

2022 AAE Conference

Pharmacology Pre-Conference

Managing Allergic Asthma:

**SCIT, SLIT, Oral Immunotherapy and Peanut
Desensitization**

Chattanooga, TN

August 4, 2022

2:30 p.m. – 3:30 p.m.



Managing Allergic Asthma: SCIT, SLIT, Oral Immunotherapy and Peanut Desensitization

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Objectives

1. Summarize the pathophysiology, management, and treatment goals of allergic asthma.
2. Identify the principal types, indications, and safety profile of allergen immunotherapy.
3. Discuss the benefits and side effects of currently available forms of peanut oral immunotherapy.

Pathogenesis of Asthma

- Asthma is a complex, chronic disease with marked heterogeneity in clinical symptoms, severity and treatment response
- Asthma is defined by the history of respiratory symptoms, including wheeze, shortness of breath, chest tightening and cough, that vary over time and in intensity, together with variable expiratory airflow limitation
- Driven by interactions between epigenetic regulation and environmental exposure

Allergic Asthma



Agache I, Akdis CA, Akdis M, *et al.* *Allergy*, 76 (1) (2021), pp. 14-44

Allergic Asthma

Allergic asthma is asthma associated with sensitization to aeroallergens, which leads to asthma symptoms and airway inflammation

Symptoms caused by

- exposure to a perennial aeroallergen
- serum total IgE levels 30-1300 IU/mL
- not adequately controlled on ICS or other controller

Allergic Asthma

- Allergic asthma is classified as a type 1 hypersensitivity reaction¹
- Prevalence of allergic asthma is increasing globally due to air pollution and other environmental irritants²
- Involves allergen-specific immunoglobulins of the IgE class bound to high-affinity Fcε receptors on the surfaces of basophils and mast cells present in the subepithelial layer of the airways³

1. Agrawal DK, Shao Z. *Curr Allergy Asthma Rep.* 2010 Jan;10(1):39-48.

2. World Health Organization. 2022. <https://www.who.int>

3. Hu, J., Chen, J., Ye, L. *et al. Clin Trans Allergy* 2018,**8**, 27

Immunopathogenesis of Asthma

Th2 cells produce cytokines related to asthma:

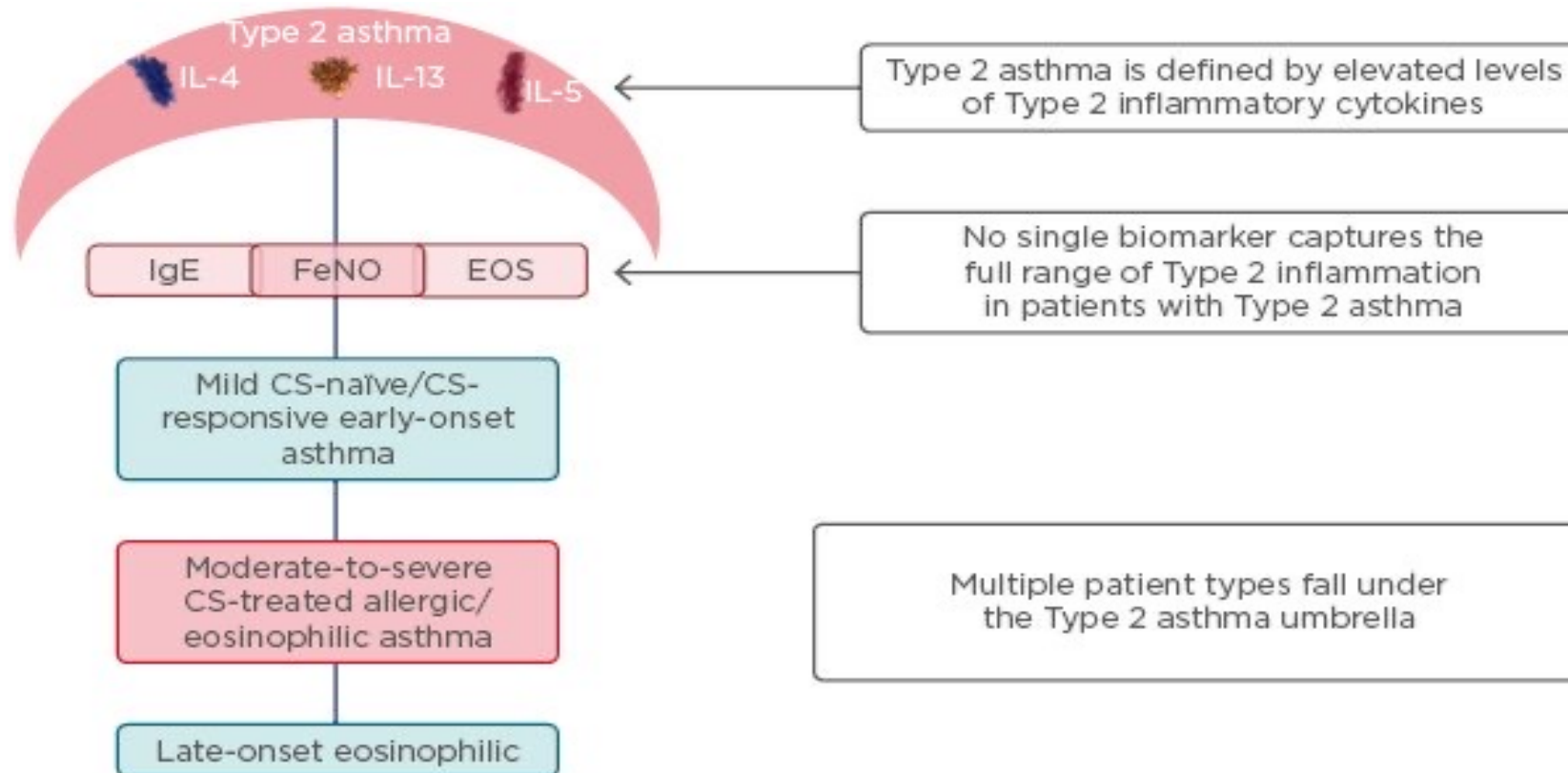
IL-5, IL-4 and IL-13

Eosinophils, basophils, and mast cells are activated by the cytokines secreted by these cells and are also involved in the type 2 immune response

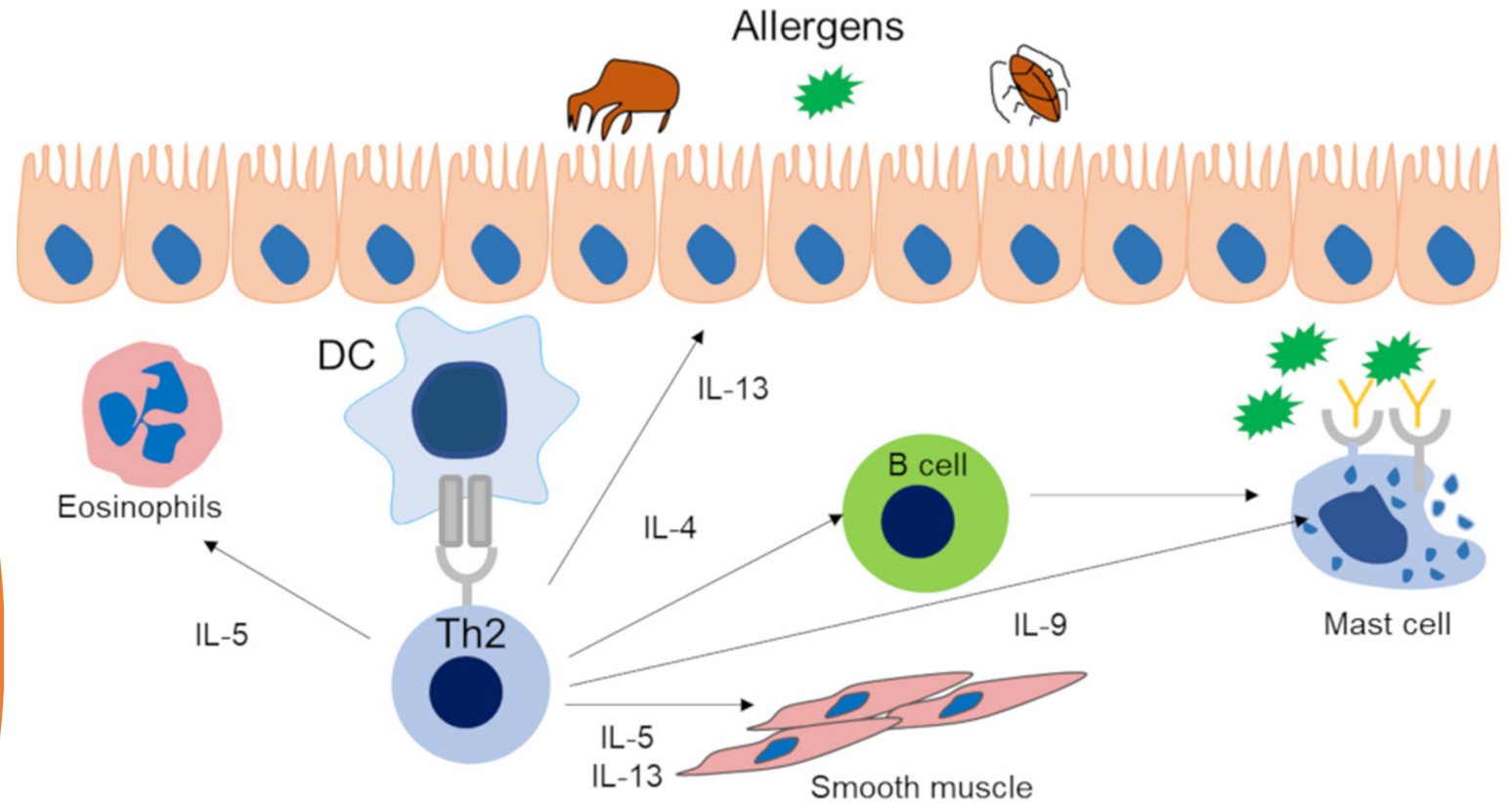
Pathobiologic Roles of IL-4, IL-5, and IL-13

- IL-4, IL-13 and IL-5 are key drivers of Type 2 inflammation in asthma
- Type 2 (T2) inflammation plays a key role in the pathogenesis of asthma
- IL-4, IL-5, and IL-13, along with other inflammatory mediators, lead to increased cellular eosinophilic inflammation
- Approximately 50% of patients with asthma have evidence of T2-high inflammation

Type 2 Inflammation



Allergic asthma is characterized by a Th2-dominated immune response



- The primary cytokines involved include IL-4, IL-5, and IL-13
- IL-4 and IL-13 are critical for IgE class switching

Clinical Characteristics of Allergic Asthma

- Allergic asthma is often accompanied by a history of eczema and allergic rhinitis¹
- Most common asthma phenotype
- The average age of onset of allergic asthma is younger than that of nonallergic asthma
- Sensitization to allergens is thought to have a significant role in the development of asthma

Allergic Asthma

- Allergic asthma mechanistically driven by type 2 (T2) inflammation, with elevated eosinophil counts being a common feature¹
- Inhaled allergens lead to increased serum IgE levels
- IgE binds to mast cells and basophils, which secrete histamine and lipid mediators that cause bronchoconstriction and activate other inflammatory cells
- Mast cells and basophils also secrete IL-4 and IL-13, causing plasma and cell extravasation and recruitment of eosinophils, the key cells involved in the inflammation²

1. ME Kuruvilla, FE Lee and GB. Lee Clin Rev Allergy Immunol, 56 (2) (2019), pp. 219-233

2. EMJ. 2018;3[4]:24-33

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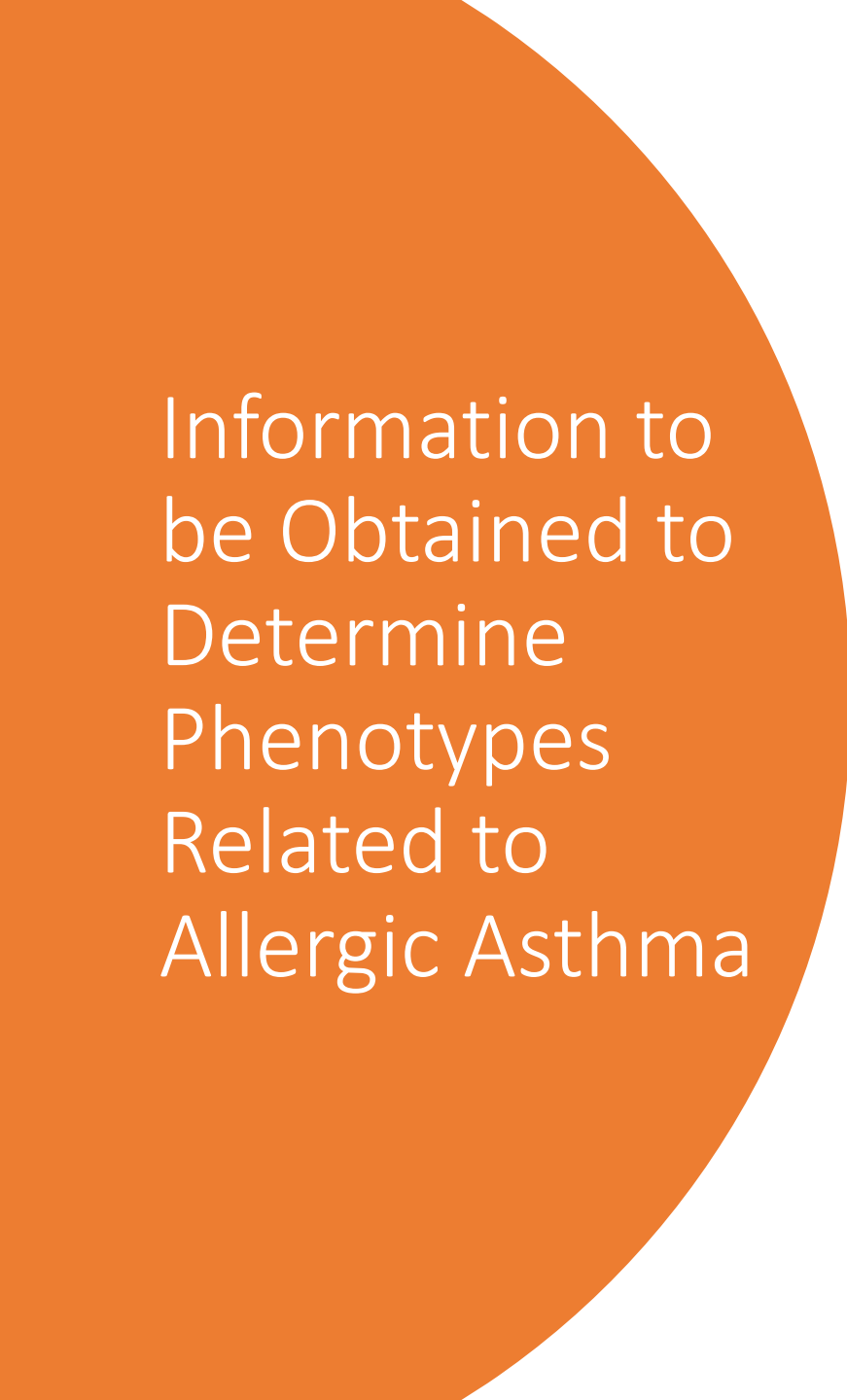
1. ME Kuruvilla, FE Lee and GB. Lee Clin Rev Allergy Immunol, 56 (2) (2019), pp. 219-233

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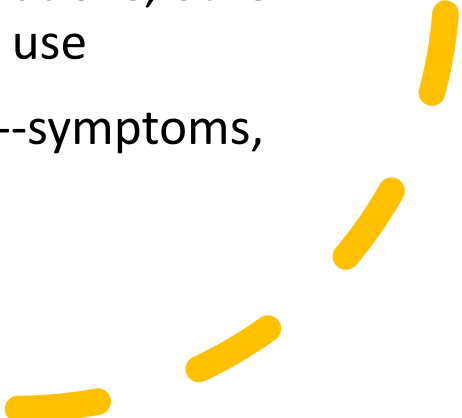
Asthma Phenotypes

- Phenotypes are recognizable clusters of demographic, clinical and/or pathophysiological characteristics¹
 - Allergic asthma
 - Non-allergic asthma
 - Adult-onset (late-onset) asthma
 - Asthma with persistent airflow limitation
 - Asthma with obesity

| Phenotype | Description | Adults | Pediatrics | Therapy |
|-------------------------------|--|---|--|--|
| T2 high | High levels TH ₂ cytokines (IL4, IL5, and IL13); biomarkers include airway and blood eosinophils, FENO, and periostin | More severe disease with higher risk of asthma attacks | Children with severe asthma are predominantly eosinophilic, although TH ₂ cytokines may not be elevated | Steroid sensitive, anti IgE or anti IL4, IL5, or IL13 |
| T2 low | Low levels of eosinophils, often associated with airway neutrophilia | Patients tend to be older; associated with low FEV ₁ and air trapping, poor steroid response | Little evidence for T ₂ low asthma in children; airway neutrophils may be protective; airway neutrophilia associated with infection | Macrolide antibiotics may have some benefit |
| Persistent airflow limitation | Low FEV ₁ or FEV ₁ /FVC post bronchodilator, post steroid trial | 40–60% with severe asthma, older age, longer asthma duration, smoking (93) | 25% of children with severe asthma have PAL; associated with increase in airway smooth muscle (94–96) | Optimize long acting bronchodilators, down titrate steroids to lowest dose to control symptoms |
| Atopic | Sensitisation to aeroallergens and elevated IgE | Associated with early onset asthma persisting into adulthood | Most children are atopic and have co-morbid atopic diseases | Steroid responsive; T ₂ targeted therapies as above |

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Information to be Obtained to Determine Phenotypes Related to Allergic Asthma

1. Immediate family history of allergy and asthma
 2. Age of onset
 3. Sex
 4. Occupation
 5. Personal history of allergic rhinitis, food allergy, atopic dermatitis
 6. History and/or presence of nasal polyps or sinusitis
 7. Potential allergic triggers, including seasonal variation and symptoms when exposed to freshly cut grass, house dust, molds, and animals
 8. Clinical markers of severity --prior hospitalizations, other unscheduled visits, oral glucocorticosteroid use
 9. Clinical markers of severity and/or control --symptoms, activity limitation, FEV1
 10. Specific IgE tests
- 
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Biomarkers in Allergic Asthma

- Peripheral blood eosinophilia may be seen in allergic or nonallergic asthma and may correlate with airway obstruction and predict exacerbations
- Less remodeling by computerized tomography in allergic versus nonallergic patients is also reported



Biomarkers in Allergic Asthma

Biomarkers are an option in addition to the skin prick test that helps to distinguish atopic from nonatopic asthma endotypes

Total IgE and tests for atopy → specific IgE and skin prick tests for allergens

Allergic asthma often presents with TH2-high biomarkers:

- elevated blood and sputum eosinophil counts
- FENO
- periostin in adults

Three Treatment Options for Patients with Allergic Asthma

Allergen avoidance

Pharmacotherapy including biologics

Biologics, targeting the TH2 pathway, have been shown to be effective in the treatment of allergic asthma¹

Allergen immunotherapy (AIT)

Treatment Goals for Allergic Asthma

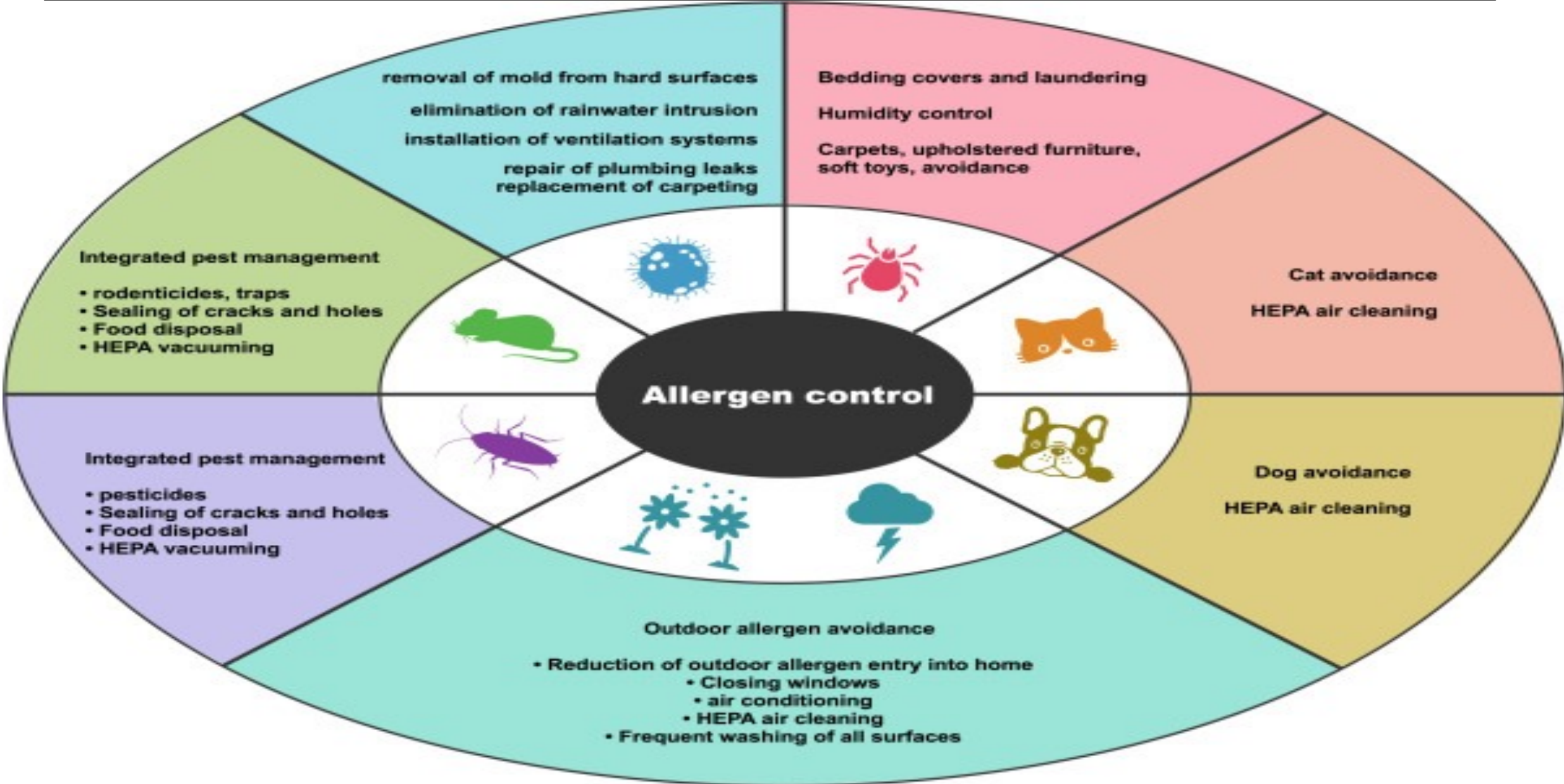
- Prevent hospital, emergency room or urgent care visits
- Achieve long-term control of asthma
- Reduce symptoms
- Maintain normal activity level
- Prevent exacerbation
- Prevent accelerated loss of pulmonary function (FEV1)
- Avoid harm from medical therapy

Treatment Goals of Allergic Asthma

Guideline-based management of asthma focuses on disease severity and choosing the appropriate medical therapy to control symptoms and reduce the risk of exacerbations



Allergen Avoidance



Allergens that
have been
associated with
allergic asthma

- Cockroach Dander (cat, dog)
- House dust mite (Dermatophagoides pteronyssinus, Dermatophagoides farina)
- Mold spores (Alternaria)
- Cladosporium [Hormodendrum]
- Helminthosporium
- Aspergillus
- Penicillium
- Pollens -- regional tree, grass, and
weed pollens

Treatment Modalities

Biologic Therapies

Anti-IgE
Omalizumab

Anti-IL-5
Benralizumab
Mepolizumab
Reslizumab

Anti-IL-4/IL-13
Dupilumab

Anti-thymic Stromal
Lymphopoietin (TSLP)
Tezepelumab

Summary of Biologics

| Biologic | Target | Commonly used criteria | Asthma trials |
|------------------------|------------------------|--|--|
| Omalizumab (Xolair) | IgE | IgE \geq 30 IU/mL – 700 IU/ml – adults IgE \geq 30 IU/mL – 1300 IU/ml - pediatrics positive SPT response or specific IgE levels to perennial allergens | Significant improvement of asthma control and Asthma Control Test scores |
| Mepolizumab (Nucala) | IL-5 | Blood eosinophil count \geq 300 cells/mL | Decrease exacerbations by 39% to 52% |
| Reslizumab (Cinqair) | IL-5 | Blood eosinophil count $>$ 400 cells/mL | Decrease exacerbations by 50% to 59% |
| Benralizumab (Fasenra) | IL-5 receptor α | Blood eosinophil count $>$ 300 cells/mL | Decreased exacerbations by 45% to 51% Improvement in prebronchodilator FEV1 by 0.106-0.159 L Improvements in ACQ-5 scores |
| Dupilumab (Dupixent) | IL-4 Ra | Blood eosinophil count $>$ 150 cells/mL FENO $>$ 25 ppb | Decreased exacerbations by 46% to 48% Improvement in prebronchodilator FEV1 by 0.13-0.14 L Improvements in ACQ-5 scores Improved prebronchodilator FEV1 |
| Tezepelumab | TSLP | Trial criteria: uncontrolled asthma on ICS/LABA; history of exacerbation FEV1: 40% to 80% of predicted value; post-BDR $>$ 12% | Phase 2 trials showed improvement in exacerbation rates by 62% to 71% Reduction in blood eosinophil counts, serum IgE levels, and FENO values |

Treatment Modalities

- Allergen-specific immunotherapy target type-2 (T2) inflammation
- Allergen immunotherapy is effective in decreasing symptoms and medication use in select patients with mild-to-moderate allergic asthma
- Patients who receive allergen immunotherapy for allergic rhinitis may have a decreased risk of developing asthma

Immunotherapy

Immunotherapy is recommended as an adjunct treatment to standing pharmacotherapy



Allergen Immunotherapy (AIT)

- AIT reduces symptoms and medication use associated with allergic rhinitis with or without conjunctivitis and allergic asthma
- Allergen immunotherapy is the only modality that can modify the immune response upon exposure to aeroallergens and venom allergens
- Allergen immunotherapy (AIT) is the only modality that can modify TH2-directed immune responses and reduce allergic nasal and ocular symptoms upon exposure to aeroallergens

Two major AIT modalities

Subcutaneous allergen immunotherapy (SCIT)

Sublingual allergen immunotherapy (SLIT)

Subcutaneous immunotherapy (SCIT) a solution containing an allergen(s) is injected under the skin

Sublingual immunotherapy (SLIT), which may be dosed at home, consists of exposure to the allergen via an aqueous solution or tablet formulation placed under the tongue

Comparison Between Sublingual Allergen Immunotherapy (SLIT) Tablets and Drops

| Variable | SLIT tablets | SLIT drops |
|------------------------------|--|---|
| Evidence-based medicine | <ul style="list-style-type: none"> • Strong pharmaceutical clinical development • Robust quality evidence • Large phase 3 studies included • Long-term and sustained effect demonstrate (1- to 5-year clinical trials) | <ul style="list-style-type: none"> • Weak pharmaceutical clinical development • Poor to moderate quality evidence • Small studies included • No available long-term and sustained effect demonstrated |
| Quality of SLIT products | Good-quality products are available All SLIT tablet products use biologically standardized and quantified allergen extracts | Good-quality products are available Some studies used non-standardized products |
| Legal framework | Regulatory procedure approval before marketed in EU and United States Under EU price and reimbursement regulation | Commercialization approval In EU and United States, there is no price regulation |
| Single vs multiple allergens | Tablets mainly use single allergen source (or highly homologous) Supporting the concept of one product for the homologous allergen group | Combination of various allergens sources can be mixed Allergen extracts from different nonhomologous groups are used |

Comparison Between Sublingual Allergen Immunotherapy (SLIT) Tablets and Drops

| Variable | SLIT tablets | SLIT drops |
|--|---|---|
| Use in polysensitized patients | If there is no allergen cross-reactivity, there is need to use different products | There are allergen mixtures In same vial, various allergens can be included |
| Cost | Expensive | Cost Expensive Less expensive |
| US Food and Drug Administration product approval based on phase 1-3 trials | Four products | None |
| Dose administered | Exact dose per tablet is given Always mono-dose | Error range per vial or preparation Usually, multidose vials |

U.S. Food and Drug Administration (FDA) Approved Sublingual Immunotherapy (SLIT) Allergy Tablets

| Generic Name | Brand Name | Use | Usual Dosage |
|---|------------|---|--|
| Dust mite oral extract | Odactra | Dust Mite Allergy 18-65 years old | Once per day year round |
| Timothy grass pollen sublingual extract | Grastek | Treatment of allergy to timothy and similar grasses 5 – 65 years old | One tablet once a day First dose in allergy clinic starting 12 weeks prior to grass season |
| Grass pollen sublingual extract (sweet vernal, orchard, perennial, rye, timothy, Kentucky blue) | Oralair | Allergic rhinitis with or without allergic conjunctivitis Ages 10-65 years old | One tablet once a day First dose in allergy clinic starting at least 4 months prior to the start of grass pollen season |
| Short ragweed pollen sublingual extract | Ragwitek | Treatment of allergy to ragweed 5 – 65 years old | One tablet once a day First dose in allergy clinic Start 12 weeks prior to ragweed season |

Subcutaneous Immunotherapy (SCIT)

- SCIT for inhalant allergens is effective treatment for allergic rhinitis, allergic asthma, and some patients with atopic dermatitis.
- SCIT can be administered for 3 to 5 years and produce continuing relief of symptoms for years after discontinuation
- Immunotherapy is recommended for allergic asthma as an adjunct treatment to standard pharmacotherapy

Subcutaneous Immunotherapy (SCIT)



GRASTEK[®]
Timothy Grass Pollen Allergen Extract
Tablet for Sublingual Use 2800 BAU



ODACTRA[®]
House Dust Mite (*Dermatophagoides
farinae* and *Dermatophagoides
pteronyssinus*) Allergen Extract
Tablet for Sublingual Use 12 SQ-HDM



RAGWITEK[®]
Short Ragweed Pollen Allergen Extract
Tablet for Sublingual Use 12 Amb a 1-U

RAGWITEK[®] .18-65 years
GRASTEK[®] 5-65 years
Orlair 5-65 years
Odactra 18-65 years

- Immunotherapy is recommended as an adjunct treatment to standard pharmacotherapy.
- 2014 FDA approved 3 SLIT
- Advantages:
 - Self-administration
 - Oral administration
 - Possible lower anaphylaxis risk

Contraindication for SCIT or SLIT

- **Absolute contraindications** : serious immunologic disease, major cardiovascular disease, cancer, chronic infections, lack of compliance, severe psychological disorders
- **Relative** contraindications: pregnancy
- Severe asthma or uncontrolled asthma regardless of its severity is major risk factor for serious or even fatal adverse reactions
- Partially controlled asthma is a *relative* contraindication

Contraindication for SCIT

- History of eosinophilic esophagitis
- History of severe local reactions from sublingual allergen immunotherapy
- History of severe systemic allergic reactions
- Hypersensitivity to inactive products -->. Gelatin, mannitol, sodium hydroxide
- Severe, unstable or uncontrolled asthma

Initiating Allergen Immunotherapy

- Clinical evaluation and physical examination
- Identification of specific allergen sensitivity to the relevant allergens
- Shared decision making:
 - Discuss patient of goals
 - Risks versus benefits
 - Long-term commitment to the treatment plan



Current Practice in Testing for Aeroallergens

- GINA recommends SPT or sIgE testing for relevant allergens if not already done as part of the assessment of comorbidities and phenotyping for those with severe asthma
- Patterns of aeroallergen sensitization help in defining asthma phenotypes
- Allergy test results can guide clinical precision medicine for chronic airway disease in individual patients, including AIT

Current Practice in Testing for Aeroallergens

- Negative allergy test results prompt a search for other causes of symptoms.
- Known aeroallergen sensitizations stimulate recommendation of environmental remediation advice and AIT when appropriate
- Testing will address common patient concerns about allergy, predicting exacerbations and response to therapies – may improve adherence
- Positive allergy test results can be considered as one of the referral criteria for specialist care

THE
BIG 9
FOOD
ALLERGENS



milk



fish



peanuts



soy



tree nuts



shell fish



wheat



eggs

sesame



healthline

Allergic Asthma and Food Allergy

- Food-induced allergic disorders are adverse immunologic potentially life-threatening reactions that occur on exposure to a food¹
- Food allergies affect 32 million Americans¹
- Approximately 1 in 13 children or 2 in every average-size American classroom¹
- Food sensitization, particularly to egg, has increased the risk of developing allergic asthma¹
- Coexistence may negatively influence the severity of both conditions³

1. di Palma E, Gallucci M, Cipriani F, Bertelli L, Giannetti A, Ricci G. Medicina (Kaunas). 2019 Aug 21;55(9):509.

2. Whitsel RM, Bjelac JA, Subramanian A., et al. Cleveland Clinic Journal of Medicine Feb 2021, 88 (2)104-109.

3. Caffarelli C., Garrubba M., Greco C., et al. Front. Pediatr. 2016, 4, 34.



Allergic Asthma and Food Allergy

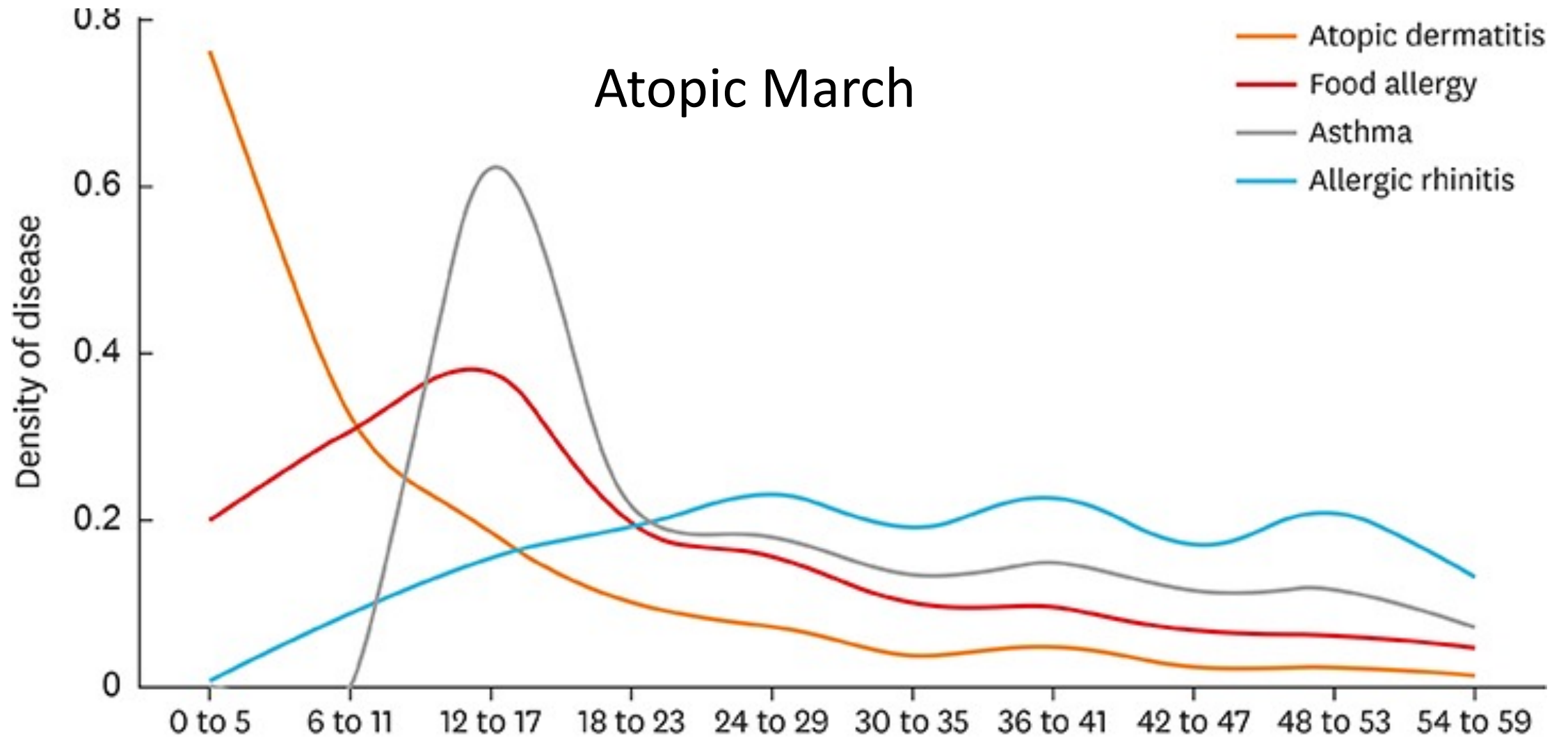
- Research has shown that having one atopic disease can predispose to having another¹
- Coexistence may negatively influence the severity of both conditions²
- Food allergy is seen in one-fourth of children with asthma and significantly affects symptom control³

di Palma E, Gallucci M, Cipriani F, Bertelli L, Giannetti A, Ricci G. *Medicina (Kaunas)*. 2019 Aug 21;55(9):509.


Caffarelli C., Garrubba M., Greco C., et al. *Front. Pediatr.* 2016, 4, 34.

Cherian AA, Lakshminarasappa DS, Chandrasekaran V, Chinnakali P.. *Health Sci Rep.* 2022 Jan 6;5(1):e475.

Atopic March



Food Allergy and Allergic Asthma

- Peanut allergy is one of the most common food allergies and can trigger a life-threatening reaction 
- Food allergen sensitization is recognized as an important modifiable risk factor for asthma exacerbation^{1,2}
- Current standard of care for treatment of food allergy:
 - Avoidance of the allergen
 - Treatment of anaphylaxis with auto-injectable epinephrine
 - Oral immunotherapy (OIT)

Oral Immunotherapy Peanut

Palforzia
Peanut (*Arachis hypogaea*)
Allergen Powder-dnfp



- PALFORZIA FDA approved January 31, 2020, for use in patients with a confirmed diagnosis of peanut allergy.
- Patients must maintain a strict peanut-free diet while taking Palforzia
- Initial Dose Escalation may be administered to patients aged 4 through 17 years.
- Up-Dosing and Maintenance may be continued in patients 4 years of age and older

Table 1: Dosing Configuration for Initial Dose Escalation (Single Day Dose Escalation)

| Dose Level | Total Dose | Dose Configuration |
|------------|------------|--------------------------------------|
| A | 0.5 mg | One 0.5 mg capsule |
| B | 1 mg | One 1 mg capsule |
| C | 1.5 mg | One 0.5 mg capsule; One 1 mg capsule |
| D | 3 mg | Three 1 mg capsules |
| E | 6 mg | Six 1 mg capsules |

Initial Dose Escalation supplied as a single card consisting of 5 blisters containing a total of 13 capsules.

Table 2: Daily Dosing Configuration for Up-Dosing

| Dose Level | Total Daily Dose | Daily Dose Configuration | Dose Duration (weeks) |
|------------|------------------|--|-----------------------|
| 1 | 3 mg | Three 1 mg capsules | 2 |
| 2 | 6 mg | Six 1 mg capsules | 2 |
| 3 | 12 mg | Two 1 mg capsules; One 10 mg capsule | 2 |
| 4 | 20 mg | One 20 mg capsule | 2 |
| 5 | 40 mg | Two 20 mg capsules | 2 |
| 6 | 80 mg | Four 20 mg capsules | 2 |
| 7 | 120 mg | One 20 mg capsule; One 100 mg capsule | 2 |
| 8 | 160 mg | Three 20 mg capsules; One 100 mg capsule | 2 |
| 9 | 200 mg | Two 100 mg capsules | 2 |
| 10 | 240 mg | Two 20 mg capsules; Two 100 mg capsules | 2 |
| 11 | 300 mg | One 300 mg sachet | 2 |

Table 3: Daily Dosing Configuration for Maintenance

| Dose Level | Total Daily Dose | Daily Dose Configuration |
|------------|------------------|--------------------------|
| 11 | 300 mg | One 300 mg sachet |

Safety Information

Palforzia. Prescribing information. Aimmune
Therapeutics, Inc.

https://www.palforzia.com/static/pi_palforzia.pdf

- Instruct patient, parent, or guardian that patients with asthma should stop taking PALFORZIA and contact their health care professional immediately if they have difficulty breathing or if their asthma becomes difficult to control
- PALFORZIA can cause anaphylaxis, which may be life-threatening (9.4% in clinical trials)
- Prescribe injectable epinephrine
- Dose modification may be necessary following an anaphylactic reaction
- Observe patients during and after administration of the initial Dosage Escalation and the first dose of each Up-Dosing level, for at least 60 minutes

Discontinuation of PALFORZIA

- Patients who are unable to tolerate doses up to and including the 3 mg dose during Initial Dose Escalation
- Patients with suspected eosinophilic esophagitis
- Patients unable to comply with the daily dosing requirements
- Patients with recurrent asthma exacerbations or persistent loss of asthma control



Foodsafety.gov

Anaphylaxis

Patients with known IgE-mediated food allergies and asthma should have immediate access to self-injectable epinephrine and inhaled beta-agonists



<https://www.epipen.com>



<https://www.auvi-q.com/>

*thank
you*

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