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REVIEW

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What is the role of the IgE-mediated allergy in severe asthma?

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ABSTRACT

Introduction: Severe asthma (SA) is a heterogenous disease with multiple clinical phenotypes. 'Early atopic asthma' is the predominant phenotype in children with SA. This phenotype is also identified in adults with SA. However, the role of immunoglobulin E (IgE)-mediated allergy in SA is still under debate.

Areas covered: This review summarizes current evidence linking IgE-mediated sensitization to SA. Electronic search was realized in Medline and PubMed databases by using the following terms: 'severe asthma,' 'IgE-mediated' associated with 'environmental allergens,' 'aeroallergens,' 'house dust mites,' 'pollens,' 'pets,' 'moulds,' 'cockroach,' 'food allergy,' 'drug allergy,' 'venom allergy,' 'atopic dermatitis,' 'eczema,' 'anaphylaxis.' Exposure to most aeroallergens of SA patients with atopy is associated with an increased risk of severe exacerbations. Children with food allergy have more severe asthma, poor symptoms control, and a high hospitalization rate. More limited evidence exists for the other IgE-mediated conditions and SA.

Expert opinion: IgE-mediated pathways play central role in the pathogenesis of various allergic diseases, including asthma. However, the allergic burden seems to be more important in children with SA than in adults. Future research may provide a better understanding of the role of IgE-mediated allergy in SA and coexisting allergic diseases with improvement in their clinical outcomes.

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1. Introduction

Asthma is a complex disease characterized by chronic airway inflammation associated with airway hyperresponsiveness (AHR) and variable expiratory airflow, with symptoms such as wheeze, shortness of breath, chest tightness, and cough variable in intensity and over the time [1]. The number of asthma cases significantly increases during the last 25 years with more than 300 million people worldwide currently affected, and its socio-economic burden remains high despite efforts to minimize its impact [2,3]. In difficult-to-treat asthma, poor control can be due to low adherence to inhaled corticosteroids (ICS), incorrect inhaler technique, and coexisting conditions, including exposure to allergens and irritants [2]. Severe asthma (SA) encompasses a group of patients with difficult-to-treat asthma that remains uncontrolled despite adherence with maximal optimized high dose of ICS with a second controller (usually a long-acting beta-2 agonists -LABA) treatment and management of contributory factors, or that worsens when high dose treatment is decreased. SA is thought to affect approximately 3.7% of asthmatics worldwide corresponding to approximately 0.5% of the general population [4]. More than one in three asthmatic patients show at least one feature of SA [5]. In childhood, the proportion appears smaller with the estimated prevalence of 2.1% among children with asthma and 0.23% in the general population [6]. Severe asthmatics, both adults and children, have uncontrolled symptoms, high risk of exacerbations, poor quality of life, impaired lung function, increased health-care resource use, and costs [2,4].

SA is a heterogeneous syndrome that consists of various phenotypes driven by different pathways [2,7]. Several phenotypes were identified based on the age of onset (childhood or adulthood), the presence of atopy, obesity, and airflow limitation, smoking status, frequency of exacerbations, airway inflammation, and response to treatments [7]. According to the inflammatory pattern, SA is classified as T2-high when associated with increased blood eosinophil counts and/or elevation of fractional exhaled nitric oxide (FeNO), and T2-low when neutrophilic inflammation is predominant. The coexistence of eosinophilic and neutrophilic airway inflammation characterizes mixed granulocytic asthma [2,7]. T2-high asthma seems to be the dominant phenotype across all ages [8].

Allergic asthma is the most common endotype of the T2-high phenotype characterized by early onset, immunoglobulin E (IgE) sensitization to allergens, and clinically apparent reaction induced by exposure to allergens [9]. Two-thirds of patients with SA have this endotype, making allergen sensitization one of the potentially important markers of disease severity [10–15]. However, atopic sensitization is generally defined either with a positive skin prick test to allergenic extracts or specific IgE to environmental allergens with arbitrary cutoff points of a mean wheal diameter ≥3 mm, or

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Article highlights

- Allergic asthma is the most frequent and the best-known form of asthma.
- This phenotype is clearly identified in children and adult SA cohorts.
- Detailed knowledge about the relevant allergens and causative factors is essential for the management of SA.
- Exposure to aeroallergens (house dust mites, pollens, pets, molds, and cockroaches) of patients with SA and atopic background is associated with increased risk of severe asthma exacerbations.
- Food allergy in children is associated with more severe asthma, poor symptoms control, and high hospitalization rate.
- More limited evidence exists on the interplay between SA and IgE-mediated anaphylaxis, drugs and venom allergies, respectively atopic dermatitis.

sIgE >0.35 KU/l, while allergy is a hypersensitivity reaction with immunological mechanism which means objectively reproducible symptoms or signs, initiated by exposure to a defined exogenous stimulus [15,16]. Therefore, correlation of allergy tests' findings with clinical manifestations is needed for differentiating between allergic asthma with symptoms, induced by exposure to a defined allergen and disease in a sensitized subject with no relation between allergen exposure and clinical reaction (Figure 1) [15]. Recent evidence has shown that the pattern of connectivity and interactions between IgE to multiple allergenic proteins is a potentially important biomarker of asthma severity among school-age and adult patients with allergic asthma [17]. The biomarkers usually associated to allergic asthma are increased blood and sputum eosinophils counts induced by allergen exposure, high serum IgE levels and FeNO [11,18,19]. Many patients with SA have coexisting allergic conditions such as allergic rhinitis (the predominant comorbidity in all countries), eczema, food and drug allergy [12–14].

Despite the fact that atopic sensitization represents an important recognized risk factor for asthma development in children and adults [15], the role of allergy in SA is still under debate probably due to the heterogeneity of this syndrome and the possible changes over time of different phenotypes. The present review summarizes current evidence linking IgE-mediated sensitization to SA across the age spectrum and discusses the potential role of the IgE-mediated conditions in SA outcomes (Figure 2).

Electronic search queries were applied to PubMed and Medline databases up until Jully 31st, 2025. The search terms used were: 'severe asthma,' 'IgE-mediated' associated with 'environmental allergens,' 'aeroallergens,' 'house dust mites,' 'pollens,' 'pets,' 'molds,' 'cockroach,' 'food allergy,' 'drug allergy,' 'venoms allergy,' 'atopic dermatitis,' 'eczema,' 'anaphylaxis.' We selected in priority cross-sectional and observational studies, followed by meta-analyses, systematic reviews, and general reviews. A preference was given to more recent articles published in the last five years to have the most up-to-date evidence. Results were limited to publications in English.

2. Mechanisms of IgE-mediated disease

The mechanisms of SA include a complex interaction between genetic, cellular, environmental factors and involve three major domains: airway inflammation, AHR and remodeling [20]. The sensitization to environmental allergens with IgE-dependent reactions plays a fundamental role in triggering, development, and chronicity of the inflammatory responses within the disease but represents just a part of contributory mechanisms in SA pathogenesis [7,9].

The most common allergens initiating type I hypersensitivity are pollens (trees, grasses, and weeds), house dust mites (HDM), molds, cockroaches, pets (e.g. cats, dogs), insect venoms (e.g. bees, wasps), foods (e.g. peanuts, tree nuts, milk, eggs, fish, shellfish, soy, wheat, vegetables), latex (e.g. gloves, ballons) and drugs (e.g. penicillin and other beta-lactams, vaccines, monoclonal antibodies) [16]. More evidence exists for the aeroallergens involvement in asthma pathogenesis than for the other allergens [10].

The typical mechanism of type I response includes two phases (Figure 3). The sensitization phase depends on T2 cell signals which regulate allergen-specific IgE production and involves a complex interplay between the adaptive and innate immune

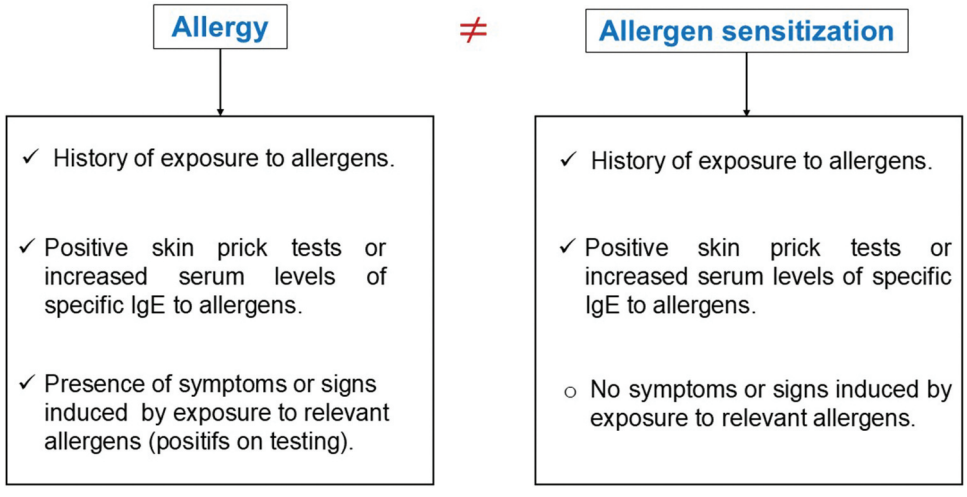

Figure 1. Differential diagnosis between allergy and allergen sensitization.
Abbreviation: IgE, immunoglobulin E.

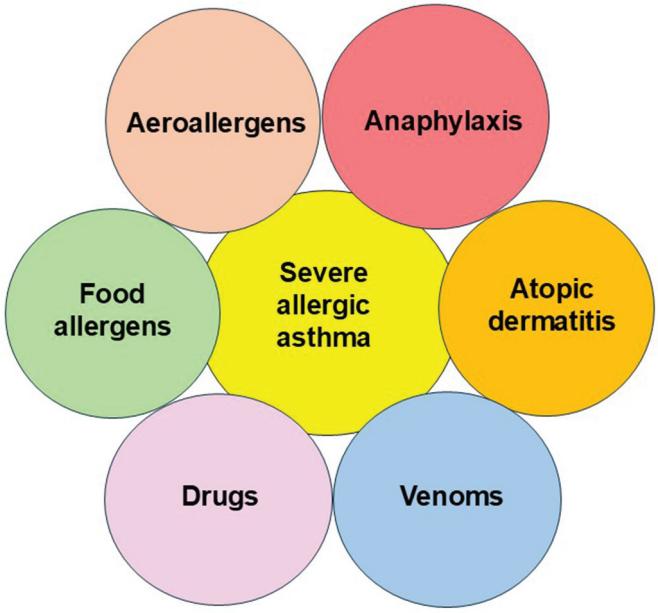

Figure 2. Factors and conditions involving IgE-mediated mechanisms currently associated with severe allergic asthma.

systems. Following the exposure to an allergen for the first time, after internalization and processing, dendritic cells (DCs) present the allergen peptides on their surface to naïve T cells inducing their activation and differentiation into various immune cell subsets without a typical type 2 immune response [16]. There are the airway epithelial cells that play a key role in inducing type 2 inflammation. In response to exposure to allergens, the alarmins released by epithelial cells (e.g. IL-25, IL-33 and thymic stromal lymphopoietin – TSLP) activate type 2 innate lymphoid cells (ILC2) who produce large amounts of cytokines, including IL-5, IL-9 and IL-13, further supporting the T2 cell response, eosinophil recruitment and mucus production [21]. IL-4 released mostly by basophils and mast cells together with IL-13 induce the differentiation of naïve T cells into Th2 cells, and trigger B cells to produce allergen-specific IgE [9,16]. Secreted IgE binds to the FcεRI expressed on the surface of mast cells and basophils, sensitizing these cells to the allergen. Subsequent exposure to allergen starts the effector phase [16]. By cross-linking of membrane-bound IgE in mast cells, the allergen induces cellular degranulation with release of histamine, tryptase, cysteine-leukotrienes, and platelet-activating factors, responsible for characteristic symptoms of the early allergic response: edema, vasodilatation, and bronchoconstriction. The events induced in the early response lead to the production of other cytokines and chemokines such as IL-4, IL-5, IL-9, IL-13, CC chemokine ligand-5, and granulocyte-macrophage colony-stimulating factor, which recruit inflammatory cells (e.g. eosinophils, T cells, mast cells, basophils, macrophages) to the site of inflammation. This process recognized as the late allergic response is characterized by mucus hypersecretion, airway inflammation, AHR, and tissue remodeling in cases of persistent allergen exposure [9,16]. Activation, migration, and prolonged

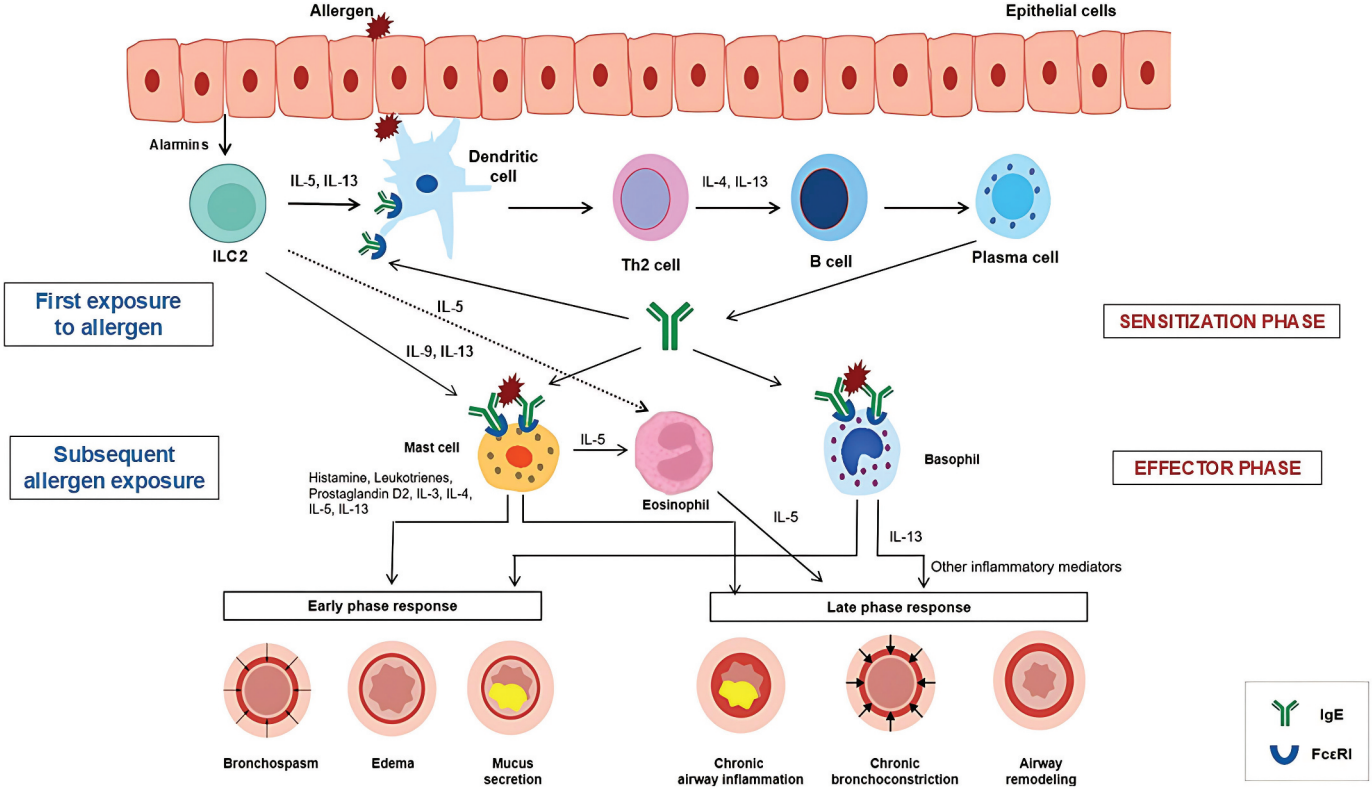

Figure 3. Immunological mechanisms involved in IgE-mediated asthma.

Abbreviations: ILC2, type 2 innate lymphoid cell; Th2 cell, T-helper-2 cell; IL, interleukin; IgE, immunoglobulin E; FcεRI, high-affinity receptor for IgE.

*Adapted from the reference [9] with permission.

life span of eosinophiles contributing to the late-phase allergic reaction and chronicity of inflammation involve hypersensitivity type IVb mechanisms (T2 cell-mediated) [16].

Even if the adult-onset SA phenotype is associated with eosinophilia without evidence of allergy and driven by type IVb mechanisms, all murine models experimenting on the role of innate cytokines in asthma used allergen exposure as a stimulus, suggesting that allergy may be the necessary factor for the development of adult-onset 'nonallergic' eosinophilic asthma, but disease changes over time and age becoming less 'allergic' but remains eosinophilic [15].

Type I hypersensitivity development is influenced by the presence of epithelial barrier dysfunction (newly classified as type V hypersensitivity). Evidence for altered barrier function of the skin or mucosa exists in allergic rhinitis (AR), atopic dermatitis (AD), asthma, and food-allergy (FA). The epithelial barrier defects (e.g. structural changes, protective antiproteases production, expression of antimicrobial products) facilitate the activation of the underlying immune system leading to chronic inflammation, but also stimulate the sensory nerves contributing to the development of allergic symptoms [16]. Direct exposure to air pollutants and other chemicals in the exposome can disrupt the epithelial barriers, affect the microbiome, initiate local inflammation (epithelitis) or aggravate many chronic diseases *via* inflammasome pathways [16,22]. Reduced barrier function in SA and disruption of tight junctions between airway epithelium cells, promote the entry of allergens, their presentation to the DCs and initiation of immune response [21,23]. Airway pollutants like ultrafine carbon and diesel exhaust particles induce the maturation of DCs as well as increased allergen-specific IgE and allergen-specific Th2/Th17 cells in lungs [24]. The protease activity of some aeroallergens, like HDM induces the release of IL-33 from epithelial cells, the stimulation of ILC2, the production of IL-13 and the ultimate disruption of epithelial tight junctions [25]. Microbial dysbiosis was linked to the development and exacerbation of allergic diseases [16]. Asthmatic patients with suboptimal controlled disease have higher microbial diversity in the lower airways compared to healthy subjects [26]. Microbial diversity increases also the risk of rhinovirus-induced asthma exacerbations in children and correlates with a poor corticosteroid response especially in cases with the microbiome dominated by *Haemophilus parainfluenza* [27].

These data highlighted the complex regulation of type I, type IVb and type V hypersensitivity related mechanisms that trigger IgE synthesis, crucial in allergy development. Despite progress, the role of allergy in SA is not yet fully understood, but efforts should be made in this domain to identify underlying mechanisms of disease progression which will impact both on the choice of add-on therapies and on the discovery of novel therapeutics.

3. Sensitization to aeroallergens and severe asthma

Different indoor and outdoor aeroallergens contribute to the development of asthma and the disease's burden [28]. Seventy percent of patients with SA aged > 12 years are atopic and 62% are sensitized to perennial allergens. However, only 45% of these patients have AR symptoms, the most frequent IgE-mediated comorbidity of SA [13].

Higher environmental levels of HDM allergens and pet dandruff, are associated with more severe asthma [29,30]. The role of fungal allergens was also studied. It was demonstrated that fungal allergy is connected to an uncontrolled asthma, greater severity of the disease and subsequent complications like bronchiectasis and allergic bronchopulmonary aspergillosis (ABPA) [31].

3.1. HDM

HDM are the most frequent cause of respiratory allergy worldwide, with 1% to 2% of the world's population might be affected, which is approximately 65 to 130 million persons [32]. HDM are the earliest respiratory cause of sensitization and are considered as the main indoor allergens with regular exposure [33,34].

The main HDM allergens are proteins from *Dermatophagoides pteronyssinus* (Der p1, Der p2 and Der p10) and *Dermatophagoides farinae* (Der f1 and Der f2) [35]. Sensitization to Der p2 and Der f2 appeared to be more common in adults patients with SA [36], while Der p1 was associated with the development and greater severity of asthma in childhood [37]. Recently Der p23 was identified as another major HDM allergen [38] and a study showed that the sensitization to Der p23 in children with moderate-to-severe asthma could worsen the clinical phenotype [39].

More evidence for the association between HDM sensitization and asthma severity exists in pediatric population. Exposure to levels of Der p1 above 2–10 µg/g in bedroom floor dust is associated with asthma severity regardless of sensitization status (odds ratio OR 2.93 [1.37–6.30]) [40]. These findings are consistent with earlier study demonstrating positive association between asthma severity, measured as symptom frequency, and Der p1 levels measured in bedroom floor dust: an increase in Der p1 concentration from 2 to 10 µg/g was associated with a 25% increase in shortness of breath ($p < 0.05$) [41].

An observational case–control study including asthmatic children showed that the prevalence of SA is higher in HDM-sensitized patients compared to those non-sensitized (26.7% vs 3.3%, $p = 0.017$). Similarly, the proportion of patients having uncontrolled disease was greater in patients with HDM-positives tests than in those negatives (50.0% vs 43.3%, $p = 0.001$). HDM sensitization was associated in this study with cough dominant clinical phenotype (96.7%) [42]. Asthmatic children with serum levels of total IgE > 288.0 kIU/L and specific IgE to *Dermatophagoides pteronyssinus* >44.1 kIUA/L have higher probability to have a more severe disease (AUC = 0.736 and AUC = 0.843) [43]. A skin wheal size to Der p1 allergen greater than 3 or 4 mm was positively associated with more frequent asthma symptoms, AHR and increased risk of hospital admission in children [44,45]. Several studies suggested that monosensitization to HDM is associated with milder asthma phenotype and better prognosis compared with polysensitization in asthmatic children [46–48].

Higher prevalence of HDM sensitization was found also in adult patients with SA (58.3%) compared to those with

moderate or mild asthma (48.1%, respectively 43.1%) ($p < 0.001$). The sensitization to *Dermatophagoides pteronyssinus* was associated with increased risk by 1.48 (1.04–2.11) for SA in adult asthmatics ($p < 0.05$) [49]. Being sensitized to HDM and exposed to high concentration of allergens (>2 µg Der p 1/g dust) was found as risk factor for hospitalization due to severe asthma exacerbation (OR 2.38 [1.06–5.34], $p = 0.035$) [50].

A study investigating the evolution of IgE responses to allergens of HDM during childhood revealed four longitudinal trajectories: (1) no/low sensitization; (2) group 1 allergens (Der p1, Der f1); (3) group 2 allergens (Der p2; Der f2); and (4) complete mite sensitization (Der p1, Der p2, Der f1, Der f2). Among children with wheezing, those in the complete mite sensitization trajectory (but not other longitudinal mite trajectories) had significantly higher risk of severe exacerbations (OR, 3.39 [1.62–6.67]) [51]. In addition, acute asthma exacerbations related to rhinovirus infection are significantly associated with sensitization to HDM in children. Higher titers of serum-specific IgE to HDM than 17.5 IU/mL were associated with increased risk for acute wheezing provoked by rhinovirus among asthmatic children [52]. Similar findings were reported in adult population with an increased risk by 5.08 (1.56–21.57) ($p = 0.008$) for hospital admissions due to severe asthma exacerbation in sensitized patients exposed to inhalant allergens and having viral infection [50].

Effective avoidance of exposure to HDM in allergic asthmatic children by living at high altitude for 9 continuous months allowed decrease of nonspecific AHR but also reduced allergen sensitivity, bronchial hyperreactivity by allergen challenge, and late allergen-induced bronchial reactions. These results suggest that HDM allergens play an important role in inducing AHR and longtime exposure could contribute to the development of SA [53].

3.2. Pollen

Pollen is well-known trigger of seasonal asthma. Less than 100 species of pollen-producing plants cause allergies. Some major allergens were identified from different plants: Bet v1 in the *Betulaceae* family, Ole e1 in the *Oleaceae* family, Phl p5 in grass pollen, Cup a1 in the *Cupressaceae* pollen, Par j1 and Par j2 in Parietaria from *Urticaceae* family. Pollen allergens and allergenicity are influenced by climate, humidity, temperature, and air pollution. Climate change and increase in air pollution affect plant distribution and physiology resulting in more allergenic pollen. Pollen season for the tree species tends to start earlier and the intensity has increased in the last years [54]. Combined exposure to pollens and air pollutants like fine particulate matter 2.5 (PM2.5) has synergistic effect and is associated with poorer asthma control in children and adolescents [55].

The size of the pollen is much larger than HDM which induces less penetration in the lower airways. However, the high humidity before thunderstorm can cause rupture of pollen grains releasing smaller particles that can penetrate the lower respiratory tract causing asthma attacks ('thunderstorm asthma' - TA) [54]. Numerous cases of TA are reported all over the world. People at risk for TA are generally already sensitized to pollen allergens, although anyone could be affected. Currently only grass, Parietaria, and Olea pollen have been suggested as possible triggers in TA [56].

Many studies report that exposure to high pollen concentrations increases the risk of severe asthma exacerbations as assessed by asthma-related emergency department (ED) visits. Exposure to >50 grains/m^3 of grass pollen was associated with 2-fold higher risk for ED admission for TA in UK in people >14 years of age [57]. Strongest associations were found in children under 18 years of age between ED visits or hospitalizations for severe asthma exacerbations and the increase in grass pollen concentration from >0 to 50 grains/m^3 in the previous 2 days. Similar results were reported for tree pollen. Severe asthma exacerbations were related to weed pollen increase in individuals younger than 60 years of age [54]. In addition, respiratory viral infections in children are more frequently associated with severe asthma exacerbations requiring hospitalization during the increase of ambient grass pollen concentrations [58]. An exposure to grass pollen lagged up to 3 days may decrease the lung function parameters among subjects under 18 years of age [54].

Recent findings suggest that the measure of pollen allergen levels (e.g. Phl p5, profilin) for the assessment of exposure could be more interesting than the pollen count [59,60]. Grass major allergen Phl p5 levels are more consistently associated with allergic respiratory symptoms than grass pollen count [60]. Profilin is a panallergen found in pollen, latex, and plant foods. The sensitization to profilin is highly variable (20–30% of patients with pollen allergy), depends on geographical distribution and other concomitant allergies. The highest concentration of profilin in the environment corresponds to the peak of pollen grains in the air, mainly from grasses and olive trees [61,62]. A real-life study showed that patients sensitized to this panallergen had more symptoms and higher intensity of symptoms than those not sensitized suggesting that sensitization to profilin can be considered as a marker of severity in patients with rhino-conjunctivitis and asthma due to pollen allergy [59].

In a large adult asthma cohort, 35% of SA patients had positive skin tests for pollens, but clinical significance of this sensitization is unknown [14]. Future research is needed to establish the role of the sensitization to pollens in SA.

3.3. Pets

Pet allergy is considered as an important cause of SA [63]. More than 50% of households in the U.S. have a dog, a cat or both and a large national survey including participants 6 years or older showed similar prevalence of allergic sensitization for dog and cat with both being approximately 12%. Among asthmatics sensitized to these pets, 44.2% of the asthma attacks were attributable to exposure to high levels of dog allergen in the bedroom and 30.3% attributable to cat allergen [64]. In a large European adult asthma cohort, 29% of patients with SA had positive skin tests to cat and 31% to dog [14].

Children with SA displayed higher levels of IgE antibodies toward cat (17 kUA/l [5.0–54] vs. 3.9 kUA/l [0.7–33], $p = 0.027$),

dog (3.8 kUA/l [1.1–22] vs. 1.2 kUA/l [0.5– 4.2], $p = 0.012$) and horse (7.4 kUA/l (0–32) vs. 0.7 kUA/l [0– 4.8], $p = 0.014$) compared to those well controlled. Sensitization to lipocalins from dog – Can f2 and horse – Equ c1 were more frequent in children with SA than in those with controlled asthma (22% vs. 0%, $p = 0.009$; respectively 51% vs. 25%, $p = 0.03$) [65]. These high prevalences could be related also to the cross-reactivity between cat, dog and horse due to sensitization to the component lipocalin Fel d4/Can f6/Equ c1 [66]. A specific IgE response to more than three animal-derived components (lipocalin – nMus m1, rEqu c1, Fel d4, rCan f1, 2; kallikrein – rCan f5 and secretoglobin – rFel d1) was more common in SA children than in those with controlled asthma and associated with bronchial inflammation (66). In the same line, another study showed that polysensitization to Fel d1, Can f1, Can f2, Can f3 increased blood eosinophils, FeNO, and AHR, possible markers of asthma severity [67].

3.4. Fungi

Molds are both outdoor and indoor persistent allergens with seasonal variation depending on meteorological conditions (e.g. rain, humidity, temperature, wind) and air pollution. Thunderstorms and rains favor spores discharge in the air. The most common fungi associated with allergic sensitization are *Alternaria, Aspergillus, Botrytis, Epicoccum, Fusarium* and *Penicillium*. Three different mechanisms are described in asthma induced by fungal allergy: inhalation of spores or hyphae acting as allergens in sensitized patients (Severe Asthma associated with Fugal Sensitization – SAFS), colonization of airway associated to sensitization to fungal antigens (Allergic Bronchopulmonary Mycosis), or cutaneous infection with *Trichophyton* in asthmatic patients sensitized to involved fungi. Thermotolerant fungi (e.g. *Aspergillus, Penicillium, Candida*) can colonize the airways inducing persistent allergenic stimulation even in the absence of airborne exposure while non-tolerant fungi (e.g. *Alternaria, Cladosporium*) have allergenic effects directly through their spores disseminated in the air [63].

In the general asthma population, the prevalence of sensitization to molds ranges from 7% to 20%, and in SA patients from 35% to 75%. Sensitization to *Alternaria* and *Cladosporium* species was more frequently associated with SA in European population [15]. A Japanese study including adult asthmatics showed that patients sensitized to fungi had 5-fold increased risk for uncontrolled asthma. In particular, sensitization to *Penicillium* and *Aspergillus* species was identified as risk factor for poor control of asthma [68]. Fungal sensitization in children with persistent asthma was associated with disease severity [69].

Sensitization to *Alternaria alternata* increased the risk for severe asthma exacerbation in asthmatic children and TA hospital admission in adults [63,70]. Mold sensitization is more common in adult asthmatic patients with severe asthma attacks requiring hospitalization [63].

Sensitization to *Aspergillus* and *Penicillium* was associated with lower lung function and radiological abnormalities (bronchiectasis, tree-in-bud, fleeting shadows, collapse/consolidation and fibrosis) [71]. Adult asthmatic patients sensitized to *Aspergillus fumigatus* had 2.2-fold increased risk to have high therapeutic pressure for symptom control [68].

SAFS is the term used for the patients having SA and evidence of fungal sensitization, but do not meet the criteria for ABPA [72]. SA patients sensitized to Aspergillus are more at risk to have uncontrolled disease (OR 6.07 [1.80–20.51]), frequent exacerbation (≥2/year), and greater systemic corticosteroid requirement (OR 3.05 [1.04–8.95]) [73]. The criteria for ABPA include the presence of asthma, *Aspergillus fumigatus* specific IgE > 0.35 kUA/L, serum total IgE >500 IU/mL, and at least 2 of the following: *Aspergillus fumigatus* specific IgG >27 mgA/L, bronchiectasis on CT chest, peripheral blood eosinophilia >500 cells/μL. The rAsp f1, f2, and f4 are specific allergens to *Aspergillus fumigatus* and their measure could be helpful for the diagnosis of SAFS and ABPA [72]. *Tricophyton* asthma is due to inhalation of spores from skin fungal infection (athlete's foot, onychomycosis) in sensitized asthmatics and associated with disease severity [15].

3.5. Cockroach

Cockroach allergies are recognized as an important cause of asthma. Allergens from common species such as *Blatella germanica* (e.g. Bla g 2, 4, 5, and 6) and *Periplaneta americana* (e.g. Per a 1, 3, and 7) are easily detectable in most of inner-city homes and able to induce sensitization. Exposure to high levels of cockroach allergens at home is a recognized risk factor for symptoms in sensitized people. Cockroach-induced asthma is associated with a more severe disease, persistent perennial symptoms, greater health-care use, and poor outcomes [63].

Asthmatic children sensitized and exposed to high levels of cockroach allergens had more respiratory symptoms, increased risk for hospitalization and unscheduled medical visits for asthma per year compared to other children [74]. A Polish study showed that asthmatic children with cockroach sensitization (24% of the study population) had more often SA, poor lung function and higher AHR than children with other allergies [75]. Adult asthma patients with increased cockroach-specific serum IgE levels had greater airflow obstruction and lung hyperinflation than those with normal levels [76]. Community-based asthma intervention strategies should prioritize reducing cockroach allergen exposure.

Table 1 summarizes current data on the effects of exposure to aeroallergens in sensitized patients with asthma influencing disease severity.

4. Relationship between other IgE-mediated conditions and severe asthma

4.1. Anaphylaxis

Anaphylaxis is considered the most serious manifestation of allergic disorders. The World Health Organization defines anaphylaxis as 'a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potential life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes' [77]. Many triggers can induce anaphylaxis, the most common being foods, drugs and *Hymenoptera*

Table 1. Evidence of aeroallergens' effects on asthma contributing to disease severity in sensitized patients.

Aeroallergen	Symptoms control	Exacerbations	Hospitalizations or ED visits	AHR	Lung function	Therapeutic pressure
HDM	↓	↑	↑	↑	–	–
Pollens	↓	↑	↑	–	↓	–
Pets	↓	↑	–	↑	–	–
Molds	↓	↑	↑	–	↓	↑
Cockroach	↓	↑	↑	↑	↓	–

Abbreviations: ED: Emergency Department; AHR: airway hyperresponsiveness; HDM: house dust mites.
'↓' decrease; '↑' increase; '-' unknown.

venoms, although in some cases the cause of the reaction remains unknown (idiopathic) [78].

According to the findings in a UK cohort, the incidence rate of anaphylaxis was 21.3 per 100,000 person-years (95% CI, 17.6–25.4) in the no asthma cohort, 43.0 cases per 100,000 person-years (95% CI, 37.0–49.7) in individuals with non-severe asthma and 65.4 cases per 100,000 person-years (95% CI, 51.7–81.6) in individuals with SA. The risk of anaphylaxis was 2-fold greater in non-severe asthma group and 3-fold greater in SA group compared with no asthma cohort. The rates of anaphylactic shock in the three groups (no asthma, non-severe asthma and SA) were 2.5, 5.6, and 14.2 cases per 100,000 person-years, respectively. The corresponding relative risks (RR) for the subgroup of anaphylactic shock cases were 2.3 in non-severe asthma and 5.7 in SA [79].

Increased incidence of anaphylaxis was found in males in the group of age 0–9 years, while women (especially those with SA) have higher risk of anaphylaxis at adult age [79,80]. The most common causes of anaphylaxis in SA population were drugs (35%), food (23%) and insect stings (14%). The incidence of drug allergies was highest in SA population, while the food-related anaphylaxis in those with non-severe asthma. Asthma patients at risk to develop anaphylaxis are those with AR (OR 1.8 [1.4–2.3]), AD (OR 1.7 [1.1–2.5]), and current users of antibiotics (OR 1.6 [1.1–2.4]). The most frequent symptoms of anaphylaxis in SA patients were skin reactions (73%), respiratory (46%) and cardiovascular (14%). More than half of patients with SA and anaphylaxis needed hospitalization or ED visit [79]. SA patients are at risk for anaphylaxis and poor outcomes, so they should be treated with more vigilance than others.

4.2. Drugs allergy

The prevalence of drug allergy seems to be significantly higher in patients with SA (22.3%) compared to other asthma groups and most frequently associated with anaphylaxis (as described in the previous section) [14,79]. No data exist specifically for the relationship between SA and drugs IgE-mediated allergy (e.g. beta-lactams, cetuximab) without anaphylaxis. More is known about the aspirin-induced hypersensitivity and SA but the mechanism is not IgE-mediated so not detailed here [80]. Poorly controlled asthma has been identified as a risk factor for the occurrence of immediate hypersensitivity reactions to iodinated contrast media highlighting the need of an accurate evaluation of patients before their administration [81,82].

4.3. Venom allergy

Along with food and drug allergy, venom allergy ranks among the top three causes of anaphylaxis worldwide. *Hymenoptera* venom allergy can provoke severe systemic reactions following a bee, wasp (paper wasp, yellow jacket or hornet) or ant (fire ants) sting. Systemic reactions have been reported in up to 3% of the adult population and in less of 1% of the pediatric population [83]. An increased incidence of respiratory symptoms during sting-induced anaphylactic reactions was found in atopic patients [84]. Asthma patients have enhanced risk of anaphylactic shock after insect stings (hazard ratio HR = 1.37 [1.33–1.41]). This risk is higher in SA patients (HR = 1.64 [1.53–1.77]) [85]. Despite a low prevalence of venom allergy in SA population, this association should be managed quickly and efficiently to prevent potentially fatal reactions [14,84].

4.4. Food allergy

FAs are immunological adverse reactions to various foods that may involve IgE-mediated immediate hypersensitivity, delayed non-IgE mediated mechanisms or contributions from both IgE-mediated and non-IgE-mediated immune pathways [9]. IgE-mediated allergy has an acute onset (within 2 h after exposure) with respiratory, skin and gastrointestinal symptoms, whereas non-IgE-mediated food allergy (e.g. eosinophilic esophagitis) has a delayed onset of symptoms (from 1 to 24 h) predominantly cutaneous and/or digestive [86]. Most commonly food allergens include milk, eggs, tree nuts, peanuts, soy, wheat, fish and shellfish with variation across ages. A large study in Chinese preschool children showed that exposure to indoor plant-related allergens (particularly nonflowering plants) during the first year of life and the previous year increased the risk for FA (notably milk allergy), while keeping cats during the first year of life is associated with higher risk for fruits/vegetable allergy [87]. IgE-mediated FA can affect all ages, impacts quality of life, and can lead to very severe reactions (even fatal anaphylaxis) as well as cross-reactive IgE responses to inhalant allergens [9]. Asthma and FA have been shown to frequently coexist, especially since they often share common risk factors (family history of allergy and atopic dermatitis), but how they interact and influence each other is not yet fully understood [86].

The prevalence of FA in adult population is estimated at 10.8% with half of patients reporting a severe reaction [88]. Almost 50% of food allergic individuals have asthma and the prevalence of FA in asthma population ranges from 10.3% to

16.0% [14,89]. FA was reported by 3.3% of patients with SA in a large worldwide cohort but its prevalence seems to be higher in Europe (8.7%) [13,90]. SA patients with early onset disease are more likely to have FA than those with late onset of their asthma (13.0% vs 1.8%, $p = 0.006$) [13].

Food sensitization early in life (within the first 2 years of life) doubles the risk of developing asthma. The foods that play a more important role in predisposition to asthma are peanuts, milk, and egg. The risk seems greater in people with multiple FA compared to those with monosensitization [89]. Recent data showed that children with both FA and asthma exhibited a metabolomic profile aligned with that of FA alone but not asthma suggesting that pathogenetic mechanisms in FA are dominant in the co-presence of asthma [91]. FA in asthma patients is associated with more severe disease with poor symptom control, higher rates of hospitalization, ED visits, need of mechanical ventilation, and use of systemic corticosteroids, but also worse lung function and lower response to asthma therapy [28,89,92]. FA has been identified as a risk factor for life-threatening asthma in pediatric population [86]. Asthma patients with FA have increased risk for anaphylaxis [93]. Conversely, the presence of asthma increases the risk of anaphylaxis in patients with FA [15]. Food-related anaphylaxis tends to result in predominantly respiratory symptoms. Severe bronchospasm during food-induced anaphylaxis was most likely in patients allergic to peanuts or nuts with SA (RR 6.8 [4.1–11.3]) than in those with mild asthma (RR 2.7 [1.7–4.0]) [94]. These data argues for synergistic interactions between mechanisms operative in different atopic disorders that can influence disease manifestations [91].

Although allergic reactions to food commonly occur after ingestion, reactions to airborne food allergens are also reported by inhalation of dust, steam, vapors and aerosolized proteins generating during the processing of foods in children and occupational settings [63,94]. Most asthmatic reactions to inhaled food allergens are IgE mediated and specific inhalation challenges are needed for diagnosis confirmation [63]. Wheat is one of major food allergens that can induce baker's asthma with albumins and globulins (LTP, Tri a14, alfa amylase inhibitor) more involved than gluten (glutenins, alfa, gamma, omega 5-gliadin) in such reactions. Severe asthma attacks were also described through inhalation of heat proteolytic resistant food allergens such as seafood (fish and shellfish), plants (LTP), spices, milk (casein), eggs (lysozyme, ovomucoid) and mushrooms [63,94].

Several patients with pollens allergies can have symptoms of eating uncooked fruits, raw vegetables, spices, and nuts due to cross-reactivity between pollen and food allergens, recognized as 'pollen food allergy syndrome (PFAS)' [95,96]. Prevalence of PFAS varies by geographic location and is between 2% and 70% based on the study. Commonly PFAS is considered as a low-risk disease limited to oral symptoms, but up to 3% of patients experience systemic symptoms and 1.7% - anaphylactic shock. Sensitization to birch pollen has been shown to be cross-reactive to multiple fruits, vegetables, and nuts (e.g. Bet v1 associated with Mal d1 from apple, Bet v2 with Pru p4 from peach) but usually the symptoms occurring after ingestion are mild or moderate. More severe reactions (including respiratory symptoms) are described in people sensitized to Art v3 (mugwort), a LTP cross-reacting to Pru p3 (peach) as well as Cas s8 (chestnut) [95].

FA are complex diseases. Early phenotyping is the key for improving their management and preventing progression. Despite a significant burden in the pediatric population, the impact of FA appears to be lower in the adult population, likely due to possible resolutions over time [15,96]. In addition, although allergic reactions to food can trigger asthma attacks, FA generally does not present with chronic or isolated respiratory symptoms [9].

4.5. Atopic dermatitis

AD is the most atopic of all allergic diseases as antigens processed in the skin elicit an IgE response with chronic inflammation. Childhood onset of AD is often associated with FAs, asthma, and AR [97]. Although AD and FAs usually precede allergic asthma or rhinitis, a clear causal relationship for the typical sequence in the development of these diseases – formerly named the 'atopic march' – remains to be confirmed [15]. It is known that progression of the atopic march is facilitated in patients who develop IgE to foods and inhalant allergens and strongly associated with filaggrin loss-of-function gene mutations [97]. The prevalence of AD ranges from 2.7% to 20.1% across countries in the pediatric population and was estimated at 17.8% in young adults in a European cohort [98,99]. Evidence from longitudinal studies suggests that approximately one-third of patients with AD develop asthma and early-life AD doubles the risk for developing asthma later in life [15]. In a large UK birth cohort, children with asthma were three times more likely to have severe-frequent AD and twice as likely to have a moderate-frequent disease compared to those without asthma [100]. In the International Severe Asthma Registry the prevalence of AD was 9.6% [12]. More data is needed to understand the relationship between AD and SA.

5. Conclusions

Allergic asthma with atopic sensitization and IgE-mediated inflammation is the most frequent and the better-known phenotype of asthma. Atopic sensitization plays a critical role in the development, progression and persistence of pediatric SA. The phenotype of childhood onset asthma with a high prevalence of atopy is clearly identified in cluster analyses realized in the adult SA population and associated with severe allergic disease. Patients with SA have a much higher atopic burden with high rates of sensitization to various allergens. Exposure to allergens of patients with SA and allergic background is associated with increased risk of severe exacerbations, hospitalizations, poor symptoms control, worse lung function and anaphylaxis. A multidisciplinary approach is needed to improve the management of patients with SA and IgE-mediated comorbidities. Future research may provide a better understanding of the role of IgE-mediated allergy in SA and the underlying mechanisms of disease progression which will impact both the choice of add-on therapies and on the discovery of novel therapeutic targets.

6. Expert opinion

SA is a heterogenous disease with various phenotypes identified by cluster analyses in different cohorts across the world. Allergic asthma is the most common phenotype characterized by sensitization to aeroallergens which leads to clinically apparent reactions following exposure to allergens and airway IgE-mediated inflammation. The onset of allergic asthma is most often in childhood and is usually accompanied by other comorbidities including AD, FA, and AR. The phenotype of early-onset atopic asthma is robust and persistent over time although there is a wide variation in disease severity. Current evidence suggests that atopic sensitization is critical in determining the severity of asthma in the pediatric population and undoubtedly associated with very severe allergic diseases. In contrast, the contribution of allergy to SA in the adult population seems to be more limited. It is possible that allergy is a risk factor for the development of adult-onset 'nonallergic' eosinophilic asthma, but the clinical manifestation of asthma changes with time and age due to interactions with other environmental conditions (e.g. pollution, smoking, infectious agents), so it becomes less 'allergic' but remains eosinophilic. Future studies are needed to verify this hypothesis and to better understand the role of allergy in adult SA.

As expected, more data exists concerning the relationship between aeroallergens and SA. Exposure to high concentrations of allergens from HDM, pollens, pets, molds and cockroaches has been associated with severe asthma exacerbations, hospitalizations and ED visits. Several data suggest also a negative impact on lung function parameters by exposure to several aeroallergens (e.g. pollen, molds, cockroach). Children with SA have a much higher allergic burden than adults. FA, more frequently found in pediatric population, is associated with more severe asthma, poor symptoms control, and a higher rate of hospitalizations. Except several epidemiological data, limited information exists on the relationship between SA and anaphylaxis, drugs IgE-mediated allergy, venoms allergies, respectively AD. Patients with SA have a significantly increased risk for anaphylactic shock induced by drugs, foods or insect stings than those with mild-moderate asthma, but currently it is not clear what is the principal disease and what are the comorbidities, what are the factors influencing the evolution or not of the 'atopic march' and the mechanisms involved in these interactions. Studies that will assess the relationship between coexisting allergic diseases in patients with different sensitizations will provide important insights into this domain. A good start in this way could be the constitution of multidisciplinary teams for the management of patients with coexisting allergic diseases. This approach may improve clinical outcomes of allergic diseases in practice, but it will also open the door for new translational research that could help us to better understand the interplay between SA and other allergic diseases.

Another interesting area of research would be the study of the impact of therapeutic interventions like allergen immunotherapy or biologics available as add-on treatment for SA (especially the anti-IgE antibody – omalizumab) on outcomes of IgE-mediated allergic diseases and their capacity to modify disease history. Such data is mandatory for improving the management of patients with SA and allergic comorbidities.

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