatenuis, Cladosporium, Aspergilli mix	SPT	ХА	NA	Significant difference between serum slgE values in these polysensitized patients. These serum slgE measurement in polysensitized patients seems to be more appropriate than SPT
Griffiths <i>et al</i> <sup>804</sup> 2017	Food allergy	118	SPT ImmunoCAP or ISAC	Nut allergy	Clinical history	SPT-56 ISAC-65 ImmunoCAP-71	NA	In this difficult diagnostic group, the ImmunoCAP test should be the preferred single test for possible allergy to nuts, wheat, other specific foods, and anaphylaxis of any cause
Kumar <i>et al</i> <sup>805</sup> 2015	BA AR	20	ImmunoCAP	Cockroach Housefly Mosquito	TqS	92.8 91.6 85	66.6 37 50	slgE has a higher sensitivity and PPV when compared to SPT, but the test lacks specificity. SPT being more specific continues to be the gold standard in allergy
Keslo <i>et al</i> <sup>806</sup> 1991	BA AR	104	Phadebas RAST Modified RAST PharmaciaCAP system	Cat D. spteronyssinus Alternaria Junegrass Short ragweed	TY	Phadebas RAST-62 Modified RAST-90 PharmaciaCAP system-74	Phadebas RAST-99 Modified RAST-87 PharmaciaCAP system-96	If the results of these <i>in</i> <i>vitro</i> tests are used as the sole guide, the performance characteristics of the CAP make it the preferred test
Wang et al <sup>sor</sup> 2007	Food allergy	50	Phadia Immuno CAP AgilentTurbo- MP, and Siemens Immulite2000	Egg, Milk, Peanut, Cat, Birch, and Dermatophagoides-farinae	Clinical history	NA	NA	Several values for the food allergens were discrepant around the 50% and 95% positive predictive values for clinical reactivity

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# Summary

- 1. SPT in collaboration with clinical history is the most accurate diagnostic test for the diagnosis of respiratory allergy.
- 2. Intradermal test has higher sensitivity, but its diagnostic accuracy is limited.
- 3. In vitro test, i.e serum sIgE is both less sensitive and less specific compared to SPT for the diagnosis of respiratory allergy.
- Q 4. Which test is considered as gold standard test for the diagnosis of respiratory allergic diseases?

SPT is considered as gold standard for the diagnosis of respiratory allergy. As explained in the answer to question no. 3 of section C, the sensitivity and specificity of SPT is better when compared to the sIgE test. Even though, SPT is generally considered less sensitive than IDT, the higher specificity of the test make the diagnostic accuracy of SPT better.<sup>777</sup> Apart from diagnostic efficacy, SPT is simple, inexpensive, reliable, reproducible test and provides quick results, but it does require a certain amount of co-operation from the patient. Also, SPT can be performed with virtually any allergen.<sup>716,744</sup> All these factors further add to the advantages of SPT over the other diagnostic tests.

# Summary

SPT is considered as the gold standard for the diagnosis of respiratory allergy.

# Q 5. What are the qualifications required for performing *in vivo* (SPT) allergy testing?

Various societies have recommended that in vivo allergy testing (SPT) can be performed by trained nurse/technician under the supervision of an experienced allergy physician or an allergy specialist. Under certain circumstances, especially in places where there are very few allergy specialists, SPT may be performed by the general practitioner (pediatricians, general physicians, thoracic physicians) who have additional training in allergy from recogonised institutions. Some authors suggest that to ensure basic competency by making sure that the person performing allergy testing should carry at least 10 skin tests over a period of several days on different types of patients under the supervision of an experienced nurse and allergy specialist.<sup>748</sup> This is important because the tests carried out

by the trained staff are highly reproducible.<sup>813</sup> However, the availability of formal training programmes for performing SPT in India is limited to workshops and training courses.

Also, while performing the *in vivo* testing, ensure the presence of an experienced physician well versed in the management of anaphylactic reactions along with all the necessary requirements for the same.

Further, to achieve the quality assurance among the technicians, consistency in skin test performance should be demonstrated using skin testing proficiency protocols. Some European studies suggest a coefficient variation of less than 20% after histamine control applications. A coefficient variation of less than 30% was used in a recent Childhood Asthma Management Study.<sup>771</sup> Proficiency testing helps to improve the diagnostic accuracy and reproducibility of SPT.<sup>815</sup> Various methods of proficiency testing are available in the literature.<sup>771,816</sup>

Formal training for performing SPT should include proficiency testing and quality assurance technique for SPT. One of the proficiency testing protocol that can be followed is as follows:

- Using desired skin test device, perform skin testing with positive (histamine 1–10) and negative controls (saline 1–10) in an alternate pattern on a subject's back.
- Record both histamine and saline results at 15 minutes by outlining wheals with a felt tip pen and transferring results with transparent tape to a blank sheet of paper.
- Calculate the mean diameter as (D + d)/2; where 'D' - largest diameter and 'd' orthogonal or perpendicular diameter at the largest width of D.

# Histamine

- Calculate the mean (±SD) of each mean wheal diameter
- Determine CV = SD/mean
- Quality standard should be a CV value of less than 30%

# Saline

• All negative controls should be 3mm wheals and 10mm flares.

# Summary

- 1. An allergy specialist/physician or pediatrician formally trained in allergy testing should perform in-vivo allergy testing.(3A)
- 2. A nurse/technician trained in allergy testing can also perform in vivo allergy testing under the supervision of an experienced allergy physician. (3A)
- 3. An experienced physician well versed in the management of anaphylactic reactions along with all the necessary requirements for the same should be present, whenever invivo allergy testing is being performed. (UPP, A)

# Q6. What is the appropriate time for performing allergy testing? Can it be performed during acute phase of the allergic disease?

Allergy testing, especially *in vivo* tests like SPT, should be performed at least 4–6 weeks after the allergic reaction. This is proposed because in the patients who had an episode of systemic allergic reaction in last 4–6 weeks, there are high chances of false negative results.<sup>817,818</sup>

It should be avoided in patients having symptomatic asthma at the time of testing due to the increased risk of exacerbation during testing.<sup>819</sup> A peak flow of less than 70% in patients with asthma is a relative contraindication. Allergy testing, especially *in vivo* testing, should be performed in individuals with controlled asthma. It should be deferred until the disease control is achieved, as evidenced by the studied literature.<sup>809,820</sup>

It has been advised to measure sIgE levels or perform titrated skin tests, especially in patients who are highly suspicious of developing anaphylaxis.<sup>746</sup>

SPT may be avoided during respective allergy season when the patient is having increased symptoms of allergy or elevated baseline tryptase levels, since the two are the risk factors for the development of anaphylaxis.<sup>821</sup>

# Summary

- 1. SPT should not be performed during acute phase of the disease/uncontrolled asthma. (3A)
- 2. SPT should be done after at least a gap of 3–4 weeks from systemic allergic reactions. (3A)

# Q 7. What are the indications for skin prick testing?

The diagnostic potential of SPT was first recognized by Blackley.<sup>822</sup> SPT can be done to:

• Diagnose type I hypersensitivity reaction mediated allergic disease. It has been

used for diagnosing sensitization to different proteins.<sup>823</sup> SPT is the most common test used by an allergist for the diagnosing allergic rhinitis/conjunctivitis, food allergy, atopic dermatitis/eczema, asthma.<sup>774,824</sup> However, the role of SPT in diagnosing food allergy is still not well established, since it has both IgE and non-IgE mediated responses and also SPT has low specificity (40%–80%) in diagnosing food allergy. Oral food challenge test and component resolved diagnosis (CRD) have a promising role in diagnosing food allergy.<sup>713,825,826</sup>

- Identify common aeroallergens in a given region.
- Measuring the sensitivity and specificity of various other diagnostic tests for allergic diseases. Allergy skin testing using the prick/puncture method is considered to be one of the best combinations of sensitivity and specificity. <sup>774,827,828</sup> In most of the studies, SPT is used as the reference standarad test to identify the sensitivity and specificity of various *in vitro* tests, especially serum sIgE.<sup>776,778</sup>
- Various guidelines/studies also suggest that SPT should be used for diagnosing type I hypersensitivity reactions caused by food allergens, aero-allergens, or certain chemicals and drugs, as a reference standard for determining the specificity of various *in vitro* allergy diagnostic tests and also as in epidemiologic studies to determine trends or regional differences of various allergens.<sup>716,746,777</sup>

## Summary

# SPT to be performed

- 1. For the diagnosis of respiratory allergy by inhalant allergens (1A), food allergens (3B) and drugs. (2A)
- 2. As reference standard for in vitro tests for the diagnosis of respiratory allergy. (1A)
- 3. For determining bio-equivalent potency of allergen extracts. (1A)

# Q 8. What are the contraindications for skin prick test?

There are various situations where SPT cannot be done either because of the risk of the disease exacerbation or due to mis-interpretation of the results (Table 13). SPT should not be done for diagnosing allergic disease in pregnancy due to the risk of anaphylaxis. In vitro tests, such as serum sIgE should be preferred over SPT for diagnosing allergic diseases during pregnancy.<sup>829–831</sup> This is either because of a small risk of developing hypotension and induction of uterine contractions and constriction of umbilical artery in case if the patient develops anaphylaxis during the test.<sup>746</sup> Although, SPT can be safely performed in lactating mothers, but still due to lack of evidence of safety and complications of SPT during lactation, it should be avoided during lactation. It should also be avoided in the presence of dermographism and urticaria, as there are high chances of false positive results in such skin conditions. However, in a study comparing the results of SPT in individuals with and without dermatographism, it was found that SPT can be reliable in persons with dermatographism, although false positive results were observed with mild reactions. The study concluded that SPT can be done in the presence of dermatographism and careful repetition of positive SPT in such cases will decrease the chances of false positive results. Further research in this aspect is required.<sup>832</sup>

SPT should not be performed in patients who are taking drugs which may hinder the action of epinephrine (if needed for anaphylaxis), *e.g.*,

beta-blockers and ACE-inhibtors. Beta-blockers are relatively contraindicated in SPT as these may increase the risk and severity of the anaphylactic reaction in atopic individuals and make the treatment of anaphylaxis difficult.<sup>833</sup> Several case reports demonstrating the increased severity of systemic allergic reactions to immunotherapy, drugs, foods and insect stings in patients taking beta-blockers and ACE-inhibtors have been published till date.<sup>834,835</sup> Beta-blockers and ACEinhibtors should be avoided in individuals who are at risk of anaphylaxis but considering the cardiovascular status of the patient (since these prolong life expectancy in cardiac patients and should not be avoided in them).<sup>836</sup>

Similarly, SPT should be deferred in patients who are taking medications (which interfere with the test results) which cannot be stopped before the test, such as anti-histamines, steroids and tri-cyclic anti-depressants.<sup>837–839</sup> SPT should also be avoided in infants and young children and if required it should be conducted under the supervision of a trained pediatrician. This is because the size of wheal produced in infants is small<sup>840</sup> and hence, may be difficult to read, and possibility of high risk of adverse reactions (0.12% in young children and 6.5% in infants <6 months).<sup>841,842</sup> SPT should be deferred in uncooperative patients also.

	Participants	
Chogtu <i>et al</i> <sup>348</sup>	2219	Taking drugs which interfere with test results
Prasad <i>et al</i> <sup>378</sup>	48	Pregnant and lactating females
Kumar et al <sup>572</sup>	4835 screened (SPT done in 4263)	Those with comorbidities like TB,HTN, DM and pregnant females
Wood et al <sup>778</sup>	120	Testing was deferred if patient experienced discomfort following allergen challenge or drop of FEV <sub>1</sub> >50% after single challenge
Sharma <i>et al</i> <sup>783</sup>	700	Smokers and history of parasitic infestation
Mostafa et al <sup>821</sup>	180	Individuals on oral or inhaled corticosteriods, anti-histamines 4 weeks before the test, pregnancy, dermographism, severe asthma, un-cooperative patients, cardiac disease and in whom epinephrine is contraindication
Menardo <i>et al</i> <sup>840</sup>	78	Patients with skin disease and taking drugs that interfere with the test results
Gong et al <sup>843</sup>	144	Taking drugs which interfere with test results
Kumar <i>et al</i> <sup>845</sup>	216	Patients with other associated pulmonary diseases including TB, COPD and systemic diseases, <i>e.g.</i> DM, HTN and heart diseases were excluded
		Patients with mechanical causes of airway obstruction, steroid dependent and psychologically unstable cases were also excluded
Rasool <i>et al</i> <sup>846</sup>	400	Pregnant and lactating females

#### Table 13. Studies reviewed for contraindication of SPT
This has been found in the literature that most of the physicians avoid conducting SPT in the above-mentioned conditions either due to the risk of complications or due to interference with the test results.<sup>843,844</sup> Similar, contraindications have been mentioned in AAAI (2008), European standards (2013)<sup>746</sup> South African Family practice (2014) and ASCIA (2016) guidelines and allergy testing-overview (an Indian Review) for SPT, as well.<sup>713,716</sup>

#### Summary

SPT is contraindicated in following conditions:

- 1. Pregnancy and lactation (3A)
- 2. Dermatographism (2A)
- *3. Absence of normal skin (1A)*
- *4. Un-cooperative patient (UPP,B)*
- 5. Patients who are taking drugs which may hinder the action of epinephrine (if needed for the anaphylaxis), e.g., beta-blockers and ACE-inhibtors.(1A)
- 6. Patients who are taking medications (which interfere with test results) those can not be stopped before the test, e.g., antihistamines, tri-cyclic anti-depressants and steroids(3A)
- 7. Relative contraindication: Young children: it should not be performed in young children and when needed, should be performed under the supervision of a pediatrician trained in allergy.(3B)

# Q 9. What is the lower limit of age for performing SPT?

The age from which SPT can be safely performed has been a topic of controversy. Potter<sup>847</sup> state that around **three or four months of age** is appropriate. Bousquet *et al*<sup>848</sup> agreed that there is **no lower age limit** for performing SPT.

The overall risk of adverse reactions in young children and in infants below 6 months is 0.12% and 6.5%, respectively.841,842 In a retrospective analysis of children being tested for atopy, generalized reactions occurred in 6 infants younger than 6 months who had positive SPT results to fresh food specimens.842 All infants received prompt treatment and recovered well. The overall rate of generalized reactions was 521 per 100,000 tested children. In a 12-year survey of fatal reactions to allergen injections and skin testing, one fatality was confirmed after SPT with multiple food allergens. This patient also had moderately persistent asthma, and 90 food prick tests were applied at one time.<sup>849</sup> Hence, proper precautions should be taken while performing SPT in children. In a literature review on systemic reactions from SPT, it was observed to avoid duplication of the skin tests (especially, in children with extensive eczema) since it increases local antigen load, and hence, risk of adverse reactions.<sup>831</sup> Also, little children cannot verbally complain of the symptoms of allergic reaction, like itching, asphyxiation, chest tightness and apprehension.<sup>850</sup>

In addition to the risk of adverse effects, another aspect is the interpretation of the results. In a study done on 78 children (0–3years), it was found that the skin of children <2 years is hyporeactive to histamine control, the size of allergen induced wheal was 2–5mm and that positive skin testing, especially to inhalant allergens, is rare in this age group.<sup>840</sup> Similarly, in another study done on 365 subjects between the age group of 1–85 years, it was found that the skin is hyporeactive below 3 years of age, the size of wheal reaction increased after 4 years and then declined after 60 years of age.<sup>851</sup>

In another study, it was found that the prevalence of positive SPT increased with age, both SPT and serum sIgE should be used for diagnosing allergic diseases at early age due to disagreement between the two and skin allergenic reactivity increases with the age and is transient at 1 year but associated with atopic dermatitis.<sup>852</sup>

The review of the literature revealed that minimum age for performing SPT varied from 0 to 8 years.<sup>581,853</sup> Therefore, preferably SPT can be performed in children >5 years of age (Table 14). This is because:

- 1. There are increased chances of developing atopic dermatitis (upto one year of age) and other complications.<sup>841,842,852</sup>
- 2. Skin in children is hyporeactive to histamine (positive control), especially in those aged less than 6 months.<sup>840</sup> Size of the wheal produced in children is small, and hence, difficult to interpret.
- 3. Un-cooperative behaviour of the children (of age <5 years) is common.

Most of the guidelines recommend that SPT may be done in adults and children from

birth onwards but should be performed under the supervision of a specialist in children due to an increased risk of adverse reactions and complexity of interpretation.<sup>746,814</sup>

# Table 14. Studies reviewed to identify the lower limit of agefor performing SPT

Author <sup>Ref</sup> Year	Number of Participants	Lower Limit of Age (in years)
Sharma <i>et al</i> <sup>359</sup> 2018	134	20
Kumar <i>et al</i> <sup>572</sup> 2017	4835 screened (SPT done in 4263)	30*
Crobach <i>et al</i> <sup>772</sup> 2009	365	34*
Wood <i>et al</i> <sup>778</sup> 1998	120	18
Suaad <sup>781</sup> 2016	128	15
Bignardi <i>et al</i> <sup>800</sup> 2019	794	6
Barbee <i>et al</i> <sup>812</sup> 1981	311	8
Mostafa <i>et al</i> <sup>821</sup> 2020	180	25
Menardo <i>et al</i> <sup>840</sup> 1985	78	0
Gong <i>et al</i> <sup>843</sup> 2019	144	34.6
Aggarwal <i>et al</i> <sup>844</sup> 2019	100	10
Kumar <i>et al</i> <sup>845</sup> 2006	216	8
Sameer <i>et al</i> <sup>846</sup> 2013	400	6
Abruz <i>et al</i> <sup>854</sup> 2011	538	34.4*
Ueno <i>et al</i> <sup>855</sup> 2007	51	~3

#### \*mean age

#### Summary

*Based on the literature review and the experience of the expert panel, it is recommended that* 

- 1. SPT should preferably be done in children >5years of age. (2A)
- 2. With the strong clinical indications, SPT may be done in children <5 years under the supervision of a pediatrician trained in allergy testing. (3B)

## How to choose antigens?

This has already been discussed in answers to question number 7 and 8 of Section B, not being repeated here for the sake of brevity.

# Q10. What is the maximum number of allergens that can be tested at one time?

It is difficult to give the exact number of allergens to be tested at one time, as the number of alleregns to be tested depends upon the prevalence of allergens in a given region as well as various factors which might interfere with the testing procedure, interpretation of the results and adverse reactions. It is required that the two allergens should be applied at a gap of 2-3cm so as to prevent false positive results due to overlapping.777 Also, the surface area of volar aspect of forearm is variable in different individuals. In a multi-centre, open label, study by GAALEN, a pan European panel, consisting of 18 allergens was proposed to be used for SPT depending upon the prevalence of inhalant allergens.856 In a 12-year survey of fatal reactions to allergen injections and skin testing, one fatality was reported in a patient tested with 90 commercially available food allergens.<sup>849</sup> As per the available literature, the maximum number of allergens used for SPT in one sitting have varied from 58 to 78 without any reported complications or mis-interpretation of the results (Table 15).844,857 In the position paper of World Allergy Organisation on IgE allergy diagnostics, it was mentioned that the number of allergens should be kept limited due to the risk of cross-reactivity which is very common among pollens.<sup>744</sup> Also, the number of allergens to be tested in infants and young children should be kept much lower than the adults, because of the higher risk for the development of adverse reactions, and also, infants and young children are usually not sensitized to as many allergens as adults.744,777

The literature reveals that the maximum number of allergens tested in children below 5 years of age were 5–15 (Table 16).<sup>359,722</sup>

Some guidelines recommend the maximum number of skin tests which can be done at a time as 70 prick/puncture and 40 intra-cutaneous tests for inhalant allergens and  $\leq$ 30 for patients who have a history of anaphylaxis during the

Table 15. Studies reviewed to determine the maximum number of allergens that can be tested at one time during SPT

Author <sup>Ref</sup>	Number of Participants	Number of Allergen Tested
Mishra <i>et al</i> <sup>329</sup>	60	64
Chogtu <i>et al</i> <sup>348</sup>	2219	34
Sharma <i>et al</i> <sup>359</sup>	134	62
Prasad <i>et al</i> <sup>378</sup>	48	58
Kumar et al <sup>572</sup>	4835 screened (SPT done in 4263)	14
Patel et al <sup>655</sup>	24	3
Sharma <i>et al</i> <sup>783</sup>	69	60
Kumar <i>et al</i> <sup>805</sup>	49	68
Aggarwal <i>et al</i> <sup>844</sup>	100	78
Kumar <i>et al</i> <sup>845</sup>	216	14
Rasool <i>et al</i> <sup>846</sup>	400	14
Abruz <i>et al</i> <sup>854</sup>	538	50

Table 16. Studies reviewed to determine the maximum number of allergen that can be tested at one time during SPT in paediatric age groups

Author <sup>Ref</sup> Year	Study Design	Sample Size (Age in years)	Number of Allergens Tested
Tariq <i>et al</i> <sup>249</sup> 2000	Population Birth Cohort	1218 (<4)	12
Raj <i>et al</i> <sup>381</sup> 2013	Prospective Cohort	180 (5-18)	12
Kumar <i>et al</i> <sup>572</sup> 2017	Cross-sectional	4263 (2- 82 )	58
Shyna et al <sup>657</sup>	Cross-sectional	69 (6-15)	7
Yadav <i>et al</i> <sup>722</sup> 2020	Descriptive	60 (5- 15)	15
Menardo <i>et al</i> <sup>840</sup> 1985	Descriptive	78 (Infants)	5
Sahiner <i>et al</i> <sup>858</sup> 2013	Retrospective	432 (<2 )	8
Chan <i>et al</i> <sup>859</sup> 2005	Descriptive	149 (2-10)	5
Ciprandi <i>et al</i> <sup>861</sup> 2008	Prospective	139 (3-7)	12

testing.<sup>777</sup> While others state that relatively small allergen panels (*e.g.*, 8–12 inhalant allergens) would usually be considered adequate for the testing by general practitioners or in the respiratory laboratories. Use of panels between 6 and 60 allergens at a time is advocated by different authorities.<sup>748</sup> Some practitioners prefer to use standardized allergen extracts when available.<sup>744</sup> The number of allergens to be tested and selection of antigens should be based upon patient's clinical and environmental history, occupation and socio-economic factors.<sup>716</sup>

# Summary

- 1. The maximum permissible number of allergens that can be used for SPT in one sitting in adults could be upto 60.(2A)
- 2. In paediatric age group, maximum number of permissible allergens that can be tested in one sitting should be less than 12. (2A)
- 3. However, a minimum number of allergens on an individualized basis as per the clinical history, age, prevalence of aero-allergens, exposure factors and pollen calendar should be used for SPT.(2A)

# Q11. How should the patient be prepared for allergy testing?

- The testing procedure and the risk of complications should be explained to the patient before hand. Informed written consent should also be obtained for the same.<sup>748</sup> (See Annexure–I).
- Patient should be appropriately screened for the status of asthma and the presence of other contraindications to SPT as discussed in question number 9. The test should be deferred if any contraindication to SPT is present.
- The patient should have a light breakfast at least 2 hours before the test.
- Someone should accompany the patient to help in case if the patient develops any adverse reaction, like anaphylaxis.
- In case of male patients with hairy arms, it is required to shave the arms at least 48 hours before the procedure.
- Certain medications which may interfere with the test results should be stopped for a particular period of time.<sup>838,839,862</sup> These medications include:
  - short-term and long-term antihistamines,

- ➤ oral corticosteroids,
- tri-cyclic anti-depressants and other anti-depressants with anti-histamine activity,
- topical steroid ointments may interfere with the test results.

On the basis of the available literature, it is suggested to stop all these medications 1–2 weeks prior to testing. Some workers perform the test only after stopping the steroids for more than 3 weeks before the test.<sup>317,572,778,821</sup> Topical steroid ointments may interfere with the test results.<sup>863</sup>

However, different authors differ in their opinion on the effect of different drugs on SPT results. In a retrospective study, it was found that selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and proton pump inhibitors (PPIs) do not interfere with SPT. Tri-cyclic anti-depressants, H<sub>1</sub>-blockers, benzodiazepines, quetiapine, and mirtazapine should be stopped before SPT, if possible. H<sub>2</sub>-antagonists, bupropion, eszopiclone, trazodone, or zolpidem had minimal interference with the test results.837 In a single dose, doubleblind, non-cross-over study to determine the effect of tri-cyclic anti-depressants on wheal and flare of SPT, it was found that desipramine suppressed the wheal for 2 days while doxepin suppressed the wheal for 4 days, and hence, doxepin should be stopped at least 7 days before the testing.838

Some guidelines recommend omalizumab to be stopped for 4 weeks before performing SPT<sup>1</sup>. However, few studies state that omalizumab has the potential to suppress the reactivity of skin for upto 6 months.<sup>864,865</sup> Hence, based on the available literature, withholding period for various drugs before SPT has been proposed as given in table 17. Also, the patient should be enquired about the use of certain drugs which interfere with the action of epinephrine during anaphylaxis, *e.g.*, beta-blockers and ACE–inhibtors.<sup>833–836</sup> Table 18 shows withholding period of various drugs before SPT as per various studies.

### Summary

The steps of patient preparation before SPT include:

1. The testing procedure and the risk of complications should be explained to the patient before-hand. Informed written consent should also be obtained for the same. (Consent proforma given in the detailed guidelines; Annexure-I).

- 2. The test should be deferred if any contraindication to SPT is present.
- 3. The patient should have a light breakfast atleast 2 hours before the test.
- 4. Someone should accompany the patient to help in case if the patient develops any adverse reaction, like anaphylaxis.
- 5. In case of male patients with hairy arms, it is required to shave the arms atleast 48 hours before the procedure.
- 6. The medications which may interfere with the SPT results and the duration for which these drugs should be withheld before performing the SPT is given in table 17

#### Q 12. What is the procedure of performing SPT?

The various materials required for performing SPT include:

A. Allergens. The choice of allergen depends on the prevalence of certain allergens in a given region and on the basis of allergy history as discussed in previous sections. Hence, the number and choice of allergens to be tested should be decided on an individualized basis, taking into account the allergy history, the aeroallergen prevalence, exposures to other allergens and the pollen calendar.

# Table 17. Proposed withholding period of various drugs before SPT

Drugs	Withholding Period
Long-acting antihistamines	7 days
Short-acting antihistamines	72 hours
Tri-cyclic antidepressants	2 weeks
Long-term systemic steroids	2-3 weeks
Long-term topical steroids	2-3 weeks
Omalizumab	4 weeks

Table	18.	Withholding	period	of	various	drugs	before	SPT
as per	vai	rious studies						

Author <sup>Ref</sup>	Drugs Stopped Prior to Test	Duration
Patel and Choudhary <sup>317</sup>	Steroids	3 weeks
Wood et al <sup>778</sup>	Short-acting antihistamines Long-acting antihistamines (loratidine, cetirizine, fexofenadine, and hydroxyzine)	72 hours 7 days
	Tricyclic antidepressants	6 weeks
Kumar et al <sup>805</sup>	Antihistamines systemic steroids	1-4 weeks Continue inhalers
Mostafa et al <sup>821</sup>	Oral or inhaled corticosteroids Antihistamines	4 weeks

- **B. Positive and negative controls.** These are important especially during interpretation of the test results. Some patients may show dematographism or wheal from pin prick alone. A wheal of >3mm to negative control indicates dermatographism, SPT should not be done in such patients.<sup>746,748</sup> A Wheal <6mm to positive control indicates any of the following conditions:
  - (i) either, the patient is taking antihistamine or drugs with anti-histamine activity, or,
  - (ii) patient's skin is non-reactive.

Two available negative controls are 50% glycerol or saline buffer. It is recommended to use glycerinated saline buffer as negative control since it is easy to use. Similarly, out of codeine (9% solution) and histamine, histamine is the commonly used positive control. Histamine is commonly available in two concentrations (6mg/mL and 10mg/mL). In most of the studies, 10mg/mL of histamine solution is used as positive control (Table 19).<sup>317,348,359,378,572,581,778,783,800,809,840,843–846,854,855,857,866–869</sup>

- C. Devices for SPT. The various devices used to perform SPT include<sup>748</sup>
  - (i) single point which includes stallergens prick lancet, ALK Spain SPT lancet and Stallerpoint,

- (ii) dual tip which includes ALK duotip,
- (iii) multi-point which includes ALK multitest.

In allergy survey conducted by Oppenheimer and Nelson,<sup>771</sup> it was found that most of the physicians used multi-test CMI (cell mediated immunity), while Masses *et al*<sup>870</sup> observed that **IV needle** and the two metal lancets are the best tolerated.<sup>771</sup> SPT tape method has also been described but further studies are required to confirm its advantages over other techniques.<sup>843</sup> Lancet tip is most commonly a single sharp point multi-point lancet helps to test multiple allergens simultaneously.

### Summary

Lancet with a point length of 1mm is the preferred device as evidenced by the literature reviewed.

# **Procedure (Figure 4)**

Before beginning to perform SPT, it should be ensured that emergency kit to manage anaphylaxis (if it happens) has been prepared and ready. It should contain prefilled adrenaline syringe, hydrocortisone, injection atropine, antihistamine and equipment for intubation. Also, oxygen supply should be available.

- 1. Re-assure the patient and explain the test procedure.
- 2. *Site.* The test can be performed on volar aspect of the forearm, outer upper arm and back. The

Author <sup>Ref</sup>	SPT Positive Control	Negative Control	Site	Device Used	Duration of Test (minutes)
Kumar et al <sup>569</sup>	NA	NA	Volar aspect of forearam	26.5G needle	15–20
Kumar et al <sup>572</sup>	Histamine (5mg/mL)	Saline (10mg/mL)	NA	NA	
Patel et al <sup>655</sup>	NA	NA	Volar aspect of forearam	26G needle	NA
Wood <i>et al</i> <sup>778</sup>	Histamine (1.8mg/mL)	50% glycerine	NA	NA	15
Barbee <i>et al</i> <sup>812</sup>	Histamine (1mg/mL)	50% glycerine	Volar aspect of forearam	NA	20
Mostafa et al <sup>821</sup>	Histamine (6mg/mL)	Diluent with 50% glycerine	NA	Single-head metal lancet	15
Gong et al <sup>843</sup>	Histamine (10mg/mL)	Saline (10mg/mL)	Volar aspect of forearam	Single head metal lancet and tape with 4 chambers	15
Abruz <i>et al</i> <sup>854</sup>	Histamine (10mg/mL)	Glycerol saline	Volar aspect of forearam	Sterile lancet	20
Ueno <i>et al</i> <sup>855</sup>	Histamine diphophate (10mg/mL)	Saline (10mg/mL)	Volar aspect of forearam	Plastic twin-tip needles (Duotip-Test)	20

# Table 19. Studies reviewed to determine commonly used positive and negative control, site, device and testing time



Figure 4. Technique of SPT.

reactions produced on back are more than those produced on forearm.<sup>871</sup> The allergen should be applied at a site 5cm from the wrist and 3cm from ante-cubital fossa.<sup>29</sup> However, the most commonly used site is volar surface of forearm.<sup>872</sup>

- 3. Clean the skin site with alcohol prior to SPT.
- 4. Mark the positions (where allergen has to be applied) with a pen. The allergens should be applied 2cm apart to avoid overlapping and false positive results.
- 5. Apply the drop of allergen on skin with dropper without touching the dropper tip with the skin.
- 6. A sharp instrument (lancet) is passed through the drop at an angle of 45-60° or alternatively at 90° upto a depth of 0.9mm to 1mm.<sup>873</sup> Multiple prick devices are not preferred now-a-days, since these are more uncomfortable and produce larger wheal, thus interfering with the results.<sup>874</sup>
- 7. The test is usually read after 15–20 minutes. This is because after 20 minutes the skin response to histamine and allergen may diminish.
- 8. The drops must always be carefully blotted from each test site prior to taking measurements so as to avoid cross-contamination of allergen test

sites with the blotting tissue or the ruler used to measure the results.

(Method of recording and interpretation of SPT have been discussed in Q15)

- 9. After the test, clean the test site with alcohol.
- 10. Patient (particularly those with multiple positive results and history of anaphylaxis) should be observed for 20 minutes for any discomfort.<sup>875</sup>

(Note: there is no need to observe patients with negative or mild to moderate response to SPT allergens and with no history of asthma). This is because:

- Itching subsides within 15 minutes after the test, but in case if it persists, topical creams such as urex, steroid-based creams<sup>876</sup> or ice-packs may be tried. Some people prefer to use antihistamines after testing to avoid discomfort. But the evidence in support of these measures is lacking.
- Patients with high positive SPT and those with previous history of anaphylaxis may develop late phase reaction and anaphylaxis, they need to be kept under observation after the test.

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# Q 13. How to interpret SPT?

- A standardized approach for reading of SPT is lacking. Some authors prefer to immediately blot the allergen after SPT to minimize the risk of adverse reaction while the others leave the allergen for 20 minutes.<sup>877</sup> However, keeping in view of minimal risk of adverse reactions with SPT, it is recommended that allergen be left at the test site for 20 minutes before blotting.
- Histamine control should be read after 15 minutes of application (the peak time of reactivity).
- Allergen prick test should be read after 15-20 minutes (the peak time of allergen reaction).
- The outcome of the SPT can result in a variety of wheal shapes.<sup>878</sup> It is implicitly assumed that the wheal may be described reasonably well by an ellipse or circle, which is not always the case in practice and this method is prone to errors.<sup>879</sup>
- The various methods used for reading of SPT include<sup>855,857,880</sup>:
- mean wheal diameter, *i.e* mean value of the longest (D) and the mid-point orthogonal diameter (d) of the wheal(D+d/2),
- allergen induced wheal area,
- HEP (histamine equivalent prick) index diameter, *i.e* allergen-induced average, diameter divided by histamine-induced average diameter, and
- HEP-index area (allergen-induced area divided by the histamine-induced average area).

HEP-index area value 0.4 can be considered as an equal cut-off value of 3mm wheal average diameter. Average mean diameter is the most commonly used method in clinical practice, as this method provides similar accuracy.<sup>880</sup>

However, a few authors suggest that the longest wheal diameter is a better surrogate of wheal surface or planimetry than the mean wheal diameter, since it is easy and faster to perform and the diagnostic accuracy of the method improves with increasing surface area of the wheal. But it is difficult to measure the longest diameter in case the reaction is produced in the shape of pseudopodia. Adequate evidence to prove the advantage of longest wheal diameter over the mean wheal diameter is lacking.<sup>814</sup>

As evidenced from the literature, still mean wheal diameter is the most widely used method in practice.<sup>348,359,378,572,581,655,778,783,821,843–846,854,855,866,868,869</sup> (Table 20). In survey conducted by Oppenheimer and Nelson,<sup>771</sup> the most commonly used criteria for allergy testing was mean wheal diameter >3mm of negative control.

## Table 20. Grading for the SPT<sup>813</sup>

Wheal Diameter	Interpretation
0-<3mm	Negative=Negative control
3-5mm	1+
6-8mm	2+
9-11mm	3+
>11mm	4+

The SPT reaction should be measured on the longest and shortest perpendicular axis and the numbers are added and divided by 2 (mean diameter). The result should be recorded as a single figure each for wheal. The measurement of skin reaction after SPT should be done as described in figure 5.



### Figure 5. Measurement of mean wheal diameter.

Recently, new more precise methods of measuring wheal area, such as handheld scanners with appropriate computer software, end-point titration, and morphometry have been developed.<sup>881–884</sup>

A format of reporting form and recording of SPT with other details of the patient is given in *Annexure II*.

A mean wheal diameter of >3mm is taken as positive response to an allergen. A 3mm is taken as a cut-off because:

- better reproducibility,<sup>878</sup>
- studies have indicated that for many allergens, a wheal size (lower cutoff) set at a larger size than 3mm of negative control would correlate better with clinical allergen reactivity,<sup>885,886</sup>
- since trauma may affect wheal size an allergen response less than 3mm generally should not be regarded as positive.<sup>572,886,887</sup>

However, some authors state that even a cut-off of 0mm for SPT reaction to identify the subjects with detectable sIgE (>0.35 kU/L), the most appropriate cut-off appeared to be over 0mm. But appropriate evidence for the same are lacking.

**Qualitative scoring** (0 to 4+, 0 or + is no longer used by many clinicians because of marked interphysician variability in scoring and interpretation of this method.<sup>770,813</sup> However, some authors prefer to use the grading system especially before starting allergen immunotherapy (Table 21):<sup>813</sup>

Several factors may affect interpretation of the skin test results (Table 22). These include:<sup>888</sup>

- Use of ceratin drugs, like anti-histamines, long-term steroids or tri-cyclic antidepressants may interfere with the test results, thus giving false negative response.
- *Age.* Skin reactivity increases with age initially in the first decade and then declines. Wheal produced in children <2 years is smaller. Maximum skin reactivity is seen from puberty to 50 years.
- *Skin pigmentation.* The test is difficult to interpret in dark skin. Although, the accuracy of interpretation in dark skin increases with the increase in the size of wheal so produced.
- Short-term exposure to ultra-violet B radiation. It reduces wheal and flare intensity by as much as 50%.<sup>889</sup>
- *Other factors,* like inter-observer variation, faulty technique, type of device used for pricking and depth of the prick may also interfere with the results.
- *Certain skin conditions,* like dermographism, eczema may also interfere with testing results.

- *Some diseases,* like malignancy, chronic renal failure, diabetes may reduce skin test response.
- *Various physiological factors,* like menstrual cycle, circadian rhythm can also interfere with the results. But evidence to prove the same is lacking.
- *Seasonal variation* in SPT response has also been seen; the response is highly positive in the respective allergic season.

## Summary

A mean wheal diameter of >3mm more than simultaneously performed diluent control (i.e. negative control) is taken as positive response to an allergen on SPT. (2A)

# Q 14. What are the complications of SPT?

SPT is considered a relatively safe procedure, except for a few minimal complications. The complications which can occur during SPT include:

# Local

- 1. Local skin swelling is seen rarely in patients due to late phase response of IgE. This swelling can be painful in a few cases. It is more common in IDT. It usually resolves within 36 hours.
- 2. Localised wheal or flare.<sup>748</sup>

# Systemic

- 1. Systemic reactions usually begin within 15 to 30 minutes.<sup>831</sup>
- 2. Few fatal reactions have been reported in the literature. Very few fatalities have been reported during allergy testing till date, out of which seven were during IDT and only one child died during SPT with 90 aeroallergens.<sup>819,849</sup>
- 3. Prevalence of systemic reactions related to SPT with inhalant and food allergens is low but not absent. It was estimated to be less than 0.05%.<sup>890,891</sup> The prevalence of systemic reactions in young children appears to be high with a reported rate of 0.12%<sup>7</sup> and 6.5% in infants <6 months.</p>

Various risk factors for the development of reactions on SPT include:

- Infants especially <6 months<sup>842</sup>
- Past history of anaphylaxis to food

# Table 21. Studies reviewed to determine commonly employed to interpret SPT

Author <sup>Ref</sup> Year	Aim	Participants	Technique	Outcome
Oppenheimer and Nelson <sup>771</sup> (Allergy Survey) 2006	To determine the extent of the diversity in skin testing practices among allergists	539 Physicians	Smallpox needle Duotip-Test (twist technique) Duotip-Test (prick technique) Quintest Multitest CMI DermaPik (twist technique) DermaPik (prick technique)	Interpretation Commonly used criteria: wheal <b>3mm</b> >negative control (71.6% used) 14.9% used wheal > <b>5mm</b> negative control 13.5% used same size as that of histamine as positive reaction <b>Reporting</b> 53.8% used 0-4 scale (28.3% used ortho- gonal diameters)
Ueno <i>et al</i> <sup>855</sup> 2007	To retrospectively assess the diagnostic value of absolute wheal size and SI according to the outcome of controlled oral food challenges	51	SPT was performed with plastic twin-tip needles (Duotip Test, Lincoln Diagnostics, Illinois, USA) Twenty minutes after SPT, diameters of the wheals were determined	Skin index showed a better correlation with the outcome of oral food challenge than wheal diameters alone
Konstantinou <i>et al</i> <sup>857</sup> 2010	Comparis on of mean wheal diameter with longest diameter taking as gold standard the surface of the wheal skin response	74	<ul> <li>Pricking done with lancet on volar aspect of forearm</li> <li>Fifteen minutes after SPT, macroscopically evident wheal and flare reactions were marked with a pen</li> <li>(width of stroke 0.3mm) and transferred to paper with a transparent scotch tape. The paper- transferred wheals were scanned with a Hewlett- Packard PSC 1510 scanner</li> </ul>	<pre>Longest wheal diameter alone is not only a better surrogate marker of a wheal surface, in comparison with the mean diameter, but also easier and faster to measure The larger the surface of the wheal, the more appropriate the use of the longest diameter alone Reactions represent as ellipse or pseudopodia commonly and none represented as circle Longest was statistically significantly larger than mean when the surface of the wheal was 17mm<sup>2</sup> (rho longest) &gt;0.860 versus rho (mean) &lt;0.660; p&lt;0.05). Such a surface corresponds to a maximum diameter of approximately 7mm and a mean diameter of approximately 6mm</pre>
van der Valk <i>et al</i> <sup>880</sup> 2016	Measurement and standardisation of SPT	172	The SPT was performed by applying a drop of the allergen extract on the skin of the volar aspect of the forearm Twenty minutes after the skin tests, the contours of the wheal were encircled with a fine-tip pen and transferred to a record sheet by translucent tape	Scanning method for SPT measurement is more accurate to measure the wheal area in a type-I allergy than the average diameter Average wheal diameter gives an over- estimation or under-estimation of the actual area up to 50% HEP-index area value of 0.4 can be considered as an equal cut-off value of 3mm wheal average diameter Average diameter method is also useful, because this method is equally accurate in predicting cashew nut allergic reactions

Table 22.	Studies	reviewed	to ic	dentify	the 1	most	commonly	y p	performed	method	to	interr	oret	SP	ſ

Author <sup>Ref</sup>	Interprtation
Chogtu <sup>348</sup>	Mean wheal diameter >3mm
Prasad <i>et al</i> <sup>378</sup>	Mean wheal diameter >3mm of negative control
Kumar <i>et al</i> <sup>572</sup>	Grading done
Patel and Choudhary <sup>655</sup>	Mean wheal diameter >3mm of negative control (grading done as 2+3+4+)
Wood et al <sup>778</sup>	Wheal greater than or equal to one half of the diameter of the histamine control and at least 3mm larger than the diameter of the negative control
Suaad <sup>781</sup>	Wheal >3mm negative control
Sharma <i>et al</i> <sup>783</sup>	Grading done
Kumar <i>et al</i> <sup>805</sup>	Wheal >3mm of negative control
Mostafa <i>et al</i> <sup>821</sup>	Largest wheal >3mm
Gong et al <sup>843</sup>	Wheal >3mm
Mishra <i>et al</i> <sup>868</sup>	Grading done
Vander valk <i>et al</i> <sup>880</sup>	Wheal >negative control and >5mm or between 3-5mm if >70% of positive control. Wheal <3mm in negative.

- Multiple allergens<sup>881</sup>
- Testing with non-commercial food and latex extracts
- Extensive eczema
- Uncontrolled asthma

Various systemic complications include:

- 1. *Anaphylaxis.* Accidental systemic introduction of allergen can cause generalized urticaria, angioedema including airway angioedema, bronchospasm, and hypotension. The rate of systemic allergic reaction is 0.04%.<sup>890</sup>
- 2. Vasovagal syncope. It is important to differentiate between vasovagal syncope and anaphylaxis during SPT, since the management of the two conditions differs (Table 23).<sup>892</sup>

# Non-Allergic Complications<sup>748</sup>:

- 1. Risk of transmission of infection. This has never been documented, although theoretically possible.
- 2. Headache
- 3. Malaise

# Q 15. What are indications for intradermal testing in respiratory allergy?

As discussed earlier in answer to question no. 4, IDT has a low specificity and high sensitivity in comparison to SPT.<sup>774,785</sup> Hence, it has a limited role in the diagnosis of respiratory allergy.<sup>893</sup>

In a retrospective study,<sup>894</sup> clinically significant positive IDT results were seen after negative SPT. These findings were most commonly observed with dust mites, fusarium, cockroach, cocklebur, rough marsh elder and ragweed. In another retrospective chart review749 it was found that approximately 20% of patients with negative SPTs with high suspicion for allergy to specific allergens were found to have a positive IDT. The study concluded that if there is a high suspicion for allergy, especially for indoor allergens, in patients with negative SPT, IDT may be useful.749 However, in a large epidemiologic study from Tucson, Ariz, patients with histories of allergic diseases were evaluated with SPT and IDT and it was seen that in the presence of a negative SPT, a positive IDT reaction was observed more commonly in asymptomatic subjects than in symptomatic subjects.<sup>895</sup>

IDT has been shown to be useful in the diagnosis of venom hypersestivity.<sup>750,751</sup> IDT has an established place in the diagnosis of drug allergy (beta-lactam drugs, cephalosporin, etc).<sup>752</sup> IDT is often contraindicated for food allergy due to an increased risk of systemic reaction in exquisitely sensitive patients.<sup>777</sup>

Different guidelines<sup>744,746,814</sup> recommend that IDT may for used in the diagnosis of insect **venom hypersensitivity**, immediate allergy to **beta-lactam drugs**, other drugs, immediate hypersensitivity to some vaccines. These also state that skin tests for foods are potentially dangerous, are overly sensitive, increase the

#### Table 23. Difference between vasovagal reaction and anaphylaxis

Clinical Features	Vasovagal Reaction	Anaphylaxis
Duration	May develop before, during or after injection	Usually begins within 15–30 minutes after injection
Consciousness	Patient may experience dizziness but loss of consciousness is rare	Loss of consciousness occurs in severe cases
Respiration	May be slow with a period of apneoa in some cases	Coughing, chest tightness, breathlessness and wheezing are common
Pulse	Weak and slow	Rapid and sometimes irregular
Skin	Diaphoresis and pale skin	Angioedema, urticaria and pruritis Skin becomes warm
Blood pressure	Hypotension	Hypotension progressing to cardiac arrest
Gastrointestinal complaints	Nausea and vomiting	Nausea, vomiting, pain abdomen and diarrhoea
Management	Reassurance Recumbent positioning with elevation of legs Proper ventilation in the testing room	Intravenous epinephrine, steroids and anti- histaminics Intubation may be required in some cases
Prevention	Do not perform the test in sitting position Perform it in lying down position	Enquire about the history of anaphylaxis in the past

chance of a false-positive test result, and hence, are not recommended.

#### Summary

# The IDT can be done in the following indications

- 1. Patients with strong suspicion for allergy to specific allergens and negative SPT. (3B)
- 2. Venom allergy. (2A)
- 3. Drug allergy (beta-lactams, insulin, opiates, anesthetics, neuromuscular relaxants, proton-pump inhibitors, enzymes, chemotherapeutic agents, vaccines). (2A)

# Q 16. What is the relevance of serum total IgE in the diagnosis of respiratory allergy?

The role of IgE in immediate-hypersensitivity (allergic) reactions is well understood. Subjects who are readily triggered to produce IgE antibodies after exposure to common environmental allergens are defined as atopic.<sup>896</sup> Assessment of IgE antibodies is usually performed in order to evaluate atopy and IgE levels usually higher in atopic disorders.<sup>778,838</sup> An elevated total IgE is more likely to be correlated with multiple positive sIgE and SPT than normal IgE. IgE measurements in serum are performed more frequently as part of routine allergy testing. It is easy to perform with less expensive new methods and equipment. Use of long-acting antihistamines will not affect the results of serum examinations, while it can affect skin test results.896 It should be restricted to diseases in which the role of IgE has been well documented, such as allergic rhinitis,

bronchial asthma, atopic eczema, food, venom- and drug-induced anaphylaxis and bronchopulmonary aspergillosis.<sup>896</sup>

High total IgE levels may not always be attributed to atopy. There are some conditions where total IgE will be high but cannot demonstrate specific IgE antibodies against common environmental allergen as measured by SPT or serum sIgE antibodies.<sup>716,744,896,897</sup>

These include the following:

- Sensitization only to uncommon allergens
- Parasitic infestations
- Smoking
- HIV, Epstein-Barr Virus infection
- Multiple myeloma patients producingIgE
- Primary immunodeficiencies
  - Immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX)
  - Omenn syndrome
  - Wiskott-Aldrich syndrome
  - Comel-Netherton syndrome
  - Hyper-IgE syndrome
  - Atypical complete Di-George syndrome

There is no well-defined cut-off for serum total IgE for the diagnosis of various respiratory allergic disorders. It varies significantly with age, smoking habits and geography.898 Serum IgE concentration is largely age dependent. Very low levels of IgE are found in infancy with a progressive increase for first decade. Total serum IgE then declines from the second through the 8th decades of life.744 Several studies have reported serum IgE levels of 73-225 IU/mL as a marker for the presence of atopy with varying sensitivity and specificity.242,899-910 The reported mean total IgE levels of normal non-atopic population in various studies are between 30-66 IU/mL.903,906,908-912 Mean value of total IgE based on Indian Studies is varies from 65-128 IU/mL in non-atopic population and 269-1136 IU/m L in atopic population.845,867,912-917 Majority of Indian studies are hospital-based

compared to studies conducted overseas. The Euro-Prevall INCO study on prevalence of food sensitization and probable food allergy among adults in India<sup>923</sup> reported that the mean value of total IgE was 529IU/L. Another study by Yadav *et al*<sup>912</sup> reported the mean value of total IgE in non-allergic normal children of less than 15 years of age was 65.8IU/mL.

According to the available literatures, the agewise cut-offs for total IgE are 63–132 IU/mL, 100– 163IU/mL and 100–196 IU/mL in the age group of <6 year, 6–14 years and >14 year respectively.<sup>899–910</sup> Tables 24 and 25 shows characteristics of various Indian and non-Indian studies reviewed to identify relevance of total IgE in diagnosis of respiratory allergy.

The extent of tissue involvement appears to

Kumar et all <sup>845</sup> Delhi 2006 Hospital-basedBA, AR Food allergy216Cut-off->265 Healthy controls-41Maximum patients (n=56) with elevated IgE (201 to 8800U/mL) were in 21-30 years age group scrum total IgE of 265IU/mL or more with marked positive SPT (4mm or more) can serve as marker for atopy and food sensitization. slgE, three times of normal controls correlates wellSharma et all <sup>867</sup> BA, AR700BA-634 AR-327 Controls-150The IgE levels in Indian allergic patients are significantly related to atopy, but due to wide overlap of IgE levels in patients and healthy subjects, its diagnostic significance in Indian normal Indian childrenYadav et al <sup>942</sup> Non-allergic normal Indian children350Cut-off-65.8Mean serum IgE value was 65.8±4.0 IU/mL being significantly high in males (75.0±2.7 IU/mL) as compared to females (56.6 ± 3.0 IU/mL).Population-based0-15 years of ageControls-163.8 BA-588High Serum Immunoglobulin E levels were found in childhood asthmatics as compared to normal subjects.Itary PradeshBACase-60 Controls-519Controls-152 Severe BA-1045.32High in asthmatics as compared to normal subjects. On an average, the levels increased as the severity of an average, the levels increased as the severity of asthmatic at al <sup>7145</sup> Mesena et al <sup>7145</sup> AR AR134312.18Total serum IgE can be considered as a supportive and suggestive indicator of atopy in allergic rhinitis the sing asthma increasedMespital-based-14 years of age134312.18Total serum IgE can be considered as a supportive and suggestive indicator of atopy in allergic rhinitis <th>Author<sup>Ref</sup> Place, Year Type of Study</th> <th>Allergic Disease</th> <th>Sample Size</th> <th>Mean Value of Total IgE</th> <th>Conclusion</th>	Author <sup>Ref</sup> Place, Year Type of Study	Allergic Disease	Sample Size	Mean Value of Total IgE	Conclusion
Sharma et al Delhi 2006BA, AR700BA-634 AR-327 Controls-150The IgE levels in Indian allergic patients are significantly related to atopy, but due to wide overlap of IgE levels in patients and healthy subjects, its diagnostic significance in Indian population seems to be limitedYadav et al P194Non-allergic normal Indian children350Cut-off-65.8Mean serum IgE value was 65.8±4.0 IU/mL being significantly high in males (75.0±2.7 IU/mL) as compared to females (56.6 ± 3.0 IU/mL).Population-based0-15 years of ageControls-163.8Mean serum IgE value was 65.8±4.0 IU/mL being significantly high in males (75.0±2.7 IU/mL) as compared to females (56.6 ± 3.0 IU/mL).Rathoria et al P13BA 	Kumar <i>et al</i> <sup>845</sup> Delhi 2006 Hospital-based	BA, AR Food allergy	216	Cut-off->265 Healthy controls-41	Maximum patients (n=56) with elevated IgE (201 to >800IU/mL) were in 21–30 years age group Serum total IgE of 265IU/mL or more with marked positive SPT (4mm or more) can serve as marker for atopy and food sensitization. sIgE, three times of normal controls correlates well
Yadav et al 1994Non-allergic normal Indian children350Cut-off-65.8Mean serum IgE value was 65.8±4.0 IU/mL being significantly high in males (75.0±2.7 IU/mL) as compared to females (56.6 ± 3.0 IU/mL).Population-based0-15 years of ageKSS	Sharma <i>et al</i> <sup>867</sup> Delhi 2006 Hospital-based Case-control	BA, AR	700	BA-634 AR-327 Controls-150	The IgE levels in Indian allergic patients are significantly related to atopy, but due to wide overlap of IgE levels in patients and healthy subjects, its diagnostic significance in Indian population seems to be limited
Rathoria et al913 Uttar Pradesh 2018BA 5-15 years of age S-15 years of age Controls-58BA-58 Controls-58 BA-881.8High Serum Immunoglobulin E levels were found in childhood asthmatics as compared to normal subjectsHospital-based	Yadav <i>et al</i> <sup>912</sup> 1994 Population-based	Non-allergic normal Indian children 0–15 years of age	350	Cut-off-65.8	Mean serum IgE value was $65.8\pm4.0$ IU/mL being significantly high in males ( $75.0\pm2.7$ IU/mL) as compared to females ( $56.6\pm3.0$ IU/mL).
Roopkala et alBACase-60 Controls-12 BA-756 Severe BA-1045.32High in asthmatics as compared to normal subjects. On an average, the levels increased as the severity of asthma increasedHospital-basedAR134312.18Total serum IgE can be considered as a supportive and suggestive indicator of atopy in allergic rhinitisHospital-basedVVVVProspectiveVVVV	Rathoria <i>et al</i> <sup>913</sup> Uttar Pradesh 2018 Hospital-based	BA 5–15 years of age	BA–58 Controls–58	Controls–163.8 BA–881.8	High Serum Immunoglobulin E levels were found in childhood asthmatics as compared to normal subjects
Meena et al915AR134312.18Total serum IgE can be considered as a supportive and suggestive indicator of atopy in allergic rhinitisRajasthan 2016Hospital-basedFor spectiveFor spectiveProspectiveFor spectiveFor spectiveFor spective	Roopkala <i>et al</i> <sup>914</sup> Karnataka 2010 Hospital-based	BA	Case-60 Controls-13	Controls-152 BA-756 Severe BA-1045.32	High in asthmatics as compared to normal subjects. On an average, the levels increased as the severity of asthma increased
	Meena <i>et al</i> <sup>915</sup> Rajasthan 2016 Hospital-based Prospective	AR 6–14 years of age	134	312.18	Total serum IgE can be considered as a supportive and suggestive indicator of atopy in allergic rhinitis

Table 24. Charecteristics of various Indian studies reviwed to identify the relevance of IgE for diagnosis of respiratoy allergy

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Cont...

Author <sup>Ref</sup> Place, Year Type of Study	Allergic Disease	Sample Size	Mean Value of Total IgE	Conclusion
Lama <i>et al</i> <sup>916</sup> West Bengal 2013 Hospital-based	BA 3–12 years of age	134	BA-269 Controls-146	The elevated level of total serum IgE may demonstrate the allergic aetiology of asthma in the subjects studied
Kumar <i>et al</i> <sup>917</sup> Puducherry 2017 Hospital-based	BA	77	1136	The assessment of sputum eosinophil count is simple, inexpensive, non-invasive, and direct measurement of airway inflammation. It could be the preferred method in monitoring airway inflammation and guided management in day-to-day practice
Mahesh <i>et al</i> <sup>923</sup> (Europrev all- INCO) Karnataka 2016 Population based Case-control	Food allergy (other BA, AR, skin allergy)	Subjects screened– 11791 Case–241 Controls– 347	Mean-529	Very high levels of sensitization were observed for most foods, including those not commonly consumed in the general population. For the levels of sensitization, the prevalence of probable food allergy was low
Anupama <i>et al</i> <sup>924</sup> Karnataka 2005 Hospital-based	ВА	Case-132 Controls-30	Controls-127.5 BA Mild-213 Moderate-489 Severe-1059	Presumably provide a better clue to atopy and the detection of specific IgE would be a prerequisite for both the definitive diagnosis and the therapeutic strategy for bronchial asthma
Goel <i>et al</i> <sup>925</sup> Delhi 2008 Hospital-based	Smokers–25 Reformed smokers–22 Non- smokers–23	70	Smokers serum total IgE levels (328.80±161.82IU/mL) Reformed smokers 177.27±86.47IU/mL) Non-smokers (29.56±9.75 IU/mL)	Smokers had significantly higher IgE serum levels than reformed smokers and non-smokers. Smoking seems to induce an atopic orientation and allergen sensitisation in individuals

have a determining effect on serum IgE levels, with greatest involvement and highest levels in atopic eczema, the lowest levels are observed among rhinitis and the intermediate in asthmatics.<sup>906</sup> Total IgE poorly correlates with the severity of atopy, except in allergic bronchopulmonary aspergillosis, where the presence of high levels of IgE are closely related to the disease severity.<sup>113</sup>

The anti-inflammatory effects of omalizumab and its clinical benefits in patients with moderateto-severe asthma emphasize the fundamental importance of IgE in allergic inflammation.<sup>918-920</sup> Omalizumab is effective in controlling asthma symptoms and produced clinical improvement in severe asthma patients with IgE levels between 30–700 IU/mL.<sup>918</sup> It also reduced the need for systemic corticosteroids in patients with IgE levels >700IU/mL.<sup>921</sup> Exact dose of omalizumab is individualized on the basis of baseline serum IgE measurements and body-weight.<sup>922</sup>

#### Summary

1. Sensitivity and specificity of serum total IgE is very low for diagnosing respiratory allergy and it should not be considered as a reliable marker of allergy status. (2A)

- 2. Serum total IgE is one of the reliable markers for following disease severity and therapeutic response in allergic bronchopulmonary aspergillosis. (1A)
- 3. Serum total IgE values have significance in omalizumab therapy. (1A)

#### Q 17. What are the indications for serum sIgE testing?

The indications for serum sIgE testing are as follows:  $^{713,748,813}$ 

- 1. In cases with inconclusive SPTs and high suspicion of allergy based on the history.
- 2. Inability to temporarily discontinue skin test suppressive medication therapy (*e.g.*, antihistaminics, antidepressants or betablockers).
- 3. Presence of extensive skin disease (*e.g.*, dermatographism or generalizedeczema).
- 4. Un-cooperative patient.
- 5. Clinical history suggestive of high risk of anaphylaxis from skin testing.

Author <sup>Ref</sup> Place, Year Type of Study	Allergic Disease	Sample Size	Mean Value of Total IgE	Conclusion
Tu <i>et al</i> <sup>899</sup> Taiwan 2013 Population- based	BA, AR, AD	1321	Cut-off-77.7 Sen-82.3 Sp-87.1 Cut-off BA-315.0kIU/L AR-89.0 kIU/L Eczema-122.0kIU/L But with modest accuracy	Total IgE discriminate Asian children with or without atopy independent of allergic symptoms with a cut- off of 77.7 kIU/L The study confirms the insufficient diagnostic accuracy of total IgE alone to detect allergic diseases, but low total IgE levels may help exclude allergic diseases
Simoni <i>et al</i> <sup>900</sup> North Italy 2001 Population- based	BA, AR	1905	Normal versus Asthma Cut-off-Male-42 (Sn-60, Sp-63) Female-25 (Sn-60, Sp-57) Normal versus Rhinitis Cut-off-Male-40 (Sn-54, Sp-60) Female-23 (Sn-56, Sp-55)	Diagnostic sensitivity was low, but specificity was high Low levels of IgE can exclude asthma or allergic rhinitis
Kulig <i>et al</i> <sup>901</sup> Germany 1999 Population- based Prospective cohort	Children <6 years old	1160	100	Total serum IgE levels for a large population-based sample were lower than most values previously reported and suggest that for both clinical and epidemiologic and genetic studies, IgE values should be expressed with percentiles
Guilbert <i>et al</i> <sup>902</sup> Tucson, USA 2004 Population- based	Atopic Prevention of early Asthma in Kids (PEAK)Trial	284 2-3 years of age	Cut-off-100	Male children were significantly more likely to be sensitized to aeroallergens and to have a blood eosinophil level of 4% or greater (P=0.03) and a total serum IgE level of greater than 100IU/mL (P=0.0004).
Lindberg and Arroyave <sup>903</sup> USA 1986 Hospital- based	Non-allergic- 346 Allergic-301	346+301	Non allergic patients–45.4IU/mL 13 to 16 years of age Cut-off–100 for 13–16 years of age	To differentiate allergic and non-allergic–10IU/mL for less than 1 year to 100IU/mL at 13 to 16 years of age The diagnostic sensitivity and specificity of the assay, based on the cut-off values were 83% and 91%, respectively
Witting <i>et al</i> <sup>906</sup> Florida, Georgia, Albamia 1980 Population- based	BA, AR Atopic dermatitis	Controls- 544 BA without AD-570 AR only- 244 AD without BA-49 BA & AD-48	32 305 171 273 985 Cutt-off–100IU/L	Routine measurement in allergic patients helps to assess the presence and severity of atopic sensitisation Helps to differentiate allergic and non allergic asthma, but less likely in rhinitis, urticaria, eczema For patients above 5 years of age, it seems useful to consider 100IU/L sIgE the ULN For discriminating atopic from non-atopic Extend of tissue involvement appears to have a determining effect on serum IgE levels

# Table 25. Characteristics of various non-Indian studies reviewed to identify the relevance of IgE for diagnosis of respiratoy allergy

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Place, Year

**Type of Study** 

Ezeamuzie et al<sup>907</sup>

Burrows et al<sup>908</sup>

USA 1989

Borish *et al*<sup>909</sup>

USA 2005

Hospital-

Burr *et al*<sup>910</sup>

South Wales, England 1975 Populationbased

Barbee *et al*<sup>911</sup>

USA 1981 Populationbased Tucson Epidemiological

Study

Sherill *et al*<sup>926</sup>

based

Kuwait 1999

Population

based

Allergic

Disease

BA

AR

Atopic

BA-177

(phadiatop+)

Non-Atopic (phadiatop-)

Controls-2480

BA (6 years

severe or

asthma)

BA

or older with

Non-allergic

population

BA, AR

2005-2006

difficult-to-treat

Cont... Author<sup>Ref</sup>

# The Indian Journal of Chest Diseases & Allied Sciences

Sample Size	Mean Value of Total IgE	Conclusion
1057	Asymptomatic atopics–43.7 kIU/L Symptomatic atopics–213.8 Extrinsic	These results show that the normal total IgE values in the young adult Kuwaiti population are generally high and that the distribution of the values is so wide that the diagnostic value of total serum IgE in this community is likely to be very limited
2657	asthmatics–626.6 kIU/L Control–18–46	Asthma is almost always associated with some type
	BA-56-224	of IgE-related reaction, and therefore has an allergic basis, although not all the allergic stimuli that cause asthma appear to have been included in the battery of common aeroallergens we used to assess atopic status
4756	Mean of population–106	Patients with severe or difficult- to-treat asthma from the TENOR study, higher total IgE levels were observed in males, children, smokers, non-white racial/ethnic groups, and adults with childhood- onset disease In addition, IgE levels are associated with asthma severity among younger patients
574	Controls-35-41 BA-60-250	Strong allergic tendencies, as shown by personal and family history, skin tests, and serum IgE levels
3500	Cut-off-32.1	Subjects with positive skin test results have several times higher the concentration of IgE as their non- atopic counterparts
540	NA	Both persistent wheezing and early sensitization were associated with high serum IgE levels at all ages
6-7 years of	127.7 IU/L in 6-7	The cut-off levels of 258.8kIU/L in 6–7 years old

USA 1999				
Population- based				
Kim <i>et al</i> <sup>927</sup> Korea 2017 Population- pased	BA, AR, AD	6-7 years of age[3753] 12-13 years of age [3930]	127.7 IU/L in 6-7 years of age 63IU/L in 12-13 years of age	The cut-off levels of 258.8kIU/L in 6–7 years old and 38.4kIU/L in 12–13 years old for the prediction of atopy showed sufficiently high values (≥70%) in Korean children
Gergen <i>et al</i> <sup>928</sup> USA 2009 Population- pased	Results from the National Health and Nutrition Examination Survey (NHANES)	7398	51.8 IU/L in 6-11 years of age 54.4 IU/L in 12-15 years of age	Total IgE is associated with asthma only among persons who are positive to at least one allergen- specific IgEs Asthma independent of IgE is not uncommon in the US populations

310

Cont				
Author <sup>Ref</sup> Place, Year Type of Study	Allergic Disease	Sample Size	Mean Value of Total IgE	Conclusion
Carosso <i>et al</i> <sup>928</sup> 10 Western European Countries 2006 Population- based	European Community Respiratory Health Survey II	6670	The 95th percentile of IgE reference values in non- smokers was 148kIU/L in women and 169kIU/L in men	Due to the adequate specificity, IgE values exceeding the normal limits confirm a suspected atopic status; however, because of the low sensitivity, values below the cut-off seem not to exclude an atopic status with sufficient accuracy
Campos <i>et al</i> <sup>930</sup> Valencia, Spain 2005 Hospital-based	BA, AR	Cases-100 Controls-69	Controls–46.5 Cases–204 Cut-off–183	Establishing an arbitrary cut-off point of 1.65 standard deviations (SD) (equivalent to 95% of the donor population), we obtained a figure of >183kIU/L whereby 44% of all allergic individuals presented a value below this cut-off point
Hansen <i>et al</i> <sup>931</sup>	113 children with cord blood IgE	113+138	63	A total IgE level >63kIU/L at the age of 5 years can be regarded as being an elevated level
Hospital-based	levels ≥0.5 kIU/L 138 children chosen at random among those with cord blood IgE levels <0.5 kIU/L	age		A cord blood IgE level ≥0.3kIU/l in combination with atopic predisposition was predictive of allergic disease, especially allergic bronchial asthma
Dodig <i>et al</i> <sup>932</sup>	Atopic and	Atopic-4620	<6 year–73	The 95th percentile for total IgE in non-atopic children
Croatia 2006	<16 years of age	Non- atopic–3355	<16 year–100	taken as cut-off values in children up to 8 years of age, after which significant percentile discrepancies between non-atopic and atopic children were recorded
Mughales <i>et al</i> <sup>933</sup>	BA, AR Food allergy	1893	Cut-off->196	Total IgE assay is not efficient as a diagnostic test for foods, inhalant, or multiple allergies
Saudi Arabia 2016	rood unergy			The best strategy should refer to specific IgE testing guided by a comprehensive atopic history
Hospital-based Carsin <i>et al</i> <sup>934</sup> <i>ECRHS is a</i> <i>multi -centre</i> <i>study involving</i> 29 <i>centres</i> 2013 Population-	BA, AR	9175	Atopy–80 Non-atopy–26	After taking into account the number and intensity of 4 specific IgEs, the serum total IgE level was not associated with new-onset asthma in adults
based Longitudinal study				
Zetterstom and Johansson <sup>935</sup>	BA	Controls75 Case445	100	A serum IgE value above 100 kIU/L in a patient is strong evidence for the presence of an atopic disease while a value below 20 kIU/L indicates that the symptoms are due to intrinsic or infectious disease
Population- Based				

# Q 18. What is the role of nasal allergen provocation test in diagnosing respiratory allergy?

The role of nasal allergen provocation test can be divided in two groups.

A. Clinical Indications

- 1. Diagnosis of
  - (a) Persistent allergic rhinitis<sup>739,936</sup>
  - (b) Intermittent allergic rhinitis<sup>936,937</sup>
  - (c) Local allergic rhinitis<sup>938–941</sup>
  - (d) Occupational rhinitis<sup>942–945</sup>
- 2. Establishing correlation with extranasal symptoms with allergic rhinitis (including conjunctiva, middle ear, and sinus).<sup>946–950</sup>
- 3. Designing allergen composition and monitoring the clinical efficacy of immunotherapy for patients with allergic rhinitis.<sup>739,951–953</sup>
- 4. Determining clinical relevance of a specific allergen in patients of allergic rhinitis with multiple positive allergy skin tests.<sup>954</sup>
- 5. When there is discrepancy between history and SPT or sIgE result for the diagnosis of allergic rhinitis.<sup>739</sup>
- 6. To confirm nasal reactivity before starting local nasal immunotherapy.<sup>955</sup>
- B. Scientific Investigations
- 1. To study immediate and late phase responses induced by specific allergen.<sup>956-958</sup>
- Correlating cellular morphological response to specific inhaled allergen using nasal lavage, biopsy, and brushing<sup>959,960</sup>
- Detecting chemical mediators, markers of glandular exocytosis, and vascular permeability in nasal lavage following allergen provocation<sup>961</sup>
- To examine the therapeutic effects of drugs(anti-histamines, corticosteroids, cromoglycate, anti-cholinergic medications, and vasoconstrictors) on acute, late phase, non-specific, and other aspects of airway diseases<sup>962,963</sup>

According to some authorities, nasal provocation test indicated for diagnosis of persisting allergic rhinitis, intermittent allergic rhinitis, local allergic rhinitis, occupational rhinitis. It was also used for establishing correlation with extra-nasal symptoms. It may also be used for designing the allergen composition and for monitoring the clinical efficacy of immunotherapy.814 According to World Allergy Organisation (WAO) (2016), nasal provocation test is performed to confirm the diagnosis of allergic rhinitis when there is a discrepancy between the symptoms and the results of SPT and/or serum sIgE; for objectively assessing the disease severity and for monitoring the response to pharmacologic treatment for specific immunotherapy in allergic rhinitis; for studying the pathophysiological mechanisms of allergic inflammation; for diagnosing occupational rhinitis and also for diagnosing of local allergic rhinitis.964

## Summary

- Nasal allergen provocation test (NAPT) is of limited clinical value and is mainly indicated for research purposes. (2A)<sup>\$13,965</sup>
- 2. Under the current conditions in India, NAPT is advised in tertiary care centres only, keeping in view the possibility of anaphylactic reaction.<sup>966</sup> (2A)
- 3. Unavailability of standardised allergens specific to Indian conditions further limits the utility of this test.

# Q 19. What is the role of fractional exhaled nitric oxide (FeNO) and pulmonary function tests in diagnosing respiratory allergy?

# Role of FeNO in asthma

According to the unified allergic airway hypothesis, atopic patients of allergic rhinitis may have symptomatic/asymptomatic lower airway inflammation. FeNO can be used as a marker of lower airway inflammation.<sup>716</sup> FeNO levels were found to be significantly higher in patients with atopic allergic rhinitis.<sup>967-971</sup> A positive correlation is seen in between FeNO and positive SPTs in various studies involving patients with allergic rhinitis and asthma.<sup>263,869,972</sup> In asthmatics, serum total IgE correlates with FeNO levels. However correlation between FeNO and spirometric values have not been distinctly defined.<sup>970,987</sup> The FeNO levels can be influenced by anthropometric variables. Increasing levels of FeNO is seen in patients with higher age, height, weight and body mass index. Males are found to have higher levels of FeNO as compared to females.<sup>988–990</sup>

It was found that specificity was higher than sensitivity, which indicates that FeNO has a higher diagnostic potential for the diagnosis of asthma than that of ruling it out.974-986,991-999 FeNO could also help to decide whether or not to use inhaled corticosteroids by acting as a surrogate marker of airway inflammation.<sup>991</sup> FeNO correlates well with traditionally used markers of asthma control and may be a useful tool as a measure of treatment response.977,997,998 Some Societies strongly recommend that in adult asthma patients FeNO level >50ppb indicates eosinophilic inflammation and that such asthma patients if symptomatic are more likely to respond to corticosteroids. Further, it has also been found that FeNO values <25ppb indicates that both eosinophilic inflammation and responsiveness to corticosteroids are less likely.992 Some guidelines conclude that nonsmoker adults with FeNO levels of >20ppb have associated eosinophilic inflammation in the airways, whereas, others have established a cutoff value for diagnosing asthma as a >40ppb in adults and FeNO levels of >35ppb in children (Tables 26 and 27).975

# **Role of PFT in Asthma**

# A.Spirometry

It is considered as gold standard for the diagnosis and assessment of asthma.<sup>994</sup> Since spirometry is an effort dependent method, its practical utility is limited in younger children and elderly. Diagnosis of asthma can be ascertained if there is an evidence of reversible bronchoconstriction.

Global initiative for asthma (GINA) defines a positive bronchodilator reversibility test as follows<sup>994</sup>:

*Adults.* An increase in FEV<sub>1</sub> of >12% and >200mL from the baseline, 10–15 minutes after 200–400mcg albuterol or equivalent (greater confidence if increase is >15% and >400 mL).

*Children.* An increase in  $FEV_1$  of >12% predicted.

Ideal time for performing spirometry is at the time of diagnosis or at the start of treatment and after 3–6 months of controller treatment to assess the patient's personal best FEV<sub>1</sub>. It should be periodically repeated depending upon the age and the risk of the exacerbation. In adults spirometry should be done at least every 1-2 years, but it should be done more frequently in patients with higher risk, *i.e.* in patients with frequent exacerbations. In children it should be done frequently based on asthma severity and clinical course.

Asthma control tools often have lung function numerically averaged or added with symptoms, for the assessment of patient's response.<sup>980,981</sup> However, there is a high risk of exacerbations in patients with low FEV<sub>1</sub> even after adjustment for symptom frequency.<sup>982,994</sup>

# B. Impulse oscillometry

Airway resistance, reactance and impedance in the airways can be determined using sound waves by the use of impulse oscillomtery.<sup>995</sup> It can also detect peripheral airway obstruction, with minimal patient's cooperation, that may be missed by conventional spirometry.<sup>996</sup>

# C. Peak expiratory flow rate

During domiciliary care, peak expiratory flow rate can play a role in monitoring of lung functions in asthmatics. Diurnal variability in lung functions is generally seen in patients diagnosed with asthma.

# Summary

1.

- FeNO is not necessary for making a diagnosis of allergic asthma. (1A)
- 2. High FeNO levels are suggestive of eosinophilic/allergic asthma. (2A)
- 3. In adults: FeNO >50ppb and in children FeNO >35ppb signifies eosinophilic inflammation and likelihood of corticosteroids responsiveness in symptomatic asthma patients. (2A)
- 4. FeNO may be an useful tool as follow up and assessment of treatment response in asthma. (3A)
- 5. Spirometry is an essential diagnostic modality for diagnosis and follow up of allergic asthma. (1A)

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Author <sup>Ref</sup> Country Year	Study Design	Age Group (Range in Years)/ (Mean and SD)	Number of Patients	Measurement Device	FeNO Level (ppb)	Reference Standard	Senstivity	Specificity
Heffler <i>et al<sup>767</sup></i> Italy 2018	Prospective	Mainly adults (11–75)	48	NIOX Flex (c)	36	FEV <sub>1</sub> /VC (+reversibility) Bronchial provocation	0.48	0.98
Kumar <i>et al<sup>967</sup></i> India 2013	Cross-sectionl	Adults	528	NIOX chemiluminescence	19.45	FEV <sub>1</sub> /VC (+reversibility)	0.71	0.81
Arora et al <sup>977</sup> USA 2006	Prospective	Adults (17–38)	172	NIOX – no further specification	17	Bronchial provocation	0.63	0.59
Cordeiro <i>et al<sup>978</sup></i> Netherlands 2011	Observational and cross-sectional	Mainly adults (7–87)	114	NIOX Flex (c)	27	FEV <sub>1</sub> /VC (+reversibility) Bronchial provocation	0.78	16.0
Florentin <i>et al<sup>979</sup></i> France 2014	Nested case-control	Young adults (mean 25±SD 3)	178	NIOX Mino (e)	10.5	FEV <sub>1</sub> /VC (+reversibility) PEF variability	0.68	0.56
Fortuna <i>et al</i> <sup>980</sup> Spain 2007	Prospective	Adults (18–64)	50	SIR N-6008 (c)	20	Bronchial provocation	0.76	0.64
Fukuhara <i>et al</i> <sup>981</sup> Japan 2011	Prospective	Adults (48–66)	61	NA623N (c)	40	FEV <sub>1</sub> /VC (+reversibility) Bronchial provocation	0.16	0.88
Giovannini et al <sup>982</sup> Italy 2014	Cross-sectional	Mainly adults (mean 38±SD 15)	42	HypAir FENO (e)	30	Bronchial provocation	0.76	0.98
Katsoulis <i>et al</i> <sup>983</sup> Greece 2013	Prospective	Adults (22–37)	112	NIOX Mino (e)	32	Bronchial provocation	0.52	0.60
Kostikas <i>et al</i> <sup>984</sup> Greece 2008	Cross-sectional	Young adults (mean 21±SD 2)	149	NIOX Mino (e)	19	FEV <sub>1</sub> /VC (+reversibility) Bronchial provocation	0.88	0.84
Kowal <i>et al</i> <sup>985</sup> Poland 2009	Prospective	Adults (18–45)	540	Sievers 280i (c)	40	FEV <sub>1</sub> /VC (+reversibility) Bronchial provocation PEF variability	0.71	0.84
Linkosalo <i>et a</i> l <sup>986</sup> Finland 2012	Case-control	Children (6–19)	30	Sievers 280 (c)	20	Free running test	0.56	0.83

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Guidelines	FeNO Cut-offs	Comments
NICE <sup>973</sup>	Adults Positive: > <b>40ppb</b> Children (5–16 years): Positive: > <b>35ppb</b>	In children (5–16 years): normal spirometry or obstructive spirometry with a negative bronchodilator reversibility test
Scottish Consensus Statement <sup>974</sup>	ICS-naïve patients > <b>40ppb</b> Patients taking ICS > <b>25ppb</b>	Should be used in along with blood eosinophils, spirometry and a history suggesting asthma
GINA <sup>975</sup>	Adults ≥ <b>20ppb</b>	Associated with eosinophilic inflammation (in non- smokers)
ATS/ERS <sup>976</sup>	Adults High: >50ppb Intermediate 25-50ppb Low: <25ppb Children High: >35ppb Intermediate: 20-35ppb Low: <20ppb	Eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids likely Cautious interpretation required Eosinophilic inflammation and responsiveness to corticosteroids less likely Eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids likely Cautious interpretation required Eosinophilic inflammation and responsiveness to corticosteroids less likely

# Table 27. Summary of diagnostic cut-off values for diagnosis of asthma in different guidelines

# **Diagnostic Testing for Respiratory Allergy: A Glance**

- The *in vivo* tests for the diagnosis of respiratory allergic diseases are skin prick test, intradermal test, patch test and allergen provocation tests.
- The various *in vitro* tests used for diagnosing respiratory allergy include serum IgE assays (serum total IgE and serum specific IgE) and cell-based assays (basophil activation test).
- SPT when combined with clinical history is the most accurate diagnostic test, and hence, is considered as the gold standard for the diagnosis of respiratory allergy.
- IDT has higher sensitivity but limited diagnostic accuracy.
- *In vitro* test, *i.e* serum specific IgE is both less sensitive and less specific compared to SPT.
- SPT is indicated for the diagnosing of respiratory allergy (by inhalant allergens, food allergens and drugs), as reference standard for *in vitro* tests for the diagnosis of respiratory allergy and for determining bioequivalent potency of allergen extracts.
- SPT should be performed by an allergy specialist/ physician or pediatrician formally trained in allergy testing or by a trained nurse/technician under the supervision of an experienced physician, well versed in the management of anaphylactic reactions.
- SPT should not be performed during acute phase of the disease/uncontrolled asthma. It should be done after at least a gap of 3-4 weeks from systemic allergic reactions.
- SPT is contraindicated in pregnancy and lactation, dermatographism, in the absence of normal skin, un-cooperative patient, patients on drugs that hinder the action of epinephrine (*e.g.*, beta-blockers and ACE-inhibtors) or drugs which might interfere with test results (like, anti-histamines, TCA and steroids) and in young children <5 years (relative contra-indication).
- SPT should preferably be done in children >5 years of age and if strongly indicated, it can be performed in <5 years children, under the supervision of a paediatrician trained in allergy testing.

- A minimum number of allergens on the individualized basis – as per the clinical history, age, prevalence of aeroallergens, exposure factors and pollen calendar – should be used for SPT. The maximum permissible number of allergens that can be used for SPT in one sitting in adults is <60 and <12 in the pediatric age group.
- Certain medications like short-term and longterm antihistamines, oral corticosteroids, tri-cyclic anti-depressants and other anti-depressants with anti-histamine activity, topical steroid ointments may interfere with the SPT results and should be stopped 1-2 weeks prior to the test.
- The technique of performing SPT is explained in the following image:
- Lancet with a point length of 1.0mm is the preferred device. 10mg/mL of histamine solution and glycerinated saline buffer are the commonly used positive control and negative controls, respectively.
- A mean wheal diameter of >3mm more than simultaneously performed diluent control (*i.e.*, negative control) is taken as positive response to an allergen on SPT.
- The various complications of SPT include local swelling, anaphylaxis, vasovagal syncope, headache, malaise etc.
- The indications of IDT include negative SPT in patients with strong suspicion for allergy to specific allergens or in cases of venom allergy and drug allergy.
- Sensitivity and specificity of serum total IgE is very low for diagnosing respiratory allergy and it should not be considered as a reliable marker of allergy status.
- Serum specific IgE is indicated in cases with inconclusive SPT and high clinical suspicion of allergy, inability to temporarily discontinue skin test suppressive medication therapy, presence of extensive skin disease (*e.g.*, dermatographism or generalized eczema), un-cooperative patient, or patients at high risk of developing anaphylaxis during SPT.



- Nasal allergen provocation test is of limited clinical value due to high risk of anaphylaxis and unavailability of standardized allergens. It is mainly indicated for research purposes. Under the current conditions in India, NAPT is advised in tertiary care centres only. Unavailability of standardised allergens specific to Indian conditions further limits the utility of this test.
- FeNO is not necessary for making a diagnosis of allergic asthma but it can serve as a useful tool for follow up and assessment of treatment response in asthma. High FeNO levels are suggestive of eosinophilic /allergic asthma.
- *In vitro* test, *i.e.* serum specific IgE, is both less sensitive and less specific compared to SPT for the diagnosis of respiratory allergy. The indications for testing are inconclusive SPT and high suspicion of allergy based on the history,

inability to temporarily discontinue skin test suppressive medication therapy, presence of extensive skin disease (*e.g.*, dermatographism or generalized eczema), uncooperative patient and clinical history suggestive of high risk of anaphylaxis from skin testing.

- Serum IgE levels usually higher in atopic disorders. Sensitivity and specificity of serum total IgE is very low for diagnosing respiratory allergy and it should not be considered as a reliable marker of allergy status. Serum total IgE is one of the reliable markers for following disease severity and therapeutic response in allergic bronchopulmonary aspergillosis. Also, serum total IgE values have significance in omalizumab therapy.
- Spirometry is an essential diagnostic modality for diagnosis and follow up of allergic asthma.

# Annexure I

# **Consent Form**

I,\_\_\_\_\_\_, OPD Registration Number \_\_\_\_\_\_ S/O,D/O,W/O\_\_\_\_\_\_ Resident of \_\_\_\_\_\_ have been advised by Dr \_\_\_\_\_\_ to undergo skin prick test with aeroallergens/food allergens/*Aspergillus* spp/other fungus spp. I have been fully informed to my satisfaction by the attending physician, the purpose and risk involved in the test.

I hereby give my consent for the test.

Name and signature of the physician

Date and Time

Signature of patient/guardian

Date and Time

# Annexure II

# Format of SPT Reporting Form

Patient's Name				
Age/Gender				
Regd No.				
Address				
Name of Physician				
Name of Testing Technic	cian			
Diagnosis				
Last Use of Anti-histami	ne (or other medications affecting the	e response to histamine)		
Date and Time of Test				
Site of Test ( <i>i.e.</i> , Volar as	Site of Test ( <i>i.e.</i> , Volar aspect of forearm, Back etc)			
Concentration of Allergen Tested				
Device Used				
Negative Control Used/	Positive Control Used			
Allergen: (concentration)	Wheal size (mm)	Grading		
Histamine				
Buffer saline				
Allergen 1				
Allergen 2				
Allergen 3				
Allergen 4				

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