PEDIATRICS RESPIRATORY SOCIETY DELHI

Journal of Pediatric Respirology

Vol 1, Issue 3, March 2023

Special Bulletin on Pediatric Allergies

Quarterly Publication of

Pediatrics Respiratory Society

Delhi - NCR

Editorial Board

President's Message

Dear colleagues and friends,

It's my pleasant duty to share this new issue of "Pediatric Respirology" with all of you. This is a symposium on allergic disorders including recent advances on interesting topics and a case report. I am obliged and sincerely thankful to all the authors who took out time from their busy schedule to contribute articles to this issue.

A new team of office bearers will be taking over under the leadership of Dr Tilak Dandwal from 1 April 2023. I, on behalf of my team, wish them a very successful and eventful year 2023-24. During my tenure, I with support of my teammates, particularly Dr Neetu Talwar, started this PRS journal which was long awaited and subsequent issues were produced regularly. Annual PRS conference was organized at Sir Ganga Ram Hospital after a gap of 2 years due to covid pandemic. This conference was on a small scale with reasonable number of attendees. There were many reasons for that, some of which were definitely avoidable. But I feel, WE could have done a better job with a more committed and supportive team. *So, was it a missed opportunity or lost opportunity?* I really don't have an answer to that. As the President of Pediatric Respiratory Society Delhi & NCR, I wish that new team will do a better job and will organize a mega annual PRS conference in August 2023. Also, I am certain that new team of PRS office bearers will continue with publication of this journal in future with better scientific contents.

Dr Anil Sachdev
President,
Pediatric Respiratory Society
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CONTENT

Current Concepts in Diagnosis and Management of ABPA in Children

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Allergic bronchopulmonary aspergillosis (ABPA) is a fungal infection leading to hypersensitivity response in those with uncontrolled asthma, cystic fibrosis (CF) commonly and in other pulmonary disorders including bronchiectasis, post-tubercular lung disease, chronic granulomatous disease and hyper-IgE syndrome. Early diagnosis and rapid implementation of proper management are critical to prevent complications and/or disease progression. Diagnosis centres around classic clinical manifestations, radiographic findings, and immunological findings. Let us review current concepts in etiology, diagnosis, and management of allergic bronchopulmonary aspergillosis in children.

The prevalence of ABPA changes according to the population (child/adult), geographic region or diagnostic criteria used. It is believed to be underdiagnosed, especially in developing countries, because of its overlapping clinical features with may chronic lung diseases. The prevalence has been reported variable in children with asthmatic or CF (up-to 20% or higher) with a significantly higher occurrence among adults (1-6).

Etiopathogenesis

Aspergillus spores are inhaled daily, usually with no consequences. In susceptible people, the inhalation of Aspergillus conidia may colonize the lungs because of its small diameter (2 to 3 micrometres) they easily reach the pulmonary alveoli and deposit. In susceptible hosts, inhaled spores of Aspergillus germinate to hyphae and persist into the lungs, leading to the damage of muco-ciliary clearance and epithelium barrier and eventually activating a strong type 2 immune response. Aspergillus fumigatus is the most common

ubiquitous airborne fungus causative organism for ABPA. ABPA is the most common form of allergic bronchopulmonary mycosis (ABPM). Other fungi, including Candida, Penicillium, and Curvularia species, are implicated in ABPM.

The pathogenesis of ABPA involves many immunologic reactions. These are Aspergillus-specific immunoglobulin (Ig)-E–mediated hypersensitivity, IgG-mediated immune complex hypersensitivity, and abnormal cell-mediated immune response. These hypersensitivity responses cause mucus impaction in the bronchi and bronchioles, as well as inflammatory cell infiltration in bronchial walls and peribronchial tissues. All of these reactions cause bronchiectasis and broncho-centric non-caseating granulomatosis.

Type 2 immune response is characterized by the production of IL-4, IL-5 and IL-13 from innate lymphoid cells, Th2 cells and eosinophils, mast cell degranulation, eosinophil activation with an increase in total IgE, Aspergillus-specific IgE and the production of Aspergillus-specific IgG antibodies. The consequent pulmonary eosinophilic inflammation results in recurrent pulmonary infiltrates and eventually in bronchiectasis and pulmonary fibrosis.

A. fumigatus has several virulence factors to escape from the immune system including superoxide dismutases, catalases, mannitol, proteases, ribotoxin, phythiotic acid, phospholipases, gliotoxin, and hemolysin. Most of these proteins are known to be antigenic and are believed to be responsible for the immune response and fungal persistence in respiratory airways. Aspergillus proteinases are recognized by the innate immune receptors toll like receptors (TLR) TLR2, TLR4 and TLR6 resulting in the initiation of allergic airway inflammation with activation of both innate and adaptive immunity and release of pro-inflammatory cytokines. Fungal metabolite gliotoxin may also downregulate vitamin D

receptor expression in macrophages and airway epithelial cells (in CF) and increase the levels of IL-5 and IL-13.

Cystic fibrosis and ABPA

Exaggerated Th2 response: In those with CF with ABPA a skewed response towards Th2 cells with a reduction in IFN-γ production and cystic fibrosis transmembrane conductance regulator (mutation association with an increased sensitivity to IL-4. T-cell-derived IL-4/IL-13 is essential for A. fumigatus-induced lung eosinophilia and inflammation, while eosinophils seem to have immunomodulatory besides inflammatory function. Hence increased susceptibility of CF patients to ABPA might be due to an exaggerate Th2 response and a deficient Th1 response.

Impaired Muco-ciliary mechanisms: The thick mucus in the airways in children with cystic fibrosis makes it difficult to clear up the Aspergillus spores when inhaled. In children with altered lung structure, such as CF where the innate defence of muco-ciliary clearance is impaired, Aspergillus spores penetrate and adhere to collagen and fibronectin fibres in the basal lamina which facilitates persistence in airways.

Genetic predisposition: HLA-DR molecules DR2, DR5, and possibly DR4 or DR7 contribute to susceptibility; whereas, HLA-DQ2 contributes to resistance, and a combination of these may determine the outcome of ABPA in CF and asthma.

Genetic factors identified in the pathogenesis of allergic bronchopulmonary aspergillosis complicating asthma include defects in innate immunity (gene polymorphisms in surfactant protein A2, mannose-binding lectin gene, Toll-like receptor 9, Toll-like receptor 3, CARD9 gene, ZNF77 etc), Adaptive immunity, HLA associations, polymorphism (Interleukin 4 receptor alpha, Interleukin 13, Interleukin 10 promoter, Interleukin 15, Tumour necrosis factor-α, Transforming growth factor-β etc)

Hence to summarize

1. Immunocompetent individuals easily eliminate Aspergillus conidia from the airway by with no manifestations of pulmonary fungal infections. If isolated in respiratory secretions like sputum or bronchoalveolar lavage, then it only reflects colonization, not an infection.
2. Immunocompromised individuals do not eliminate Aspergillus conidia due to host immune defence imbalance which colonize airways and germinate into somatic hyphae that stimulate a chronic allergic inflammatory response that results in tissue injury, leading to the clinical features of ABPA.
3. In atopic individuals (asthmatics), CF patients, those with cavitary lung diseases, inhalation of Aspergillus fumigatus spores triggers an IgE-mediated hypersensitivity response in the respiratory tract that causes respiratory symptoms like cough with expectoration and breathlessness.

Clinical features and Staging

Clinical features of ABPA are non-specific and may mimic CF or uncontrolled asthma or other chronic lung diseases. ABPA characteristically presents with bronchospasm, pulmonary infiltrates, eosinophilia, and immunologic evidence of allergy to the antigens of Aspergillus species. The most common clinical findings are chronic productive cough and wheezing. Other symptoms are pleuritic chest pain and blood-stained sputum. Expectoration of golden-brownish mucus plugs is a characteristic finding in ABPA. The dark mucus plugs are due to the increased production of tenacious mucus in the respiratory tract and consist of inflammatory cells including eosinophils, desquamated epithelial cells, and mucin. Haemoptysis may occur due to severe airway inflammation and bronchiectasis. Constitutional symptoms such as low-grade fever, myalgia and weight loss are also common.

ABPA may occur with allergic fungal sinusitis having symptoms of chronic sinusitis with purulent sinus discharge.

Physical examination is usually not noticeable except for crackles, rhonchi unresponsive to bronchodilator treatment, absence of respiratory sounds distal to dark mucus plugs, and clubbing. In end-stage disease, cor pulmonale findings may be present. ABPA should be suspected in a patient with CF who develops wheezing or major reductions of forced expiratory volume in one second (FEV1) without evidence of a CF exacerbation, that do not respond to appropriate antibiotics, standard physiotherapy and which is not explained by another etiology.

The disease can be clinically divided into five stages. These are Stage 1 (acute stage), Stage 2 (remission), Stage 3 (relapse), Stage 4 (steroid-dependent stage) and Stage 5 (end-stage lung disease). ABPA may be detected at any stage at the time of diagnosis and the transition from one stage to another may not be in order. Many modifications in this staging are system have also been done. (7-9)

Diagnosis

The diagnosis is made through a combination of clinical characteristics, and radiologic and immunologic findings. Current concepts in diagnosis of ABPA are derived from adult guidelines. The first criterion was published by Rosenberg-Patterson in 1977 and Greenberger et al in 2002 in those with asthma and ABPA[10,11]. Cystic Fibrosis Foundation also published criterion for ABPA in CF. Subsequently International Society for Human and Animal Mycology-Allergic Bronchopulmonary Aspergillosis (ISHAM) in 2013 proposed the criterion for diagnosis of ABPA (Table 1) and also revisions. Similarly Agarwal et al in 2013, 2016 (Table 2), Asano et al and Saxena et al (2021) also proposed criterion for diagnosis of ABPA and ABPM. (7-9, 12-16)

Table 1: ISHAM criteria for diagnosis of ABPA (2013)

Predisposing conditions: asthma, CF

Obligatory: Positive type 1 Aspergillus skin test result or elevated IgE antibody levels, Total IgE level > 1000 IU/Ml And >_2 of the following:

Precipitating or IgG serum antibodies to A fumigatus, Radiographic pulmonary opacities consistent with ABPA , Eosinophil count > 500 cells/mL in steroid-naive patients (may be historical)

Modified ISHAM criteria for diagnosis of ABPA in asthma (2020)

Presence of the following:1. Asthma, 2. A fumigatus-specific IgE level > 0.35 KUA/L, 3. Serum total IgE levels > 500 IU/mL and >_2 of the following: (a) A fumigatus–specific IgG level > 27 mg A/L, (b) Bronchiectasis on chest CT scan, (c) Eosinophil count >500 cells/mL,(d) Mucus impaction on chest CT scan

Table 2: Criteria for diagnosis of ABPA by Agarwal et al., 2016

1. Predisposing condition‑ Asthma or cystic fibrosis, COPD, post‑ TB fibrocavitary disease

2. Obligatory criteria 1‑ Increased IgE against AF (>0.35 kUA/L).If this not available, Immediate skin

sensitivity to AF may be considered

3. Obligatory criteria 2‑ Total serum IgE>1000 IU/ml (2400 ng/mL)

4. Other criteria: At least 2 of three: 1. Radiographic findings consistent with ABPA, 2. Serum IgG >27 mgA/L against AF, 3. Increased total eosinophils (>500) may be historical

An elevated level of serum A. fumigatus-specific IgE (>0.35 kUA/l) and immediate cutaneous reaction to A. fumigatus antigen (performed either using a skin prick or by intradermal injection); and elevated total serum IgE levels are currently the most sensitive investigation in the diagnosis of ABPA**.**

Radiological characteristics

Thin-section (or high resolution) CT of the thorax is currently the imaging modality of choice for ABPA The radiological findings may be transient or fixed. The typical radiological findings in ABPA include central bronchiectasis and fleeting opacities. `Consolidation, evidence of mucus impaction (tramline shadows, finger-in-glove opacities and toothpaste shadows), fibrosis and collapse may be commonly seen. The pathognomonic radiological finding in ABPA is high-attenuation mucus (HAM). Other CT findings include centrilobular nodules, tree-in-bud opacities and mosaic attenuation, perihilar opacities, miliary nodular opacities, pleural effusions and pulmonary masses**.**

ISHAM-ABPA Working Group also classified in 4 categories on basis of radiologic characteristics as ABPA-S (serological positive), ABPA-B(with bronchiectasis) ABPA-HAM (HAM on CT chest) and ABPA-CPF (presence of pulmonary fibrosis, bleb, bullae, pneumothorax, parenchymal scarring, emphysematous change, multiple cyst, fibro-cavitary lesions, aspergilloma, pleural thickening etc).

Differential Diagnosis

ABPA mimics many diseases that involve both airway and lung parenchyma. Undiagnosed lung infiltrates, pneumonia, bronchiectasis make a long list of differential diagnoses. Following are few diseases which should be carefully ruled out while making a diagnosis of ABPA: Corticosteroid-dependent asthma without ABPA, severe asthma with fungal sensitivity (SAFS), bronchiectasis, chronic eosinophilic pneumonia, pulmonary tuberculosis, hypersensitivity pneumonitis.

Management

The main aim of the treatment of allergic bronchopulmonary aspergillosis is to control symptoms, episodes of exacerbation and to limit progressive lung injury. Drugs used for the treatment of ABPA mainly include Anti-inflammatory drugs (corticosteroids), Antifungal drugs, Anti IgE therapy and Antibiotics. (17-18)

Corticosteroids: Systemic corticosteroids are the primary therapy for ABPA. The steroids help to relieve the symptoms and decrease airflow obstruction, decrease serum IgE and reduce peripheral blood eosinophils. Moreover, there is a resolution of pulmonary inflammation, pulmonary infiltrates, and it prevents irreversible lung damage. Daily dosage regimes are popular but pulse dose regimes with methylprednisolone have also been described. Prednisolone is a commonly used drug for treatment. Dosages and regimes recommendations have been modified and derived from adulty studies in absence of Pediatric studies. (7,8,17,18) Two popular regimes are mostly used in treatment.

- Low Dose regime: Prednisolone: 0.5 mg/kg for 4 wk, 0.25 mg/kg for 4 wk, 0.125 mg/kg for 4 wk, then tapered by 5 mg every wk to continue for a total duration of at least 4 months
- High Dose regime: 0.75 mg/kg/day for 6 wk, 0.5 mg/kg/day for 6 wk, taper by 5 mg every 6 wk; total duration: 8-10 months

Glucocorticoids side effects: Weight gain, osteopenia, acne, skin atrophy, diabetes mellitus, glaucoma, cataracts, avascular necrosis of bone, infection, hypertension, and growth retardation in children.

Oral antifungal agents: Antifungal agents act by decreasing the fungal load that reduces inflammatory activity and act as steroid-sparing agents. Antifungal therapy may help to decrease exacerbations. Itraconazole is a commonly used drug for treatment.

Itraconazole (200 mg twice daily for 16 weeks) leads to significant reductions in corticosteroid dose, decreases IgE levels, resolves pulmonary infiltrates, improves exercise tolerance, and improves pulmonary function. Saide effects: Itraconazole interferes with the hepatic metabolism of several medications, including cyclosporine, oral hypoglycemics, tacrolimus, terfenadine, cisapride, and midazolam. Deranged liver function test results, rash, headache, edema, nausea, vomiting, and diarrhoea are the most common side effects.

Other antifungals: Newer antifungal drug like Voriconazole (300 to 600 mg/day) or Posaconazole (800 mg/day in children >13 years) shows clinical improvement with a reduction in the requirement of oral glucocorticoids, improvement in asthma control, and decline in IgE levels. Cost is a major current limitation; however, the high rate of efficacy shows that treatment with these agents as second-line therapy. Isavuconazole is a newer antifungal which is found effective but has cost limitations. Other antifungal agents, including nystatin, amphotericin B, miconazole, clotrimazole, and natamycin, are generally ineffective in controlling ABPA.

Anti-IgE therapy: Omalizumab, an anti-IgE recombinant humanized monoclonal antibody which prevents binding of IgE to Fc-epsilon RI receptor on mast cells and basophils. It is mainly used to treat uncontrolled asthma on Step 4 GINA treatment guideline. High cost limits the use. According to some studies, it is a good alternate option in patients of ABPA with CF in whom there is steroid dependency or contraindications. It has a steroid-sparing effect and decreases systemic inflammatory markers. The dosage depends upon the serum total IgE level. In ABPA, despite a high level of IgE, the routine dose of omalizumab is sufficient.

Antibiotics: To prevent or treat an associated secondary bacterial infection. The European Respiratory Society (ERS) guidelines advocate long-term antibiotic treatment for adults with bronchiectasis who have three or more exacerbations per year.

Others: Anti-Th2 therapies with mepolizumab (monoclonal antibody against IL-5), dupilumab (IL4 antagonist) and benralizumab (monoclonal antibody against IL-5Rα); and nebulized lipid amphotericin B (AMB-L) requires further studies to determine efficacy in treatment of ABPA for before standard recommendations.

Supportive measures: These include airway clearance treatment to ABPA-related bronchiectasis patients should be prescribed nebulization with hypertonic saline with salbutamol and mucus clearance valves or percussion vests. Also avoid areas and environmental conditions with high mould counts, such as decomposing organic materials and mouldy indoor environments. Pneumococcal and influenza vaccination re recommended in all patients of ABPA-B and ABPA with poorly controlled asthma.

Follow up on treatment: A regular follow up with history and examination for clinical resolution or worsening, chest radiograph, spirometry and measurement of total IgE levels every 8-12 wk (to determine the new baseline IgE). A 25% decline in serum total IgE along with clinical and/or radiological improvement, indicates a satisfactory response to therapy. A clinical or radiological worsening along with a ≥50% increase in the new baseline IgE points to an ABPA exacerbation. Monitor for adverse effects of medications and drug interactions.

Complications and Outcome of allergic bronchopulmonary aspergillosis

The complications of ABPA include recurrent exacerbations and steroid dependence, invasive aspergillosis, chronic pulmonary aspergillosis, cavitation, local emphysema, chronic or recurrent lobar atelectasis, honeycomb fibrosis and complications related to bronchiectasis like haemoptysis, recurrent pulmonary infection.

The natural history, progression, remission, and recurrences of ABPA are not well understood. Patients without central bronchiectasis at the time of diagnosis tend to maintain their lung function despite occasional exacerbations. With appropriate treatment, long-term control of ABPA is feasible, and durable remissions are common. Treatment of Stage 1 disease using corticosteroids typically results in decreased sputum production, improved control of bronchospasm, over 35% reduction in total IgE within 8 weeks, clearing of precipitating antibodies, and resolution of radiographic infiltrates. Progression of Stage 5 disease to pulmonary fibrosis may be preventable if patients maintain therapy on low-dose steroids. Persons with low FEV1 persistently have a worse prognosis.

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Biologicals in Pediatric Asthma

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Abstract

Severe asthma is defined as uncontrolled asthma despite high dose ICS–long-acting beta2 agonist (LABA), triggers avoidance, good compliance and technique, and treatment of co-morbidities. The recommended management for such children is an add on third controller such as leukotriene receptor antagonist (LTRA), add on long acting antimuscarinic agent (LAMA), low dose azithromycin, biologic agent or bronchial thermoplasty. Biological agents have shown to reduce the number of exacerbations, improve asthma symptoms and quality of life. Only few agents have been approved in children above six years of age. However, patient selection is of utmost importance before instituting this therapy. The treatment is costly and hence affordability and availability have to be considered especially in a resource limited setting.

Introduction: According to GINA 2022, uncontrolled asthma includes one or both of the following; poor symptom control or frequent exacerbations (two or more per year), whereas difficult to treat asthma is asthma that is uncontrolled despite medium or high dose inhaled corticosteroids (ICS) along with a second controller (usually long acting beta agonist) or maintenance oral corticosteroids. It may be due to modifiable risk factors such as incorrect inhaler technique, poor adherence, co-morbidities or incorrect diagnosis. Severe asthma is a subset of difficult to treat asthma and is defined as uncontrolled asthma despite adherence with maximal optimized high dose ICS–long-acting beta2 agonist (LABA) and management of contributory factors or asthma that worsens with decrease in high dose ICS–LABA. (1). The

exact incidence is not known but around 5-10% of children continue to have asthma symptoms and frequent exacerbations despite use of high dose corticosteroids (2). The recommended management for such children is an add on third controller such as leukotriene receptor antagonist (LTRA), add on long acting antimuscarinic agent (LAMA), low dose azithromycin, biologic agent or bronchial thermoplasty (1). Daily oral corticosteroid (OCS) administration is usually the last resort due to its systemic side effects. However, before starting any of these therapies it is extremely important to exclude conditions that mimic asthma, address the associated co-morbidities and exclude uncontrolled asthma due to poor adherence, incorrect inhalation technique and exposure to environmental inhalants (1).

Asthma is a heterogenous disease and endotypes have been proposed to target specific therapies. The two main endotypes identified are based on the airway inflammatory response- Type 2 (T2) - high asthma (eosinophilic type) and non-type -2 asthma or T2-low (neutrophilic type). Type 2 asthma is more common in children. This differentiation is based on blood eosinophil levels, sputum eosinophils, FeNo and clearly allergen driven asthma (3). The management of severe refractory type 2 asthma differs from non-type 2 asthma.

The add on biologic therapy for refractory type 2 asthma should be considered after assessing for adherence, increasing the dose of ICS- LABA to maximum, correcting co-morbidities and environmental factors. The biologic therapy should be given only if available and affordable in a patient with frequent exacerbations and poor symptom control with allergic or eosinophilic biomarkers and need for daily OCS (1). There are various biologicals available but only omalizumab, mepolizumab and dupilumab are FDA approved in children between 6-12 years of age. Although there is data on omalizumab, there is paucity of data regarding efficacy and safety of mepolizumab and other drugs in children. The superiority of one over another is not known if the patient is eligible for both.

1. ***Omalizumab-*** Omalizumab is humanized anti-IgE monoclonal antibody. It binds to free part of IgE and prevents its binding to the FcεR1 receptor on mast cells and basophils. It is approved for patients > 6 years with moderate to severe allergic asthma with uncontrolled symptoms with ICS. The eligibility criteria are sensitization to aeroallergen as demonstrated by skin prick test or specific IGE, increased serum total IgE levels (> 30 and < 1500 IU/mL) and more than specified exacerbations in last one year. It is administered subcutaneous every 2- 4 weeks (1). The dosage is determined by nomogram based on weight and serum IgE levels, the dose range being 75 to 375 mg (4). The efficacy and safety of omalizumab has been well established in several clinical trials. In a double-blind, randomized, placebo-controlled study by Milgrom et al in which 334 children aged 6–12 years with moderate to severe allergic asthma were randomized to receive subcutaneously administered placebo (N=109) or Omalizumab (N=225), it was found that the participants in the Omalizumab group, had more reduction in their beclomethasone dipropionate (BDP) dose as compared to the placebo group (median reduction 100% vs. 66.7%). Also more participants could discontinue the BDP compared to the placebo group (55% vs. 39%) and fewer participants had asthma exacerbations (18.2% vs. 38.5%) (5). Several other pediatric trials have also shown improvement in lung function, better control of asthma and decreased exacerbations, hospitalizations, emergency visits, daily ICS and seasonal exacerbations (6-10). However, 34% patients may still have a poor disease control despite omalizumab (11). The factors predicting good response are childhood onset asthma and allergen driven asthma. The baseline IgE levels, eosinophil count and FeNO have not been found to be predictors of good asthma control (12-14). The optimal duration of treatment is not yet determined. At least 4 months trial should be given in patients without clinical improvement. Omalizumab is safe and adverse events like anaphylaxis have been reported in only 0.1–0.2% patients.

Omalizumab is also approved for treatment of nasal polyposis and chronic idiopathic urticaria.

2. ***Mepolizumab:*** Mepolizumab is a murine humanized monoclonal antibody which binds to circulating IL-5 and prevents the IL-5/IL-5Rα interaction leading to apoptosis of eosinophils. It is approved as an add on drug for severe therapy resistant eosinophilic asthma in patients above 6 years of age. The recommended dose and the timing of administration are: 100 mg/4 weeks subcutaneously in adults and children over 12 years, and 40 mg/4 weeks subcutaneously in children aged 6 to 11 years. The eligibility criteria include more than specified exacerbations in last one year and eosinophil count > 150-300/microlitre. The evidence of efficacy and safety of Mepolizumab in children in lacking. Two trials [DREAM (Dose Ranging, Efficacy, and Safety with Mepolizumab in Severe Asthma) and MENSA (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma)] that have evaluated the efficacy of mepolizumab in eosinophilic asthma in patients over 12 years have shown significant clinical improvement in terms of reduced number of asthma exacerbations, increased FeV1, decrease in emergency department visits, hospitalizations, and improvement of asthma QoL scores (15, 16). In the SIRIUS (Steroid Reduction with Mepolizumab) study, the researchers have found a median dose reduction in daily intake of oral corticosteroids by 50% (17). Other similar trials have also demonstrated the long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma (18,19).

   The predictors for good response are high blood eosinophil count, higher number of asthma exacerbations, adult-onset asthma, nasal polyposis, maintenance dose of OCS at baseline and low lung function. Blood eosinophil count and the improvement of the lung function have been considered as parameters of response in few studies. At least 4

months of initial trial is recommended (1). The adverse events injection site reaction and rarely anaphylaxis.

Mepolizumab has also been approved for eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome, chronic rhinosinusitis with nasal polyps.

3. ***Benralizumab***: Benralizumab is a monoclonal anti IL-5 Rα antibody. It is approved as an add on treatment for patients above 12 years of age with severe eosinophilic asthma. The dosage is 30 mg subcutaneously every 4 weeks (for the first 3 doses), then 30 mg subcutaneously every 8 weeks. Various clinical trials (SIROCCO, CALIMA ZONDA) have shown significant decrease in the number of asthma exacerbations, an improvement in symptoms in patients and reduced use of systemic corticosteroids in patients with severe allergic asthma with eosinophilia as compared to controls. The safety and efficacy profile of Benralizumab have also been established (20-22).
4. ***Reslizumab:*** Reslizumab is a circulating IL-5 binding monoclonal antibody. It is approved as an add-on therapy in patients aged ≥18 years with eosinophilic severe asthma. The recommended dose is 3mg/kg every 4 weeks administered intravenously. The trials in patients aged 12 to 75 years with a poorly controlled asthma and with an eosinophil count greater than 400 cells/mL have shown a significant reduction in asthma exacerbations, improvement in lung function and asthma QoL scores in the treated group (23,24). However, further studies are needed to confirm the efficacy and safety of Reslizumab in children.
5. ***Dupilumab***: Dupilumab is a fully humanized monoclonal antibody approved for use as an add on maintenance therapy in adults and children > 6 years with severe eosinophilic/ Type 2 asthma or patients requiring OCS maintenance therapy (1). It binds to the alpha subunit of the IL-4 receptor (IL-4Ra) blocking both IL-4 and IL-13 signaling. It is also indicated for chronic rhinosinusitis with nasal polyposis and moderate-to-severe atopic

dermatitis. The currently approved dosages are: For patients > 12 years- 200 mg or 300 mg S.C every 2 weeks. For children 6-11 years- 200 mg S.C every 2 weeks (100mg if between 15-30 kg). The eligibility criteria are blood eosinophils >300 and < 1500, FeNo> 25 ppb. The predictors for good outcome include high blood eosinophils and high FeNO. The randomized trials have found a significant reduction in the number of annual severe asthma exacerbations (25,26). The adverse events include injection site reactions, upper respiratory tract infections and headache. It is particularly efficacious in patients with comorbidities, including chronic rhinosinusitis with nasal polyposis and atopic dermatitis (27).

6. ***Tezepelumab:*** Tezepelumab is the recent addition to the monoclonal antibodies that can be used in severe asthma. It binds to thymic stromal lymphopoietin (TSLP) preventing its interaction with its receptor which is implicated in the type 2 inflammatory cascade. It is currently approved for ages > 12 years. The dose is 210 mg given SC every 4 weeks. The eligibility criteria include severe asthma with severe exacerbations in last one year. It can also be given to patients with no elevated T2 markers. Two randomized trials demonstrated 30-70% reduction in a reduction in the annual rate of asthma exacerbations, improved QoL, lung function and symptom control irrespective of the allergic status (28,29).

To summarize, biologicals are novel targeted therapies against specific pathways used in children with severe uncontrolled asthma. Most of these agents are useful against allergic endotype. They have shown to reduce the exacerbations, improve symptom control, quality of life and lung functions. However, patient selection is of utmost importance before instituting this therapy. Strict adherence and compliance to treatment is needed. The treatment is costly and hence affordability and availability have to be considered especially in a resource limited setting.

Table 1: Biological drugs used in Severe Asthma

Biological agent	Mechanism of action	Indication	Age group	Dosage	Side effects
Omalizumab	Anti-IgE	Moderate to severe allergic asthma with uncontrolled symptoms with ICS with elevated IgE (Serum IgE > 30 < 1500 IU/mL) and positive specific IgE to at least one aeroallergen	Children >6 years, adolescents and adults	SC injection every 2-4 weeks,. Dose guided by nomogram Range- 75-375 mg	Local skin reaction and pain, anaphylaxis
Mepolizumab	Anti-IL5	Add on therapy for severe therapy resistant eosinophilic asthma (eosinophil count >150-300/microlitre)	Adults and children > 6 years	100 mg SC every 4 weeks in adults and adolescents > 12 years. 40 mg SC every 4 weeks in children aged 6–11 years.	Local skin reactions, back pain, fatigue, headache
Benralizumab	Anti IL-5 Rα	Add on treatment for with severe eosinophilic asthma	> 12 years of age	30 mg SC every 4 weeks (for the first 3 doses), then 30 mg SC every 8 weeks	Injection site reactions, anaphylaxis (rare)
Reslizumab	Ati-IL-5	Add-on therapy for eosinophilic severe asthma	≥18 years	3mg/kg every 4 weeks IV	Injection site reactions, anaphylaxis (rare)
Dupilumab	Anti-IL-4 receptor α-subunit,	Add-on treatment of severe asthma	Adults and adolesce	200 mg or 300 mg S.C every 2 weeks. For	Injection-site erythema, pain, edema, pruritus,

	blocking signaling induced by both IL-4 and IL-13.	with type 2 inflammation, peripheral eosinophilia and high values of FeNo. Peripheral eosinophilia (>150 cells/μL), and/ or FeNo > 25 ppb	nts > 12 years	children 6-11 years- 200 mg S.C every 2 weeks (100mg if between 15-30 kg)	transient eosinophilia, conjunctivitis, eye pruritus, blepharitis, headache.
Tezepelumab	Binds to thymic stromal lymphopoietin (TSLP)	Add on treatment for severe asthma	>12 years	210 mg given SC every 4 weeks	Injection site reactions, anaphylaxis (rare)

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Management of Allergies in Pediatric Practice

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Introduction

Over the past few decades, the prevalence of allergic disorders has increased dramatically and it has become one of the important causes of childhood morbidity worldwide. Allergic disorders can have varied manifestations in the form of allergic rhinitis, rhino-conjunctivitis, allergic asthma, eczema, urticaria or food allergy. According to a recent survey, it has been estimated that around 20-30% of the Indian population (over 1.4 billion currently) suffers from allergic disorder, of which, allergic rhinitis is most common followed by asthma (1,2). The international study of asthma and allergy in childhood (ISAAC) is one of the largest studies, conducted all across the world in 98 countries in three phases to know the prevalence, severity and associated features of allergic disorders, namely – allergic rhinitis, rhino-conjunctivitis and eczema. India, took part in third phase of the study and it was observed that in the age group of 6-7 years, 11.3 % suffered from allergic rhinitis, 4.3% from rhino-conjunctivitis and 3.4% from eczema including severe eczema while in the age group of 13-14 years, 24.4% had allergic rhinitis, 11.9% had rhino-conjunctivitis and 4.3% had eczema (3). Global data suggests wide variation, with 20 to 60 folds difference in prevalence of asthma, allergic rhino-conjunctivitis and atopic disorders. According to ISAAC, the highest prevalence of asthma was found in UK, Australia, New Zealand, and Republic of Ireland, followed by most centres in North, Central, and South America, while India was among the countries with lowest prevalence rates. Similarly, for allergic rhino-conjunctivitis and atopic eczema, high prevalence areas are very much scattered but India remains in low prevalence countries(4). But, the actual burden of allergy might be much more than depicted

in surveys and studies due to lack of awareness in general population, lack of qualified allergists and scarce standard diagnostic facilities in India. These factors leads to under-reporting and incomplete treatment, hence need was felt to review management of allergic disorders in pediatric practice, to increase awareness among general paediatricians and strengthen referral, wherever indicated.

Background

In 1906, the term "Allergy" was coined by Viennese Pediatrician Clemens Von Pirquet (5). It was derived from an ancient Greek word "allos" meaning "other" & "ergon" meaning "work of action". Originally, he used this term to indicate "altered reactivity" or biological response to foreign substance (vaccine or any other protein substance) that either leads to immunity (a beneficial effect) or hypersensitivity (a harmful effect). But over the years, the term allergy is used in a limited sense, as synonymous to hypersensitivity (6).

Allergy can manifest in various forms and can affect multiple systems- respiratory (allergic rhinitis, asthma), skin (urticarial, hives, drug reactions) or gastrointestinal system (as food allergy). In the recent past, a sharp surge in allergic disorders has been witnessed, due to complex interplay of genetic and environmental factors and with increasing industrialization, pollution is increasing which has a huge impact on respiratory allergies (7). There is significant effect on quality of life which also directly or indirectly impact on the monetary status of the family. In India there is no health insurance/ health care benefits from government, so the people have to pay out of the pocket, which further increases their vows.

Types of Hypersensitivity reactions (Figure 1)

In 1963, Gell and Coombs proposed the classification of hypersensitivity reactions in four distinct categories as Type I or Immediate Hypersensitivity reaction, Type II or Cytotoxic or IgG/IgM mediated reaction, Type III or Immune complex-mediated hypersensitivity reaction

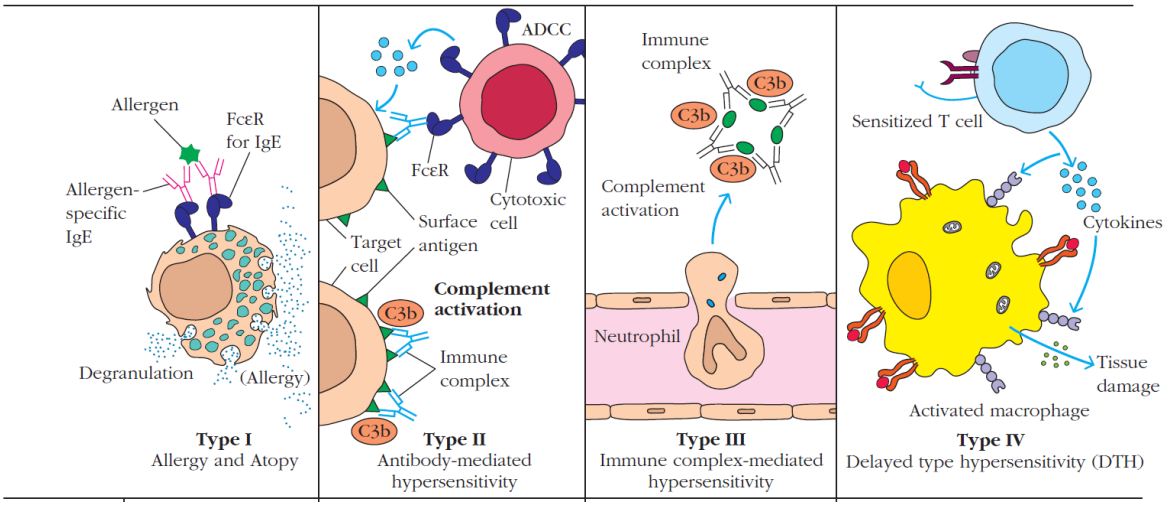
and Type IV or delayed type hypersensitivity reaction or T-cell mediated. Later on, the classification system was modified to include subtypes of type II and type IV hypersensitivity reactions. However, in clinical practice, we often encounter patients with multiple manifestations and there exists an overlap of different types of hypersensitivity reactions (8).

A. Type I Hypersensitivity Reaction

Type I hypersensitivity occurs in two phases – Early/acute phase followed by late phase.

- Early phase: Allergens (or antigens) are presented to Th-2 cells by Antigen-presenting cells (APCs) during the sensitization phase. These Th-2 cells leads to stimulation of B-cells, which in turn produce IgE antibodies in large amounts, that binds to the Fc receptors on mast cells and basophils. Subsequently, on re-exposure, the same antigen, crosslinks with specific IgE antibodies bound to mast cells and basophils. This results in the degranulation of the cells and the release of histamine, proteolytic

- **Figure I – Types of hypersensitivity reactions**



Type I – Immediate hypersensitivity reaction; Type II – Antibody-mediated hypersensitivity reaction; Type III – Immune-complex mediated hypersensitivity reaction; Type IV – Delayed Type Hypersensitivity reaction

enzymes (tryptase and chymase), lysosomal enzymes and other preformed mediators immediately. The mast cells also produces lipid mediators like prostaglandin D2 and

leukotriene C4 from arachidonic acid that are released into circulation within 15 minutes of IgE cross-linking(8).

- Late Phase: It occurs 4 to 8 hours after allergen exposure due to de novo production and release of cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF-α), IL-4, IL-5, IL-13, and granulocyte monocyte colony-stimulating factor (GM-CSF) (9).

  It can have varied manifestations depending on route of exposure like Inhaled allergens may exacerbate symptoms of allergic rhinitis or asthma. Topical contact with allergens may lead to hives and urticaria. And, exposure to allergen via the oral or intravenous route may lead to systemic symptoms. There may be a varied spectrum ranging to potentially life-threatening type I systemic allergic response known as anaphylaxis characterized by urticaria, angioedema, bronchospasm, hypotension, and, rarely, shock (10).

  Majorly, type I hypersensitivity reactions are IgE-mediated but there is a subset of type I reactions that are IgE-independent and occurs due to non-specific activation of mast cells. These can occur as a systemic response to substances such as iodinated contrast media, biologic drugs, opiates etc (10).

B. Type II Hypersensitivity reaction or cytotoxic reaction

Type II hypersensitivity reactions are antibody-mediated in which IgG and/or IgM antibodies binds to antigens present on surface of target cells and leads to destruction of target cells by various mechanisms. These target cells can be microbes or sometimes antibodies are formed against self-antigens, thereby leading to cytotoxic damage to host. It can be further classified as – type IIa and type IIb. In type IIa, cytolytic destruction of target cells happens via three mechanisms –

a. Complement-mediated cytotoxicity: Antigen-antibody complexes on target cells leads to activation of classic complement pathway, thereby creating membrane-attack

complex (C5-C9) which ultimately cause cell lysis and destruction of target cell. For example: autoimmune haemolytic anemia, immune thrombocytopenic purpura.

b. IgG antibodies attached on target cells binds to Fc gamma receptor IIb (FcγRIIb) on natural killer cells and macrophages, thereby causing them to release granules that contain perforin and granzyme to directly kill cells.

c. Finally, both IgG and IgM can bind to Fc receptors on phagocytes to activate them and initiate phagocytosis.

C. **Type III**

Antigen-antibody complexes are formed which are deposited in the tissues, thereby activating complement system and thus leads to tissue damage.

D. Type IV

Type IV hypersensitivity reactions are also known as delayed hypersensitivity or cell-mediated hypersensitivity, as originally described by Gell and Coombs (11). Later, it was further categorized into four subtypes, based on different immune mechanisms. Type IVa, is same as described originally by Gell and Coombs, whereby Th1 cells activates macrophages, which in turn releases TNF-α and IFN-γ. Type IVb reactions are Th-2 mediated which produces various cytokines like IL-4, IL-5, IL-13 to induce eosinophilic inflammation and also, activates B-cells to produce IgE antibodies. Type IVc reactions are mediated by cytotoxic CD8+ T cells, which leads to production of various mediators like perforin, granulysin, and granzyme B, thereby directly killing the target cell population. In type IVd hypersensitivity reactions, the T-cell derived CXCL-8, leads to chemotaxis of neutrophils in the tissues thereby causing sterile neutrophilic inflammation and tissue damage (12).

The table I and figure 1 summarize some common examples of various hypersensitivity reactions (13,14).

Table I: Types of hypersensitivity reactions

Type of Hypersensitivity reaction	Examples
Type I or immediate hypersensitivity	Allergic rhinitis , Asthma, Anaphylaxis, Angioedema, Urticaria
Type II or Antibody-mediated cytotoxic reactions/cell-stimulating reactions	Immune cytopenias, Grave's disease, chronic idiopathic urticaria
Type III or Immune complex-mediated complement activation	Serum sickness, vasculitis, drug-induced lupus
Type IV or delayed type hypersensitivity	
• IVa: Th1 cell–mediated macrophage activation	Type 1 diabetes, contact dermatitis, tuberculin test reactions
• IVb : Th2 cell–mediated eosinophilic inflammation	Maculopapular exanthems, DRESS syndrome, persistent asthma
• IVc: Cytotoxic T cell–mediated reactions	Steven Johnson Syndrome or Toxic epidermal necrolysis
• IVd: T cell–mediated neutrophilic inflammation	Behcet's disease

Allergy Diagnosis

A detailed and relevant history taking along with targeted physical examination plays a key role in allergy diagnosis. A proper history of symptoms with duration, periodicity of symptoms (whether seasonal/perennial), any temporal correlation with exposure of particular allergen and onset of symptoms, history of exposure to pets/household insects, family history of asthma/atopy, occupational history, any aggravating/ relieving factors should be elicited. The regional predominance of various aeroallergens (mainly pollens) as well as their seasonal variation must be known to attending doctor to shortlist and individualize the allergen panel. History taking remains the cornerstone for diagnosing allergic disorders.

Laboratory Evaluation

The laboratory tests should be selected on the basis of patient's history, environmental triggers/factors and other operational issues (like availability, cost issues, risk involved). There are some tests for cause identification (immunological tests) and some are supportive tests or for functional assessment.

I. Immunological tests : For cause identification

Immunological tests can be further classified as "*In Vivo*" and "*In Vitro*" tests. In vivo tests include – Skin Prick Test (SPT), Intradermal, Patch and Challenge tests. While in vitro tests include – Total and Specific IgE levels and Component Resolved Diagnostics (CRD).

A. In vivo tests

i. <u>Skin Prick Test</u>

Skin scratch testing is a very old-technique, which was first described by Charles Harrison Blackley in 1873 in a patient with Hay fever (15). Since then, it has been widely studied, researched and method of skin scratch testing was modified to overcome certain drawbacks like absorption of varying amounts of allergen, which leads to difficulty in interpretation and standardization, mechanical skin irritation, bleeding at the site and chances of systemic allergic reaction (16). Finally, in 1959, Helmtraud Ebruster, brought out first publication on SPT as an important diagnostic tool in assessment of patients with allergy (17). Now, it is considered as a gold standard investigation in diagnosing Ig-E mediated allergic diseases (18). It is minimally invasive, inexpensive, easy to perform, Pain-free, reproducible technique and provides quick results within 15-20 minutes.

General principle of SPT:

SPT is useful only in IgE-mediated allergic disorders. Presence and degree of cutaneous reactivity, is used as a surrogate marker of sensitization of a target organ to a particular allergen. When an allergen extract, for which body is already sensitized, is introduced cutaneously, then allergen specific IgE which is already bound to mast cells will cross react with infiltrated allergen, thereby leading to degranulation, with release of histamine and other mediators causing local reaction in the form of wheal and flare reaction (19).

Indications for SPT:

SPT is indicated in patients where type I hypersensitivity (immediate type) is suspected, based on careful history, food or drug intake and environmental exposure. Patients with persistent or moderate-to-severe symptoms of allergic rhinitis or asthma, that are uncontrolled on therapy or difficult to control asthma, should be definitely subjected to allergy testing(20). SPT stays the gold standard to confirm sensitivity to a particular allergen but it should be always interpreted after correlating it with clinical history. It helps in management, as allergen avoidance measures can be advised, and specific immunotherapy (SIT) can be planned wherever indicated, if offending allergen is known.

Apart from clinical indications, it is also useful in various epidemiological studies, to determine the geographical distribution and regional differences in aeroallergen sensitization (19).

Contraindications:

SPT is a safe procedure with minimal risk of systemic allergic reactions. There are few conditions where risk of anaphylaxis are high like in patients with uncontrolled asthma or reduced lung function, so SPT is avoided in such cases. It should also be

avoided in patients who had a history of suspected or proven anaphylactic reaction in last 4 weeks, as there may be false negative reaction in such cases.

SPT is also contraindicated in certain skin conditions – dermatographism, acute and chronic urticaria as patient is on antihistamines and cutaneous mastocytosis (21).

Test Procedure

Before performing the test, it is prudent to take appropriate history including medications, and check for any contraindications for SPT. Another prerequisite for SPT is that it should always be performed where the resuscitation facilities are readily available, since very rarely anaphylactic reaction/ systemic allergic response can take place.

SPT can be performed either on forearm or upper back and it has been demonstrated that both the sites carry good and comparable sensitivity as well as specificity for most of the tested allergens (22). Still, forearm remains the most preferred site, since it is simple and convenient to use in majority of patients. The test area is volar aspect of the forearm, at least 2 – 3 cm from the wrist and the antecubital fossae (23). Before starting the procedure, the selected site is cleaned with 70% alcohol. The area/grid is marked for application of allergen extract. The tiny drops of allergen extracts should be placed at a distance of at least 2cms, otherwise there are high chances of cross-contamination leading to false positive or false negative results (21). First of all, histamine dichloride and normal saline are applied which serve as positive and negative controls respectively. The positive control should be read after 10 minutes, while negative control after 15 minutes (24). The positive control should be at least 3 mm or more than the negative control to establish the test validity. If the difference between the positive and negative control is less than 3 mm, then the test is invalid. If the negative control is $\geq$ 3 mm, then it indicates that the skin reactivity is high and test

remains invalid. Any wheal diameter of ≥ 3 mm than the negative control is taken as positive and any wheal size more than 8 mm is highly suggestive of sensitivity to that particular allergen (20).

Factors affecting the results

SPTs should always be interpreted after correlating with history and examination. There are certain medications that alter the results of SPT, therefore they need to be stopped at a recommended time period before performing the SPT and if it is not possible to with-hold the medication for the recommended period of time, then alternative testing method shall be used. Table 2 enlists the common medications that have major effects or suppression of skin prick test (19,20).

Table 2: Drugs to be discontinued before Skin Prick Test

S no.	**Medications**	**Duration for with-holding before test**
1.	First Generation H-1 blocker (Hydroxyzine)	> 48 hours
2.	Second Generation H-1 blocker ➢ Cetirizine, Loratidine ➢ Astemizole	 7 days 60 days
3.	Ketotifen	> 5 days
4.	Antidepressants ➢ Doxepin ➢ Desipramine	 7 days 3 days
5.	Topical steroids in test area for > 3weeks	>1 week
6.	Systemic steroids ➢ Short term (<10 days), >50mg/day prednisolone ➢ Long term (>10 days), >10 mg/day prednisolone	 >1 week >3 weeks

ii. Intradermal Test

It is based on the same principle as SPT. The intradermal test has higher sensitivity and accuracy but at the same time there is increased risk of systemic allergic reactions, therefore it is generally done in conditions where SPT is negative or equivocal and there is strong clinical suspicion regarding a particular offending allergen. In this test, 0.02-0.05 ml of diluted (1:500 to 1:1000 weight by volume) allergen extract is injected intra-dermally (23). It is diluted to decrease the incidence of systemic allergic reactions/ anaphylaxis as well as to decrease false positivity rates. There is no need of positive control if SPT was done prior to intradermal test and it had shown reaction. But, positive control is needed, in cases where it wasn't done with SPT or there was no reaction to histamine (positive control) during SPT.

iii. Patch Test

Patch test is done for diagnosis of contact dermatitis and it is based on delayed or type IV hypersensitivity reaction. In this test, patches containing allergenic protein are applied on upper back of patient. An eczematous reaction appears at the site of offending allergen, which is graded as erythema, vesiculation and ulceration. It generally takes 48-72 hours to appear, but it may take as long as 7 days. Therefore, for standardization, results are read on day 2, 4 and 7 after application of patch (25). Patch test is a very safe with negligible risk of anaphylaxis; hence it may be used in patients of all age groups. Also, it has high specificity but very low sensitivity and one major drawback is that it is time consuming.

iv. Oral Food Challenge Test

The procedure of oral food challenge should be performed in a controlled environment always. The double-blind placebo control food challenge test is the gold standard for detecting the sensitivity to suspected food items, but it becomes

practically difficult to mask every suspected food item for testing. Therefore, open labelled technique is preferred for oral challenge test.

B. In Vitro tests

i. **Total and Specific Serum IgE levels**

Total serum IgE levels may be raised in many conditions like parasitic infections, hyper IgE syndrome, EBV infection, rheumatoid arthritis etc. While, serum specific IgE (sIgE) is produced against specific allergen and these sIgE molecules are measured by Radio-allergo-sorbent-test (RAST), by using radiolabelled (I^{125}) antihuman IgE. Now, enzyme-labelled antihuman IgE are also being used widely instead of radio-isotopes (Immunocap). When compared to skin prick/puncture tests, the sensitivity of IgE testing ranges from less than 50% to more than 90% (18), therefore it is not preferred over SPT, either for diagnostic or prognostic purpose as levels do not correlate with severity of anaphylactic reaction to venoms or penicillins. Another drawback is false positivity of sIgE levels in cases where total IgE levels are very high, to the tune of ≥300 kU/L which occurs due to non-specific binding to test allergens(26).There are certain conditions where SPT is contraindicated and therefore measurement of sIgE levels are preferable like- unstable or uncontrolled asthma, where medications can't be stopped, certain skin conditions like acute/chronic urticarial, dermatographism or cutaneous mastocytosis. It is also important to measure total serum IgE for assessing the suitability of a patient for the initiation and dose of omalizumab therapy(18).

ii. Component Resolved Diagnostics

Component Resolved Diagnostics (CRD) helps in increasing accuracy of IgE-based diagnostic tests by determining the epitopes on allergens that have structural

homology with other allergens and hence by using recombinant allergen with specific epitope, it eliminates chances of cross-reactivity among different allergens.

II. Supportive tests

i. <u>Blood eosinophils levels</u>

The increased level of eosinophils in blood as well as in body fluids correlates highly with allergic disorders like allergic rhinitis, allergic asthma, ABPA, and eosinophilic bronchitis (18). But eosinophils are raised in certain other conditions as well like Hodgkins lymphoma, Addisons disease, mastocytosis, collagen vascular disease, drugs reactions, infections (HIV, Parasite & Fungal), and eosinophilic syndrome with eosinophil counts as high as >1500 eosinophils/ml (20).

ii. <u>Nasal and sputum eosinophilia</u>

This test is non-invasive, easy to perform and reproducible. Presence of nasal and sputum eosinophilia supports the diagnosis of allergic asthma

iii. <u>Fractional exhaled nitric oxide (FeNO)</u>

FeNO is a non-invasive biomarker of eosinophilic inflammation of the airway. This test is helps in diagnosing asthma and also assist in management of refractory asthma cases.

Treatment of Allergic disorders

Allergen testing is prudent in patients with allergies – whether it is inhalant, food or drug allergy, as it plays a very important role in treatment of allergic disorders. The management can be non-pharmacological and pharmacological. Pharmacological management in turn

consists of supportive treatment – for both acute and chronic conditions, and allergen specific immunotherapy in certain cases, wherever indicated.

I. Non-pharmacological management

Non-pharmacological management includes allergen avoidance and it remains the main stay of treatment in patients with allergies whether symptoms are mild or moderate-severe. Allergen avoidance is necessary in conjunction to pharmacological treatment for amelioration of symptoms as well as for effective results of therapy.

A. Environmental control measures

After identifying the offending allergen, appropriate allergen avoidance plan should be offered to patients to ameliorate the symptoms. These environmental control measures are cornerstone in treatment of respiratory allergies, such as in allergic asthma, allergen avoidance alone can help in improving lung function and normalizing markers of allergic inflammation, and it reduces the need for pharmacotherapy as well (27). Depending on the offending allergen, as determined by SPTs, definitive control measures are instituted.

i. House dust mites

House dust mites thrive on human skin scales and at humidity more than 50%, so all the measures are aimed at eliminating the mite reservoirs and decreasing the humidity in house (28). The measures taken includes (29) -

- Beddings should be washed weekly in hot water with temperature above 55° C.
- Mattresses and pillows should be encased in impermeable covers.
- Pillows and mattresses should be periodically changed.
- Use of carpets should be avoided as they serve as an important dust mite reservoir. If used, it should be steam cleaned and dried at regular intervals or it should be cleaned with high efficiency particulate vacuum cleaner. And if nothing is feasible

then acaracides such as fine powder of benzyl benzoate shall be sprinkled on carpets that reduces the mite count.

- Forced air heating systems and central humidifiers shall not be used and if used, then the filters should be frequently cleaned. Other option is use of electric baseboard heaters, if necessary.
- Dust trappers such as soft toys and open book shelves should not be kept in bedrooms
- Dehumidifiers may be advised to keep relative humidity in between 35-50%

ii. **Cockroach allergens**

Cockroach is one of the major allergens in Indian households and exposure elimination is very difficult to achieve in houses. To avoid or eliminate cockroach infestation good housekeeping and regular pest control is necessary.

iii. **Animal Dander**

Ideally, the animal should be removed from home, in cases where, children are at risk of developing allergy, or are allergic to animal dander. It is also advised to remove animal from home, even when patient have demonstrated sensitization to some other allergen but not to animal dander by skin prick test. Cat allergens are produced from sebaceous glands in skin which are around 2-4 µ in size and remain suspended in air for long (30). Even after cat is removed, these particles remain for prolonged periods especially on carpets and upholstered furniture. If families don't remove the cats from home, then they should be kept away from bedrooms and should be bathed with warm water weekly (31).

iv. Pollens

The distribution of major pollens differs in different seasons in a particular geographical area. So, it is important for allergist to be aware of local pattern of pollen predominance at a particular period of time. Based on clinical history and

seasonal variation of symptoms, SPT should be planned to find the offending allergen. Once, offending pollen is known, whether it is tree or grass or weed pollen, the precaution has to be taken during the season of that pollen. To avoid the pollen exposure, patient is instructed to stay indoors especially during peak pollen hours i.e. early mornings. The windows should be kept close and air conditioners shall be used in houses and cars (29).

B. Dietary Control measures

Dietary control measures are important in children at high risk of development of allergies. Such children are benefitted from dietary avoidance of highly allergenic substances in first few years of life as it decreases the incidence of food allergies and atopic dermatitis in early life. The food allergies which present in early life to milk, eggs and soya tend to be outgrown spontaneously later on, so monitoring is essential as these foods can be usually reintroduced into the diet, once serum specific IgE levels have dropped sufficiently. While allergies to peanuts, tree nuts, fish and seafood generally persists (29). Other indicators predicting persistence are, strongly positive skin prick test (SPT) or elevated specific IgE (spIgE) at the time of diagnosis or during follow-up.

II. Pharmacological Management

Pharmacological management includes both acute and chronic management of allergy which is mainly supportive like – anti-histamines, nasal steroids and inhaled or oral corticosteroids. The allergen specific immunotherapy has also shown promising results.

A. Allergen Specific Immunotherapy

The use of immunotherapy in allergy dates back to 1911, when Noon and Cantab demonstrated that in patient with grass pollen allergy, symptoms reduce on repetitive exposure to grass pollen extracts (32). The allergen specific Immunotherapy (SIT) is

effective in patients with IgE-mediated allergy, in which gradually augmented doses of specific allergen extract is given to allergic patients (33). The main aim is to develop immune tolerance to these allergens by repeated exposure, thereby leading to decreased responsiveness of body's immune system to these external antigens and hence decreased symptoms.

The standardized allergen extracts which are used for immunotherapy are called as allergen vaccines which when given by subcutaneous route, is called as Subcutaneous Immunotherapy (SCIT). Other routes to give immunotherapy are also being explored and is known as Local Immunotherapy (LIT), which includes oral, nasal, local bronchial and sublingual (SLIT).

Indications for allergen specific Immunotherapy (SIT)

SIT is not suitable for young children <5 years of age. It has good efficacy and is tolerated well in many conditions like (34) -

- Allergic rhinitis, allergic rhino-conjunctivitis, allergic asthma
- Past history of systemic reaction to venom of Hymenoptera and presence of specific IgE antibodies to hymenoptera venom in blood.
- Symptoms are not adequately controlled by avoidance measure and compliant use of medications
- Patient makes an informed choice for SIT, instead of long term use of medications.
- Cost of immunotherapy is less than the cost of life-long use of medications.

Contraindications for SIT

- Uncontrolled asthma
- Severe side effects with SIT in past administration.
- Malignant neoplastic disease
- Severe systemic autoimmune disease, immunodeficiency state

- Insufficient adherence
- Chronic infection like HIV, Hepatitis C.

Conclusion:

Allergic disorders are very common especially in pediatric age group. Appropriate management includes identification of offending allergen, targeted avoidance measures and specific immunotherapy along with optimal pharmacotherapy.

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Lentil Aspiration Pneumonia

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Introduction

Aspiration of lentil-based foods leading to hypersensitivity pneumonitis is a rare, but known cause of persistent respiratory symptoms. It shall be suspected in children who have some predisposing factors like history of forceful feeding of lentil-based foods in infancy, children with swallowing dysfunction like cerebral palsy or mental retardation or children with seizure disorder. (1)

Case Report

A 9 months old girl presented to some private hospital with complaints of cough for 1 month and fast breathing for 7 days. The cough was dry, paroxysmal, spasmodic with post-tussive vomiting. It was associated with fast breathing with chest indrawing for past 7 days. There was no history of fever or repeated nebulization in the past. The child was started on intravenous ceftriaxone and amikacin, which were given for 5 days and upgraded to injection meropenem and vancomycin on day 6, but in view of no clinical improvement, child was referred to our hospital. At admission, child was afebrile with heart rate was 150/min with maintained perfusion, respiratory rate was 60/ min with intercostal and subcostal retractions, SpO_2 was 94% under O_2 by nasal prongs 3L/min. On auscultation, bilateral air entry was equal with bilateral crepitations. Rest systemic examination was normal. Chest radiograph was suggestive of bilateral parahilar consolidations (Figure 1). Child was started on intravenous piperacillin-tazobactam, teicoplanin and oral Oseltamivir. Echocardiography was also done to rule out any cardiac cause and it came out to be normal. On day 3, chest radiograph was repeated, but there was no improvement. In view of no improvement, investigations for tuberculosis were done which turned out to be negative. On day 4 of admission, contrast-enhanced CT chest was done (Figure 2). CT chest revealed extensive perihilar consolidations. On day 5, broncho-alveolar lavage was done and BAL culture grew *Pseudomonas putida*. Injection Piperacillin-tazobactum was continued, and injection amikacin and levofloxacin were added. On day 6, IgG lentil was sent to AIIMS, Delhi and level was 124 mgA/L (normal range: <10 mgA/L). Child was started on oral steroids at the dose of 1 mg/kg/day. Gradually, the child improved and oxygen support was tapered off

slowly. The child was discharged on prednisolone on 1mg/kg/day and was tapered gradually over 2 months. The chest radiograph at 2 months follow-up showed marked improvement. (Figure 1b)

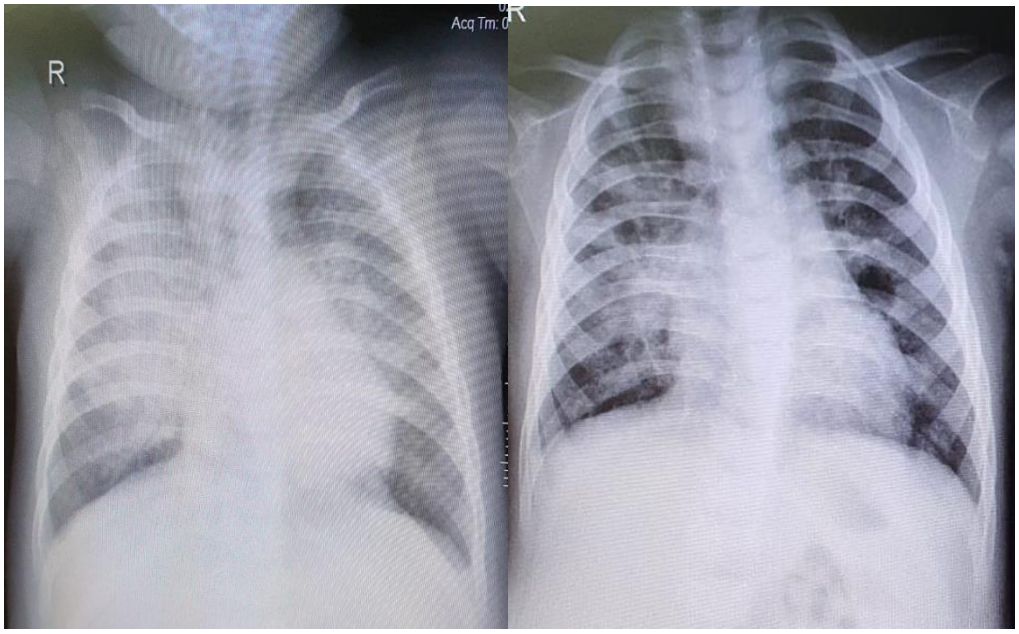

Figure 1: (a) Chest radiograph at presentation Figure 1(b) Chest radiograph after 2 months of treatment

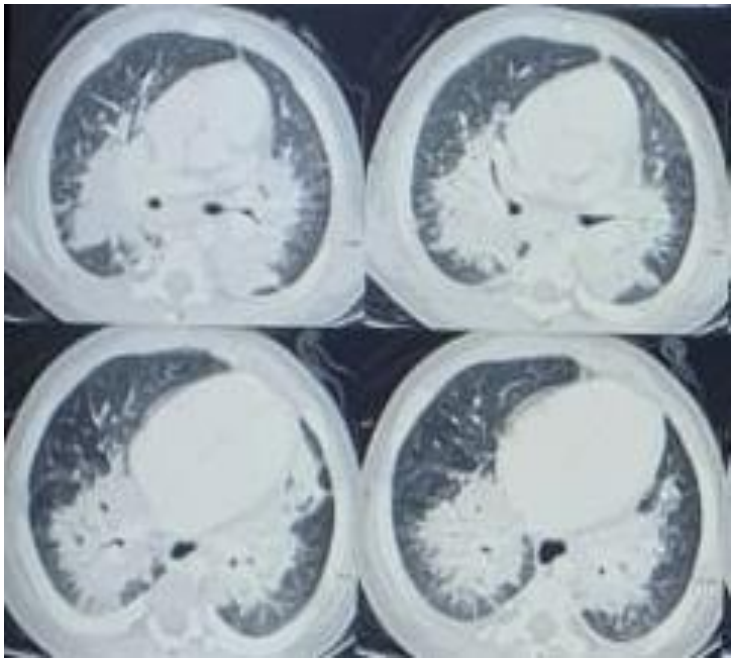

Figure 2 Computerised tomography chest- axial sections in lung window

Discussion

There is paucity of data on lentil aspiration pneumonia with only few case reports in literature till date. Aspiration of lentil occurs due to some predisposing conditions like forceful feeding of lentil based foods (legumes like peas, beans) in infancy or swallowing dysfunction in children with intellectual disability, which may lead to persistent respiratory symptoms and radiological findings similar to hypersensitivity pneumonitis. (2)

The pathophysiology of lentil aspiration pneumonia is not well described in literature. Knoblich et al. has described 41 post-mortem cases with pulmonary granulomatosis. (3) He found that cellulose in lentil is indigestible and indestructible, therefore it stays as a central foreign body, inducing immunological reaction in the form of cuff of lymphocytes, epithelioid cells and giant cells around it. This granuloma well develops within 5 days and leads to recurring cycles of granulomatosis. Later on, it undergoes compaction forming a dense fibrotic nodule. Similar finding was reported by Pablo, where in a 14 year old child, open lung biopsy was done which showed chronic granulomatous pneumonia. (1)

Dhochak et al., conducted a retrospective study which included 16 patients who had prolonged respiratory symptoms following history of forceful feeding of lentil-based foods. The mean age at onset was 9 months while mean age at diagnosis was 11 months. The most common presentation was chronic cough in 100% cases, shortness of breath in 93.5% cases, fever in 87.5%, vomiting in 37.5% and wheezing in 25 % cases. (4)

The work-up for patients with suspected lentil aspiration pneumonia includes- chest radiograph, CT of chest and lentil specific IgG antibodies. Initial Chest radiograph is generally suggestive of broncho-pneumonic pattern with diffuse, bright fine interstitial nodular pattern. (5) In the study by Dhochak et al, all 16 patients underwent CT chest which was suggestive of consolidation in 31.3% (5/16), reticulonodular pattern in 25% (4/16) while mixed pattern in 43.7% (7/16). Broncho-alveolar lavage was done in 10, out of 16 patients, in which neutrophils were raised in 70% cases and lymphocytes in 30%. Lentil specific Immunoglobulin G antibodies were sent in 9 patients and it was raised in all the 9 patients. (4) The differential diagnosis includes – fungal disease, histiocytosis X, interstitial fibrosis, primary and metastatic malignant conditions, pneumoconiosis or other granulomatous conditions. (1)

All the patients were treated with oral steroids at a median dose of 1mg/kg/day for median duration of 7 weeks and significant improvement was noted in all the patients. (4)

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