



# Severe Asthma and Allergy: A Pediatric Perspective

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Severe asthma in children is associated with significant morbidity and lung function decline. It represents a highly heterogeneous disorder with multiple clinical phenotypes. As its management is demanding, the social and economic burden are impressive. Several co-morbidities may contribute to worsen asthma control and complicate diagnostic and therapeutic management of severe asthmatic patients. Allergen sensitization and/or allergy symptoms may predict asthma onset and severity. A better framing of “allergen sensitization” and understanding of mechanisms underlying progression of atopic march could improve the management and the long-term outcomes of pediatric severe asthma. This review focuses on the current knowledge about interactions between severe asthma and allergies.

**Keywords:** allergy, allergic rhinitis, atopic dermatitis, children, difficult-to-treat asthma, food allergy, severe asthma

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## INTRODUCTION

Atopic sensitization is a well-established, but not exclusive, risk factor for severe asthma both in children (1, 2) and adults (3), all over the world (1–4). Although its role in determining asthma severity has been considered limited in the past years, some reports confirm that allergy may play a significant role especially in childhood, when early atopic sensitization is crucial to determine the severity of disease.

Though most asthmatic children achieve symptoms' control through occasional bronchodilator (BD) use or low to medium dose of inhaled corticosteroids (ICSs), a small but significant subset of patients remains with uncontrolled asthma despite treatment with high-dose inhaled glucocorticoids (Table 1) or requiring such a treatment to remain well-controlled (5). This group of children with chronic symptoms and episodic exacerbation requiring short-acting beta<sub>2</sub> agonists (SABA) is defined as affected by “difficult-to-treat asthma.” This definition includes poorly-controlled asthma due to at least one of the following: an incorrect diagnosis; comorbidities; poor adherence to therapy because of adverse psychological or environmental factors (6). “Severe asthma” is considered a specific subset of “difficult-to-treat asthma.” It is characterized by the need of higher intensity therapy in order to maintain symptom control or uncontrolled symptoms despite such therapy (6), proper diagnosis (7), and management of comorbidities and correction of unsuitable behavior for control disease.

In 2014, a task force of the European Respiratory Society (ERS) and the American Thoracic Society (ATS) updated the definition of severe asthma in pediatric patients. According to the latter, children affected by severe asthma require treatment with high-dose ICSs and either a long-acting beta-agonist (LABA) or a leukotriene antagonist for the previous year or systemic corticosteroids for at least 50% of the previous year to prevent uncontrolled asthma or asthma that remains uncontrolled despite this therapy (5).

**TABLE 1** | High-dose ICD dosages for children (mcg/d) according to Global Initiative for Asthma (GINA) guidelines.

Drug name	GINA (6–11 y)	GINA (> 12 y)
Beclomethasone dipropionate (HFA)	>200	>400
Budesonide (DPI)	>400	>800
Budesonide (nebulas)	>1,000	
Ciclesonide (HFA)	>160	>320
Fluticasone propionate (DPI)	>400	>500
Fluticasone propionate (HFA)	>500	>500
Mometasone furoate (DPI)	>440	>440

DPI, dry powder inhalers; HFA, hydrofluoroalkane.

In a birth cohort study, the prevalence of severe asthma has been estimated about 0.5 and 4.5% in all 10-year-olds and current asthmatic children when assessed in 10 year olds, respectively (8). Notwithstanding, it is associated with a significant economic burden related to more and severe symptoms needing of adjunctive medical resource use and higher health costs (9). Furthermore, the increased number of parent's working days lost during child asthma exacerbations is accompanied by less global economic productivity (10).

Since only a small percentage of asthmatic patients is affected by severe asthma, this clinical entity is still poorly known even if associated with notable morbidity. Both in children and adults, severe asthma is a heterogeneous disorder with multiple clinical phenotypes (11). However, elegant cluster analyses have shown that the role of atopic sensitization might be more important in the pathogenesis of severe asthma specifically in childhood onset asthma: more than 85% of children with severe asthma are severely atopic (12). In contrast, severe adult-onset asthma is a distinct phenotype that is usually not characterized by atopic sensitization, but often associated with nasal polyposis and sputum eosinophilia (13, 14). A brief overview of characteristics and differences between pediatric and adult-onset severe asthma is provided in **Table 2**.

Though it is well-recognized that atopic sensitization is an important risk factor mainly for pediatric asthma, the role of allergy in children affected by severe asthma is still under debate. This review aims to focus the role of allergy in pediatric severe asthma.

## THE ATOPIC MARCH

Though atopic manifestations may persist for several years and then resolve over time (15), in atopic children, adolescents, and adults allergy manifestations may evolve according to

**Abbreviations:** ABPA, allergic bronchopulmonary aspergillosis; AERD, aspirin exacerbated respiratory disease; AD, atopic dermatitis; AIT, allergen specific immunotherapy; AR, allergic rhinitis; ATS, American Thoracic Society; BD, bronchodilator; ERS, European Respiratory Society; FA, food allergy; HDM, house dust mites; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting beta2-agonist; MAAS, Manchester Asthma and Allergy Study; MAS, Multicentre Allergy Study; NSAIDs, non-steroidal anti-inflammatory drugs; SABA, short-acting beta2-agonist; SAFS, Severe asthma with fungal sensitization.

**TABLE 2** | Characteristics of severe bronchial asthma in children and adults.

Characteristics	Pediatric asthma	Adult-onset asthma
IgE-sensitization	+++	+
Poly-sensitization	+++	+
High specific IgE levels	+++	+
Clinical heterogeneity (i.e., multiple phenotypes)	+++	+++
Severe non-allergic obese female prevalent phenotype	-	+++
Severe non-allergic eosinophilic phenotype (nasal polyposis, sputum eosinophilia, and aspirin sensitivity)	-	+++

a predetermined sequence, characterized by the progression from atopic dermatitis (AD) to allergic rhinitis (AR) and asthma (16–18).

Therefore, it seems that atopic predisposition represents a major risk factor for developing all atopic diseases in patients for which the progression from AD to asthma defines the well-known “atopic march” (19). However, the temporal presentation of allergic diseases may differ from the usual progression of the atopic march due to genetic influences and environmental factors (20).

Foremost, allergens may penetrate easier a defective skin barrier, therefore leading to transcutaneous sensitization and subsequently initiating the atopic march (21). Indeed, IgE sensitization to food or airborne allergens is a significant cofactor to induce the progression of the atopic march in patients with AD (22–24). Moreover, it is widely described that the risk of developing asthma in patients with AD is strictly related to both the clinical expression of IgE sensitization and the severity of eczema (25–27).

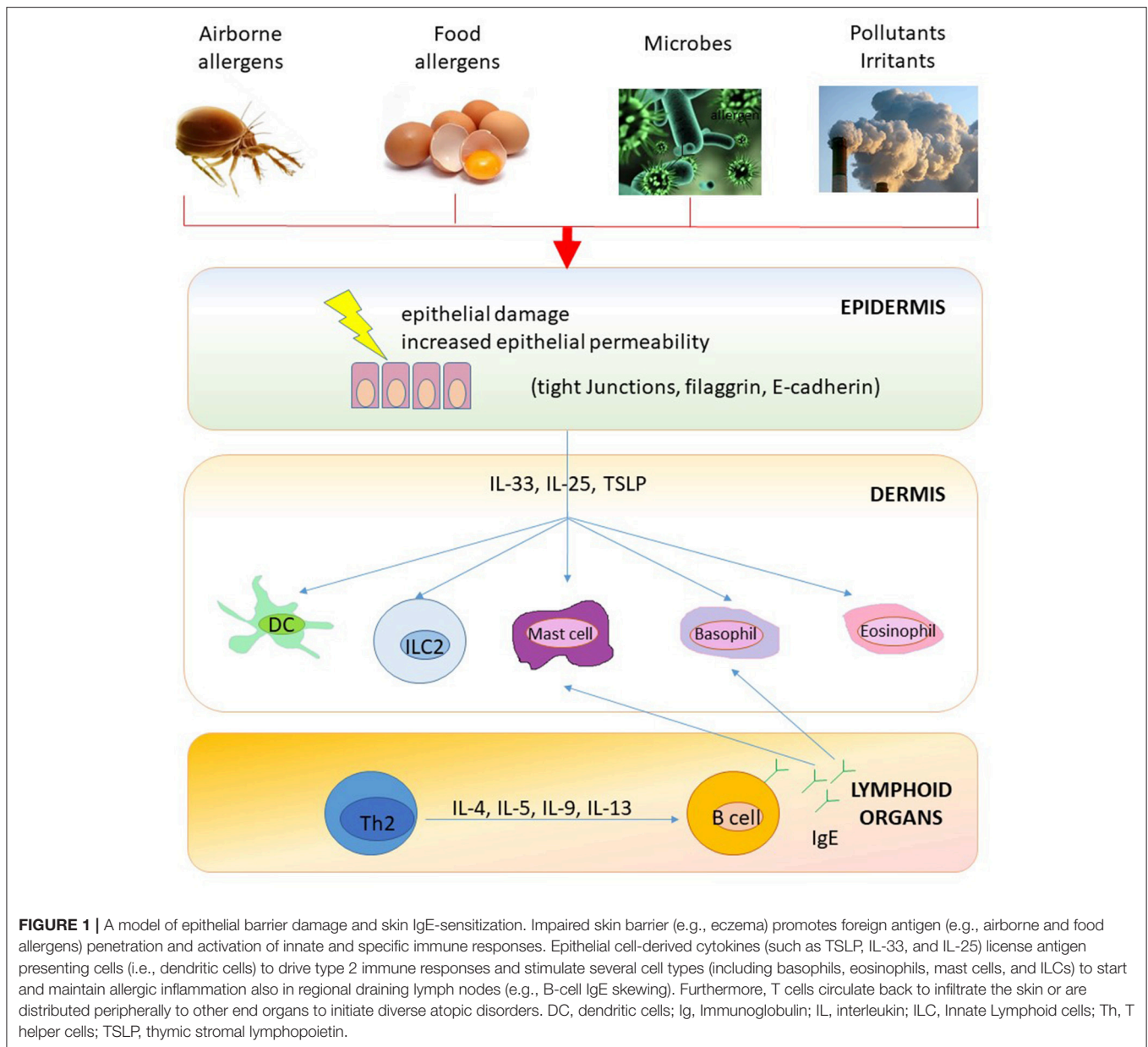
It seems that transcutaneous IgE-sensitization may precede airway sensitization (28) and that IgE-associated AD might represent the first step of the atopic march and, therefore, it may predict the upcoming development of allergic diseases, including food allergy, AR, and asthma (please see **Figure 1**) (28). Since AR is a further major risk factor for bronchial hyper-reactivity and asthma, it can precede asthma onset in the natural history of the atopic march (29–31).

## ALLERGIC COMORBIDITIES

Several factors and co-morbidities may contribute to worsen asthma control and complicate diagnostic and therapeutic management of severe asthmatic patients (**Figure 2**) (32).

### Atopic Dermatitis

Several studies reported that family history of atopy, early onset AD, higher initial severity of atopic eczema, hens' egg sensitization and male sex are associated with an increased risk of asthma in childhood (33). Furthermore, the percentage of patients with severe asthma and concomitant eczema is greater than expected and close relationship between asthma and atopic dermatitis severity has been reported (34).



Therefore, as AD and the subsequent atopic march mostly present in early infancy, primary, and secondary prevention should be attempted as early as possible to prevent asthma symptoms onset (35).

## Allergic Rhinitis

Allergic rhinitis is almost ubiquitous in children with asthma living in urban areas. The presence of allergic sensitization to inhalant allergens and rhinitis symptoms is typically associated with early onset of severe asthma (36). Patients with AR report poorer asthma control, more exacerbations and emergency visits (37) and have more difficulty in achieving symptom control (38).

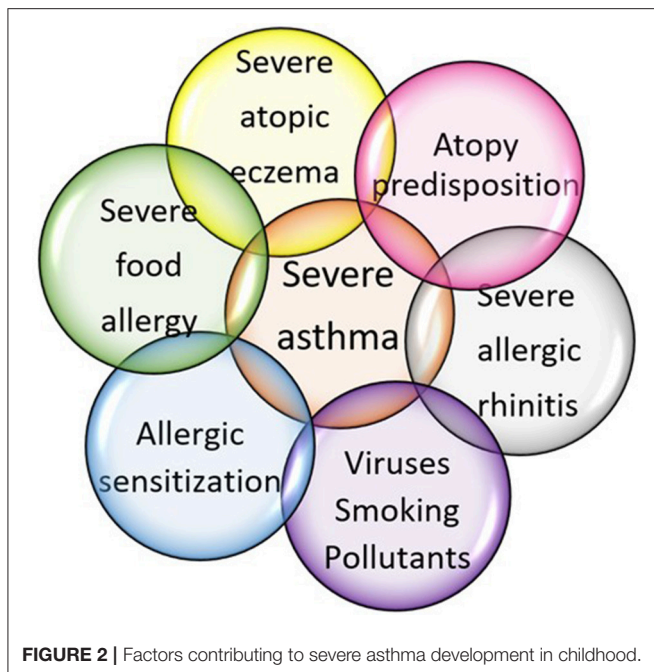
Perennial allergic rhinitis with seasonal exacerbations is considered the most severe phenotype and most likely to be associated with difficult-to-control asthma (39).

This means that treating coexisting allergic rhinitis could improve asthma control and reduce healthcare resource utilization (40).

## Food Allergy

Respiratory symptoms as clinical manifestation of IgE-mediated food allergy (FA), usually, occur immediately after exposure to the offensive food and are accompanied by skin and/or gastrointestinal manifestations. Food allergen exposure occurs usually by ingestion, but the inhalation of food proteins (through dust or aerosolized particles) may also trigger respiratory symptoms (41).

Among patients with FA, asthmatic symptoms are more frequent in children, and especially in those with concomitant atopic dermatitis. In addition to respiratory symptoms occurring



as a presentation of FA, patients with FA are at increased risk for developing asthma and often severe asthma as expression of progression of the atopic march. Symptomatic FA and food allergen sensitization are associated with asthma development both in younger and older children: it was reported that this association is stronger among children with multiple or severe FAs (42–44). Moreover, children with FA develop asthma earlier and at a higher prevalence than children without FA. The opposite is also true, as asthma is a risk factor for the persistence of food allergy (45–47).

Food allergy and food sensitization can be also considered as important markers to predict asthma severity. Indeed, it is reported that children with FA and sensitization to at least one food (e.g., egg, milk, soy, peanut, wheat, and fish) had worse lung function (48), higher rates of hospitalization, emergency department visits, use of systemic glucocorticoids (49), or need of mechanical ventilation for severe asthma exacerbation (50, 51).

### Aspirin Sensitization

Aspirin-exacerbated respiratory disease (AERD) is a chronic medical condition, usually in adults and adolescents, consisting of three clinical features: sinus disease with recurrent nasal polyps, asthma, and sensitivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). Even though asthma is not always present in AERD, asthma symptoms develop 1–3 years after the development of rhinitis or later. When present, asthma is severe and difficult to treat and often characterized by increased residual volume and diminished diffusing capacity due to increased airway remodeling (52).

## ROLE OF ATOPIC SENSITIZATION IN SEVERE ASTHMA

Previous studies showed that atopic sensitization is a major risk factor for severe asthma in children (53–55). Overall, the

expression “atopic sensitization” refers to the positivity either of serum allergen-specific IgE (sIgE) or a positive skin prick test (SPT) to allergen extracts. Arbitrary cut-off points have been set: levels of sIgE >0.35 KU/l (56) and a mean wheal diameter  $\geq 3$  mm (SPT) (57). Though these tests are highly sensitive, their mere positivity do not mean itself clinical disease. Quantification of atopic sensitization increases the specificity in relation to childhood asthma presence and severity (4), and asthma persistence in adulthood (58–60). The severity of asthma correlates with both sIgE levels and the number of sensitizations, also on the molecular level. The number of component-specific sensitizations correlate with disease severity in **grass** allergic children (61) as well as in **house dust mites** allergic (HDM) pediatric patients. In the Multicentre Allergy Study (MAS) cohort, a birth cohort started in 1990 in Germany, the number of HDM-component specific sensitizations increased with disease severity and with age. Sensitization to Der p 1 and Der p 23 before the age of 5 years was predictive of asthma at school age (62). Similarly, in the Manchester Asthma and Allergy Study (MAAS) birth cohort, asthmatic children were characterized by more complex molecular patterns of IgE sensitization to grass and mite molecules (Der p 1 and Der p 2) (63). In a French study, atopic sensitization to Der p 2 and Der f 2 was more common in severe asthma. In a cohort of 300 asthmatic children (age range, 4–12 years), higher levels of Der p 1 and pet allergen [cat (Fel d 1), dog (Can f 1)] were found to be associated with greater asthma severity (64). Similarly, in **latex** allergy sensitization to 3 (5, 6.01/6.02) of the 12 recombinant natural rubber antigens so far known was strongly linked with asthma (65).

### Fungal Allergy

Fungal allergy drives asthma severity, too (66). Sensitization to molds has been estimated: 7–20% in the general asthma population; 35–75% in severe asthma patients; 54–91% in life-threatening asthma population (67–69). The severity of exacerbation relates to the different fungi species: in particular, *Aspergillus* or *Alternaria* or *Cladosporium* spp. sensitization has been linked to severe asthma (70, 71).

Long-term or uncontrolled fungal infections are associated with a poor controlled asthma, bronchiectasis, and chronic allergic bronchopulmonary aspergillosis (ABPA) (71). The term “Severe asthma with fungal sensitization” (SAFS), introduced by Denning et al. (71), describes a specific phenotype in patients with persistent severe asthma (despite standard treatment) and evidence of fungal sensitization, and do not meet the criteria for ABPA. An EAACI Task Force sets the total IgE cut-off at <1,000 IU/ml for SAFS and >1,000 IU/ml for ABPA, a specific endotypes of asthma, with a genetic predisposition.

## ROLE OF VIRUSES, SMOKING, AND POLLUTANTS

In poli-sensitized asthmatics, daily exposure to allergens combined with other enhancing factors, such as viral infections, smoking (even tertiary one), and/or environmental pollution, influences the asthma course and severity (Figure 2). There is robust evidence concerning the synergistic effect of **viral**



**lower respiratory tract infections** (LRTI) and IgE sensitization on asthma development, particularly in children predisposed to atopy (72) and asthma exacerbation (73). Increased risks of asthma inception in atopic predisposed children include: the type of virus (more than 10-fold increased risk for asthma development with rhinovirus compared to 5-fold with respiratory syncytial virus); the severity of viral LRTI; and the age during viral LRTI (74). The risk of hospital admission due to asthma exacerbation is increased by the interaction among respiratory viral infections in combination with atopic sensitization and exposure to allergens (75).

## Cigarette Smoking

Cigarette smoking itself may influence asthma severity, through different patho-mechanisms (76). There is evidence that smoking increases itself serum IgE levels, especially in male adults (77), and rises the risk of IgE sensitization, mainly to occupational allergens (78). Nevertheless, in severe asthmatic patients, the complex association between cigarette smoking and allergy remains currently controversial.

Data reports that children exposed to **air pollution** are at major to develop IgE sensitization to inhalant allergens (79, 80). However, the immunological mechanisms underlying this link remain to be better clarified. Notwithstanding, some data suggest that ultrafine carbon black particles may induce maturation of dendritic cells *in vitro* (81), which might then facilitate sensitization to airborne allergens. On the other side, airborne pollutants may modulate the inflammatory cellular response in the lungs, thereby lowering the threshold for sensitization.

## PREVENTION STRATEGIES

As widely described above and resumed in **Table 2**, children with early onset atopy, high specific IgE-sensitization and multiple IgE-sensitizations are at increased risk for developing severe asthma in childhood. In addition, it is well-established that severe allergic diseases more frequently coexist (**Figure 2**).

Based on these premises, it is reasonable that prevention strategies and proper treatments of atopic diseases could prevent occurrence of severe asthma and viceversa. However, asthma development depends on complex and still not fully known interception of genes and environment. Therefore, effective primary prevention strategies for asthma, and especially for severe asthma in children, -though highly desirable- might be difficult to be identified both at population and individual level.

## Primary Prevention

Some studies have suggested that maternal consumption of allergenic food (such as cow's milk, peanut, or fish) and vitamin D and E intake during pregnancy could be associated to decreased risk of allergy and wheezing in their offspring, respectively (82–84).

Conflicting results have been reported about the beneficial effect of maternal breastfeeding on pediatric asthma development (85). The role of prebiotics, probiotics, and synbiotic interventions (86) and other dietary supplements (such as nucleosides and nucleotides) (87) is under investigation. Overall,

the level of evidence remains currently low or even very low because of the risk of bias, heterogeneity among studies, imprecision, and inconsistency of results, as well as indirectness of available research.

Instead, there is stronger evidence concerning maternal smoking and tobacco post-natal exposition. They are both associated to increased risk of asthma in offspring (88).

## Atopic Dermatitis

Since the epithelium plays an important role in protecting against the development of allergic diseases and the occurrence of transcutaneous IgE-sensitization may precede airway sensitization (**Figure 1**), proactive emollient therapy able to make stronger the epithelial barrier may prevent or delay the development of IgE-sensitization in children affected by AD (89).

## Allergic Rhinitis

It is well-known that AR and asthma often coexist. As they share genetic background, chronic airway inflammation pathway and similar triggers (allergen exposure, viral infections, cold air, and air pollution) (90), treatment of rhinitis can be beneficial for preventing severe asthma exacerbations.

The role of exposure to airborne allergens on AR and asthma is well-established and strict avoidance of the culprit allergen(s) is desirable though it is often hard or even impossible. Symptomatic drugs for AR, such as H1-antihistamines and intranasal corticosteroids are not recommended for asthma management (40). However, data suggest that the use of H1-antihistamines in AR children is associated with delayed asthma development (91) and improvement of asthma outcomes (92). Similarly, a significant reduction of asthma symptom scores and rescue medication use has been reported for patients with AR and coexisting asthma by using intranasal corticosteroid therapy (93). Moreover, anti-leukotrienes target both upper and lower airways and could be beneficial in patients with asthma and concomitant AR (94).

Biological drugs—such as anti-IgE therapy (i.e., omalizumab) and antibody against the  $\alpha$ -subunit of receptor for IL-4 and IL-13 (i.e., dupilumab)- have been approved for a few specific phenotypes of severe asthmatic patients at different ages (**Table 3**). They could be beneficial on both diseases: severe asthma and severe AR (95, 96). Notwithstanding, allergen immunotherapy (AIT) is considered the only etiological treatment able to prevent asthma development (97), to improve asthma symptoms in AR affected children (98), and to prevent new sensitizations in already sensitized patients (99). Furthermore, since adverse events are more common during the escalation or build-up phases of AIT, omalizumab has been suggested as “add-on therapy” to AIT (100). Nevertheless, larger studies are needed to identify patients who would benefit the addition of omalizumab to AIT, as well as optimal dosing strategies and duration treatment (101).

## Food Allergy

Strict avoidance of the culprit food(s) represents currently the standard therapeutic option for FA (102). However, accidental exposure is possible and related to severe adverse events. Allergen

**TABLE 3** | Main biological targeted treatments for severe asthma in children.

Drug (trade name), dosage	Mechanism of action	Suggested population	Adverse effects
<b>APPROVED</b>			
<b>Omalizumab</b> (Xolair), s.c. injections every 2–4 wks, depending on body weight and IgE levels	Anti- IgE; binds Fc receptor of free circulating IgE and downregulates IgE production	Age >6 yrs; 30 UI < IgE < 700 UI* ; positive skin test or elevated specific IgE level toward a perennial	Anaphylaxis (~0.2% pts); monitor for helminthic infection
<b>Mepolizumab</b> (Nucala), 100 mg in pts aged 12 yrs or older (40 mg in pts aged 6–11 yrs) by s.c. injections every 4 wks	Anti- IL-5; binds circulating IL-5	Age > 12 yrs; eosinophilic asthma	Zoster (rare); avoid if active helminthic infection
<b>UNDER INVESTIGATION</b>			
<b>Reslizumab</b> (Cinqair), approved for adults (3 mg/kg by i.v. injections every 4 wks)	Anti- IL-5; binds circulating IL-5	Eosinophilic asthma	Anaphylaxis (rare); avoid if active helminthic infection
<b>Dupilumab</b> (Dupixent), approved for adults with atopic dermatitis	Anti- IL-4 and anti-IL-13; binds common $\alpha$ -subunit of receptor for IL-4 and IL-13	Eosinophilic asthma	Eosinophilia (rare); avoid live vaccines; avoid if active helminthic infection

IL, interleukin; i.v., intravenous; pt, patient; s.c., subcutaneous; wk, week; yr, year. \*Upper limit varies according to body weight and regulatory authorities.

specific immunotherapy (AIT) alone or combined with adjuvants (including probiotics and anti-IgE monoclonal antibodies) is nowadays the only active treatment for FA (103). Nevertheless, it is highly demanding, especially in patients with a severe phenotype, who usually have allergies to multiple foods and concomitant severe asthma. For these severe patients, biologicals might be a better potential therapy alone or in combination with AIT (104, 105). However, more data are needed.

## AERD

Careful avoidance of aspirin and other NSAIDs is mandatory in patients affected by AERD in order to prevent asthmatic exacerbations. The use of acetaminophen or selective COX-2 inhibitors should be encouraged as alternative drugs. Furthermore, the addition of a leukotriene receptor antagonist (e.g., montelukast) and 5-lipoxygenase inhibitors (e.g., zileuton) to standard asthma treatment have been shown to be effective in improving asthma outcomes (106). Aspirin desensitization is currently the only causative treatment in AERD affected patients improving both upper and lower airway symptoms; however, only a very small percentage of patients benefit from this therapeutic option (107). Biologic therapies (such as anti-IgE, anti-IL-5 monoclonal antibodies, IL-4 $\alpha$  receptor antagonist, and anti-thymic stromal lymphopoietin) could be promising therapeutic options for AERD patients given their effectiveness in nasal polyposis and asthma (108).

Unfortunately, there is currently lack of data about any specific role of the treatment of allergic comorbidities in preventing the development of severe asthma in atopic children.

## OPTIMIZING TREATMENT OF SEVERE ASTHMA

The current guideline-based drug therapy of pediatric severe asthma is based primarily on data extrapolated from adult studies. High dose of inhaled **corticosteroids** (or oral corticosteroids) combined with a second controller (such

as a LABA or leukotriene modifier/theophylline) are the mainstay of treatment (5).

However, the current challenge facing physicians and researchers is to provide a “**personalized medicine**,” which is tailored to the diverse patho-mechanisms underlying clinical presentations (109).

## Allergen Specific Immunotherapy

AIT has been demonstrated to have beneficial effects in the management of childhood allergic asthma, including effects on symptom control, medication use, and airway hyperresponsiveness (110). However, trials involve children with mild-moderate allergic asthma, and studies specifically examining the efficacy of AIT in children with severe asthma are missing. Notwithstanding, the majority of studies involved monosensitized patients, whereas most children with severe asthma are polysensitized, mainly in Southern Europe. In addition, allergen immunotherapy should be commenced in patients with well-controlled asthma, a situation which is less common among children with severe asthma. Since 2003, several **targeted therapies** have been approved for severe asthma and others are still under investigation (Table 3). Furthermore, they could be beneficial in other allergic comorbidities. However, their cost is often expensive. Therefore, a precise identification and selection of good responders is pivotal.

A **regular longitudinal assessment** of outcomes of children with severe asthma is pivotal. Follow-up appointments should be devoted not only to reduce maintenance therapy to the minimal amount required to achieve control of asthma symptoms, but also to assess the atopic status of the patient and any concomitant atopic co-morbidities and, therefore, address any modifiable factors (including allergen exposure, basics of inhaler technique, and adherence).

## CONCLUSIONS

Asthma is a common disease in childhood with a minority of affected children having severe asthma. Several data suggest

that allergies may play a key role in children with severe asthma. Many children with severe asthma have coexisting allergic disease(s). Allergies to foods, molds, pollens, and pets have been associated with both asthma inception and severe asthma exacerbations. A better understanding of interactions between asthma and allergy and mechanistic implications of cofactors, such as virus infections, pollution, and smoking will allow the development of novel therapeutic

targets and, therefore, additional strategies for improving disease control.

## AUTHOR CONTRIBUTIONS

SA and FP wrote the first draft of the manuscript. AF and RC critically reviewed the manuscript. All authors read and approved the final manuscript.

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