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REVIEW

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Trajectories of allergic diseases in children: Destination unknown?

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Abstract

The trajectories of allergic diseases represent one of the most currently debated topics both when referred to childhood and likewise adulthood. Data from cohorts show their heterogeneity as well as the key role of genetic and environmental factors. More insight has been recently provided in the pathophysiological mechanisms underlying the development and amplification of T2 (hyper)inflammation. Recent data support the hypothesis of associated allergic diseases (multimorbidity) reflecting, at a given time and in given organ(s)/tissue(s), the expression of the same favorable predisposition. In particular, the impairment of the epithelial barrier, especially in subjects genetically predisposed, and the dysregulation of the host's microbiome promote the onset of allergic diseases and multimorbidity, their persistence and/or severity. These findings challenge the classical theory of the atopic march with a temporal sequence characterized by the transition from one disease (eczema) to another (food allergy, airway allergic diseases). A better understanding of the diversity of disease trajectories and the underpinning mechanisms is crucial for prevention and identification of children at risk of a "unfavorable trajectory" (early intervention, i.e., early primary or secondary prevention), for a personalized therapeutic approach based on identification of specific endotypes, and, therefore, addressing specific pathophysiological pathways (treat to target strategies). In the perspective of the so-called "remission" and "treatment-induced-remission", the whole spectrum of the long-term consequences of the disease(s) including their treatment has to be considered. The concept of disease modifying treatment able to interfere with their trajectories and overall long-term induced morbidity is emerging.

Birgit Kalb, Ekaterina Khaleva, and Mattia Giovannini contributed equally to the current work and share the first position in the article.

For affiliations refer to page 10.

KEYWORDS
allergic diseases, allergic rhinitis, asthma, biologicals, childhood, cohorts, food allergy, immunotherapy, remission, risk factors, trajectories

1 | INTRODUCTION

Population-based cohorts from birth to adulthood have improved our understanding of allergic diseases'—eczema—that is, atopic dermatitis (AD), asthma, rhinitis, food allergy (FA), and more recently eosinophilic esophagitis—trajectories in childhood and later.[1–6] What we have learned is that the concept of the atopic march does not reflect all disease courses and is …. "critically ill". We are rather now facing multiple trajectories. These include natural remission on one side but also in a few but increasing percentage of children the accumulation of allergic diseases, also called multimorbidity, on the other side.[4] Some determinants of these trajectories are now known or suspected, including personal characteristics, genetic and epigenetic factors besides all the components of the environment, also called exposome.[7] Moreover, the interaction of environmental factors with the innate and adaptive regulation of the immune system is critical for the development of these trajectories.[8] The epithelial barrier is a key actor of all allergic diseases interplaying with the local immune system and microbiota.[9,10] In contrast, the role of atopy and allergic sensitization is challenging, especially for some allergic diseases like eczema and eosinophilic esophagitis.[11] Strategies to prevent, to treat, and to modify trajectories have been validated or are under investigation. They should be considered at different levels: the patient, their familial environment, and the wider societal determinants, assuming not only medical support and intervention but also political actions and public policies priorities. Better knowledge of allergic diseases heterogeneity is key to the identification of patients at risk of following the unfavorable trajectory who will benefit from early intervention with the goal to modify and improve the disease(s) long-term prognosis. The aim of this review, summarizing a symposium organized by the Clemens von Pirquet Foundation, is to discuss key points and issues related to trajectories, to introduce the natural remission versus treatment-induced disease control concepts, and finally to propose some prevention and treatment strategies with a future perspective.

Key message

Trajectories of allergic diseases in childhood are multiple and typical atopic march is only one of them. The key role of genetic and environmental factors is now demonstrated, as well as those of the epithelial barriers' impairment underpinning the onset of allergic diseases and multimorbidity. Identification of children at risk of an unfavorable trajectory is crucial. The concepts of personalized treatment strategies and disease-modifying treatment that are able to interfere with their trajectories are emerging.

2 | TRAJECTORIES OF ATOPY AND ALLERGIC DISEASES

2.1 | Atopy and allergic diseases

Clemens von Pirquet introduced in 1906 the term "allergy" to medical language, and Arthur F. Coca and Robert A. Cooke postulated in 1923 for the first time the concept of atopy to characterize a set of diseases, including asthma and allergic rhinitis (AR).[12,13] Nowadays, atopy is considered a genetically linked predisposition to a Th2-driven immunological response (associated or not to immunoglobulin E (IgE) production), leading to hypersensitivity reactions to antigens/allergens. Atopic/allergic conditions including AD, FA, asthma, and AR and now eosinophilic esophagitis are classically categorized as T2-driven diseases. Other immune mechanisms are so far mainly known to play a role in a variety of immune-mediated diseases with pathophysiological patterns distinct from allergies.[14,15]

2.2 | Trajectories and phenotypes of single allergic diseases

2.2.1 | Eczema

The natural course of eczema is characterized by alternating periods of flares of various severity, with persistence, improvement, or even remission highly variable on an inter- and intra-individual level. Recent analytical techniques in large cohorts served to identify eczema trajectories across childhood and lifespan.[16–18] For example, in the European PASTURE cohort, an early transient in 2% and an early persistent in 6.5% of children (onset before age 2 years), as well as a late phenotype in 4.8% of children (onset at age 2 years or older) have been observed in children from birth to 6 years of age. However, most data are from populations of European ancestry. To better reflect the global situation, future cohort studies should address more diverse populations and include a wide range of geographical regions.

2.2.2 | Food allergy

The natural course of FA is essentially influenced by the type of regional diet and the nature of the individual foods. With some foods, such as milk, hen's egg, wheat and soy, the probability of natural tolerance development is high, but allergy to peanut, seeds and tree nuts, fish and sea food tend to persist.[19] A number of pitfalls must be considered regarding interpretation of the study results. While few

studies include an oral food challenge (OFC), history and/or specific IgE cut-offs are mainly used as diagnosis tool of FA. An ideal study design would include repeated OFCs which is generally difficult to justify in children for ethical reasons.

2.2.3 | Asthma

Wheezing is a very common condition in the first years of life, with multiple phenotypes and often not stable.[20,21] Considering trajectories, although most of the early wheezers do not develop asthma in childhood and adolescence, wheezing persists and progresses to asthma in up to one third of wheezer infants.[22] Beyond early transient wheeze, other phenotypes as persistent, late onset, intermediate onset wheeze have been described from birth up to 8 years of age.[22–24] Then, from childhood to adulthood, cohorts have shown many asthma trajectories in terms of symptoms and severity or based on lung function.[2,6,25–27]

2.2.4 | Allergic rhinitis

Although AR typically starts after age two, birth cohort studies reported onset of symptoms within the first 2 years in up to one third of cases. This is clinically important, as early onset AR is closely linked to food and aeroallergen sensitization, bronchial hyperresponsiveness and the development of asthma.[6,25,28,29] Genetic and environmental factors also shape AR trajectories, including intermittent, rhinitis-dominant, and multimorbid patterns.[6] Moreover, regional differences, resulting in early house dust mite or late grass pollen sensitization, further influence AR trajectories.[30]

2.3 | Allergic sensitizations trajectories

The key role of allergic sensitization trajectories has been highlighted in many large birth cohort studies.[29,31–33] Rather than a dichotomous trait (presence or absence of sensitization), timing (early or not), number and spreading (mono or multiple sensitizations), type of allergen(s) (indoor inhalant such as mites or furry animals, seasonal such as pollens' allergens, food, cross-reacting allergens such as PR-10 or LTP, albumins and tropomyosin) have to be considered. Moreover, trajectories focusing on allergic disease phenotypes and considering severity of symptoms have been shown, which might improve prediction and help to identify tailored prevention strategies.[6,25,26]

2.4 | From the atopic march to the concepts of multimorbidity and comorbidity

While "comorbidity" describes combined effects of additional conditions in reference to an index disease, "multimorbidity" means that no single condition holds priority over the co-occurring conditions.[34] Therefore, considering the effects of a first disease manifestation (index disease) such as eczema on the risk of developing other diseases such as asthma/AR reflects the concept of atopic march and comorbidities. In contrast, the concept of multimorbidity is underpinned by common pathophysiological mechanisms causing various allergic diseases during an individual's life.

It has been shown, that there is considerable heterogeneity between patients in the chronology of symptoms and allergic diseases development.[4,11,25] Thus, children with early eczema who later develop asthma followed by AR may be a subgroup within the larger group of infants with eczema with allergic diseases underpinned by shared mechanisms rather than the illustration of a typical course of atopic disease.[35] This was also confirmed at the individual level using machine learning modeling framework regarding the development of atopic diseases (eczema, wheeze, and AR) during childhood in two large population-based birth cohorts.[25] At the end, the concept of atopic march from eczema to FA and then asthma and AR is now deeply debated and probably over simplistic, rather reflecting a view at the population level and not the individual one. Multimorbidity with a specific time of expression for each atopic disease with common underlying mechanisms seems more appropriate.[4,11] Even if the risk of multimorbidity is higher in infants with eczema, multimorbidity can also start with airway allergic disease or FA.

Furthermore, it has now been demonstrated that children with allergic diseases are at risk of developing other diseases, including neurodevelopmental disorders such as anxiety, depression, sleep disorders, autism spectrum disorders, attention-deficit hyperactivity disorder, or avoidant restrictive food intake disorders.[36–38] There is a knowledge gap in understanding these comorbidities, which in turn can impact disease symptoms and the patient's quality of life. There is therefore an urgent need to better understand, prevent, and manage them.

2.4.1 | Eczema and food allergy

Eczema and food sensitization or FA in childhood are highly correlated comorbidities. A recently published systematic review, analyzing the data of 225,568 individuals with eczema, revealed that about half of children were sensitized against foods and about one third suffered from FA. The influence of eczema severity has been shown with a trend towards a severity-dependent increase in the prevalence of food sensitization and FA.[39] The key underlying mechanism might be sensitization via the cutaneous route due to a dysfunction of the epithelial barrier and associated T2 inflammation. This correlation has also been shown at the genetic level in the Caucasian population and confirmed by a recent systematic review of 27 studies.[40] Associations with FA were shown for mutations in regions encoding filaggrin (FLG), human leukocyte antigen (HLA), interleukin-10 and interleukin-13, and in SPINK5 and C11orf30. The most frequently reproducible associations were FLG loss-of-function (LOF) mutations. All loci identified so far encode proteins involved in cutaneous regulatory processes of innate or acquired immunity, immunoregulatory

processes, and/or epithelial barrier function, which may play key roles in the development of FA related to environmental food allergen exposure. In contrast, early oral introduction and continuous consumption of baked hen's egg or peanut in children with eczema favored the development of tolerance, as shown in randomized controlled trials.[41,42]

2.4.2 | Eczema/Food allergy and asthma/allergic rhinitis

Eczema is also significantly associated with the development of asthma and AR, with a positive correlation between the severity of eczema and the prevalence of allergic respiratory diseases (up to 20% of children with mild eczema, but 60% with severe eczema develop asthma).[43,44] Genetics provide also some important clues to underlying mechanisms. More than 90 loci have been identified, which have a crucial impact on eczema, asthma and AR, indicating a common genetic background.[45] FLG LOF mutations also play a key role and correlate with asthma susceptibility and severity in patients with eczema. These effects have not been demonstrated in the absence of eczema, emphasizing skin inflammation as an important prerequisite for allergic sensitization.[46] Food sensitization and FA also predispose to asthma. A large meta-analysis of birth cohort studies confirmed that early childhood food sensitization increases the risk for wheezing/asthma and AR.[47] As previously mentioned, FLG-LOF variants are associated with FA, but the observed association remained significant after adjusting for eczema.[48,49] Thus FLG-LOF mutations seem to reflect a potential pathophysiological link for multimorbidity and a phenotype of eczema, FA and airway allergic diseases.

The hypothesis of epithelial barrier damages triggered by multiple environmental factors at the skin and/or airway and/or or gut levels has been recently suggested as a key in allergic diseases and multimorbidity pathophysiology (Figure 1). They interplay tightly with local microbial dysbiosis and local/systemic immune system response, and induce a vicious circle of chronic epithelial barrier dysfunction.[50] This hypothesis is opening strategies for prevention but also targets for treatment. Considering that epithelial barrier is a key in the pathophysiology of allergic diseases, it makes sense to study pathophysiological mechanisms not only at the systemic level (blood) but also in the target organ (skin, bronchial biopsies, bronchoalveolar lavage, induced sputum, exhaled condensates, nasal brushing samples).[51] Integrated multi-omics strategy (genomics, transcriptomics, proteomics, metabolomics, and epigenomics) may allow to understand the complex molecular mechanisms underpinning allergic diseases.[52–54] Furthermore, there is an increasing evidence that dysregulation of neuroimmune crosstalk plays a key role in the pathophysiology of all allergic diseases.[55,56] The mechanisms are complex and bidirectional. Immune cells and neurons communicate via cytokines and mediators such as neuropeptides (e.g.,

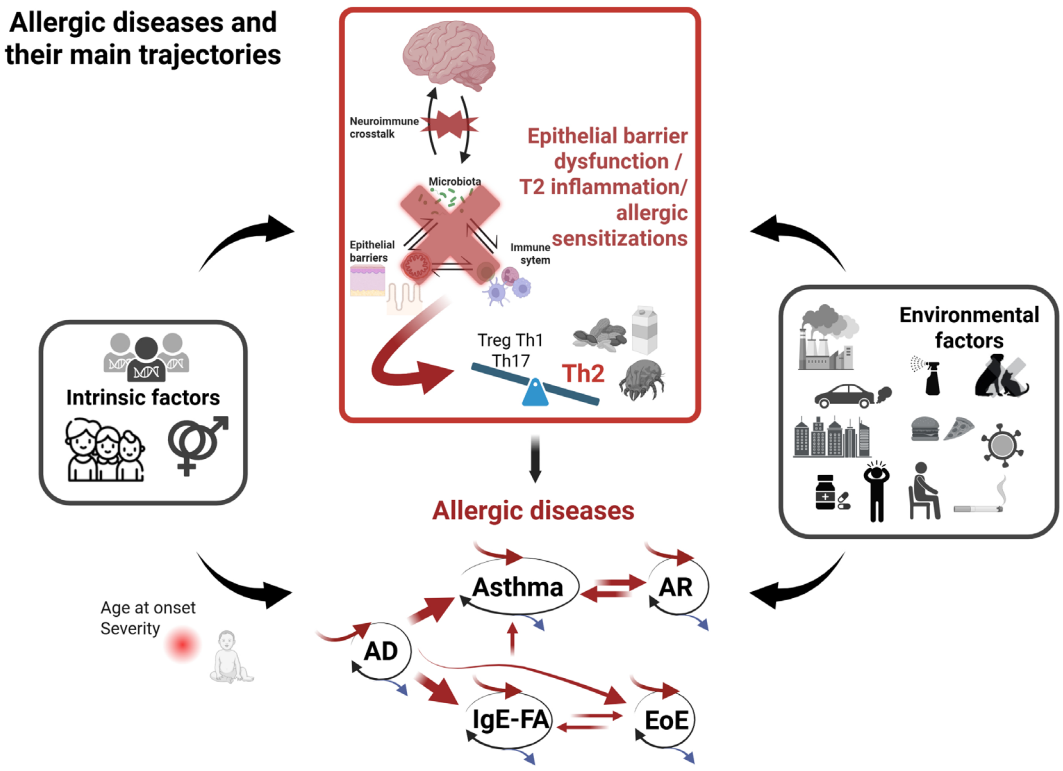

FIGURE 1 Allergic diseases and their main trajectories. Disruption of homeostasis at epithelial barrier (i.e., of the equilibrium between epithelium, microbiota and immune system) can favor the development of allergic diseases against environmental antigens. Main trajectories are shown and discussed in the review. Various intrinsic and extrinsic factors may act together, favoring both initiation or evolution of allergic diseases (red arrows). Blue arrows reflect "remission" (natural or thanks to intervention). Created in https://BioRender.com.

substance P). This may result in amplified and persistent symptoms of eczema, allergic respiratory diseases or FA.

2.5 | Pediatric allergic diseases: The concept of remission

The trajectories of allergic diseases must be considered over the long term, from infancy to adulthood, as a dynamic process. What we do know is that an allergic disease can persist throughout life, disappear and relapse (including in adulthood), or disappear definitively.[2,4,57] Disease "activity" can be controlled by the introduction of a maintenance treatment. More recently, particularly with the development of immunotherapy (IT) and biologicals for allergic diseases, the concepts of disease- modifying treatment and treatment-induced remission are emerging.[58–60] However, to date, with regards to allergic diseases and more especially asthma, there is no consensus on the definition of remission or on the criteria to be considered (clinical or more stringent criteria including biomarkers of inflammation or bronchial hyperreactivity).[61] In addition, there is no definition considering childhood-limited specificities or the frequent context of multimorbidity. Remission does not mean disappearance of underlying allergic disease mechanisms. For now, in children and pending further evidence, we favor the concept of "control" (or "desensitization") under treatment and "prolonged control" if maintained over a sustained period and retaining the term "remission" to describe patients who are asymptomatic without maintenance treatment, also highlighting that remission does not mean cure. The figures illustrate this proposal for asthma/AR/eczema (Figure 2) and FA (Figure 3).

3 | FACTORS ASSOCIATED WITH THE TRAJECTORY OF ALLERGIC DISEASES

3.1 | Factors relevant for prediction of disease course

It remains challenging to predict onset, progression or remission of allergic diseases and associated factors. They could depend on the life period including the crucial early life period (early priming) and a possible "window of opportunity" for intervention. During this time, environmental factors impact on maturation of immune system and susceptibility of immune-mediated diseases.[62] For example, the mode of delivery, feeding practices, early life medications such as antibiotics, early childcare and number of siblings, presence of pets at home, tobacco smoke exposure and timepoint of the introduction of solids have been shown to influence the development of the immune responses (Figure 1). Early identification of factors related to bad trajectories in terms of multimorbidity, severity and long-term prognosis should facilitate early intervention and better outcomes for patients and their families.

Every day, children come into contact with various exposures such as food additives, detergents, plastic, surfactants and air pollutants.[63] They may cause disruption of the skin and/or mucosal barriers which can lead to chronic dysfunction of an epithelial barrier.[9] Early use of emollients in bathing is associated with AD, whereas short term use of emollients after birth may be protective.[64] Such environmental factors also affect microbiome, immune system, and health overall leading to chronic diseases including allergies and asthma.[65–67] A link has been found between microbial dysbiosis and allergies. *Staphylococcus aureus* has been associated with reduced tolerance to foods[65,66] and severe asthma exacerbations,[68] while dysbiotic conditions of the gut influenced the allergic diseases of the skin and airways.[10] With regards to gene–environment interactions, increasing endotoxin exposure has been linked with decreased risk of sensitization and eczema in children with the CC genotype in the promoter region of the CD14 gene.[69] Exposure to microbial diversity enriching the human microbiome (biodiversity hypothesis),[70] such as living on farms,[71] or having household pets during first year of life[72] have been identified as protective factors towards asthma and atopy. Knowing protective and risk factors will enable clinicians to reduce future risk of development of allergies and initiate prevention strategies with more personalized approach (Table 1).

Different determinants of allergic diseases course have been identified based on age and sub-phenotypes.[6,20,73] The role of risk or protective factors differed between trajectories in terms of significance and strength of association. That was nicely demonstrated in a study conducted in two German birth cohorts (GINIplus and LISA) and replicated in the Swedish BAMSE cohort.[6] Seven trajectories up to adolescence have been identified, including a multimorbid

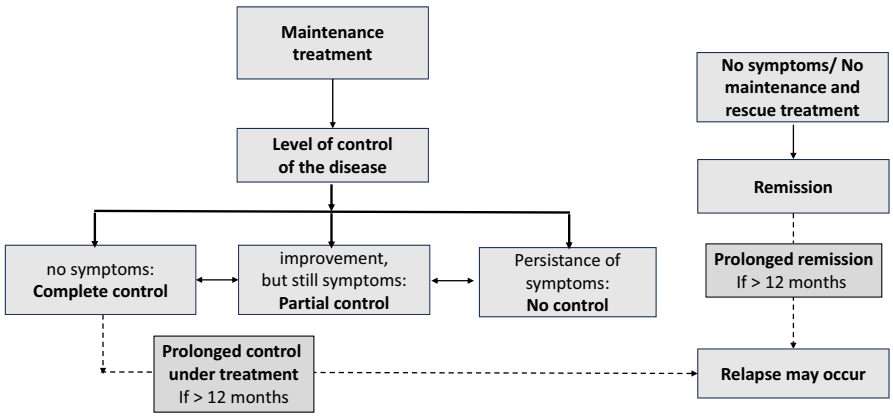

FIGURE 2 Trajectories in asthma, allergic rhinitis and atopic dermatitis: Control (different levels) under treatment versus remission.

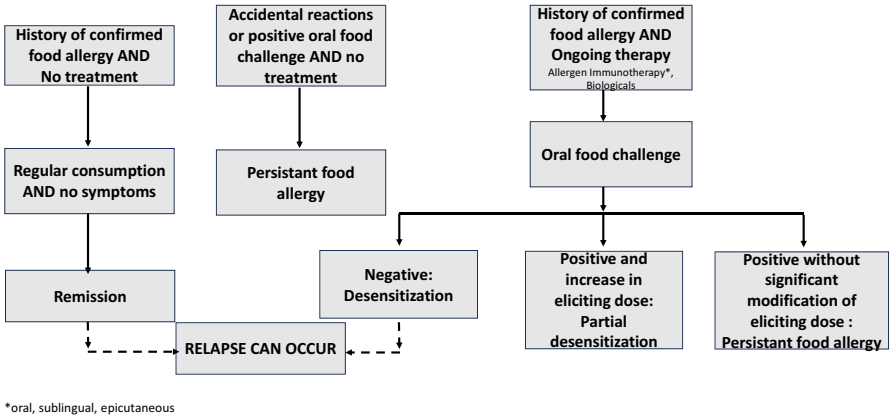

FIGURE 3 Trajectories in food allergy: Desensitization under treatment versus remission or persistant FA.

cluster (GINIplus/LISA = 4.0%, BAMSE = 8.2% of the participants). The authors have highlighted early-life determinants influencing allergic diseases development, including male sex, family history, exposure to pets, aeroallergen sensitisation, early infections as well as a genetic predisposition evaluated with a polygenic risk score.[6] Regarding childhood asthma prediction (data from three longitudinal birth cohorts: PAULINA/PAULCHEN, PASTURE), an integrated risk score was constructed and consisted of epidemiological characteristics (maternal asthma, sex, farm environment) and genome-wide molecular markers (genotype, DNA methylation and mRNA expression) at birth.[74] By adding first allergic symptoms/diagnosis (wheezing, AD, FA), the discriminative power of prediction was improved, which could be useful for clinical practice and design of future clinical studies.

Respiratory viral infections in early life such as rhinovirus and respiratory syncytial virus have been associated with increased risk of asthma development.[75,76] In particular, the 17q21 locus has been linked to greater genetic predisposition to rhinovirus-induced wheezing.[77] The COPSAC study found an interaction between *CDHR3* and *GSDMB* in the development of early childhood asthma, possibly due to an increased IL-17A response to viral infections and particularly rhinovirus C.[78] The ALLIANCE study identified a novel disease-driving mechanism induced by the 17q21 risk allele. Increased mucosal *GSDMB* expression was associated with a cell-lytic immune response coupled with compromised airway immunocompetence.[79] These findings suggest that *GSDMB*-related airway cell death and perturbations in the mucosal interferon signature account for the increased vulnerability of 17q21 risk allele carriers to respiratory viral infections during early life, opening new options for future biological interventions. Some studies have shown that immunological abnormalities in the cord blood[80] and impaired lung function[81] may precede the first wheezing episode in children who developed viral-induced wheeze later on. Multiple studies highlight the diversity of the impairment of innate immune responses to viruses, especially rhinovirus, related to altered pathogen recognition and interferon production and then anti-viral response. The impact on adaptive immunity, including the development of biased Th2 inflammation immune response, may be crucial in the heterogeneity of the phenotypes and trajectories.[82–84]

Sensitizations in early life often precede respiratory allergic diseases. In BAMSE and MAAS cohorts, early sensitisation to Ara h 1 (peanut), Bet v 1 (birch), Fel d 1 (cat), Phl p 1/Phl p 5 (grass), and Der p 1/Der f 2 (dust mite) identified children with a high risk of asthma and/or rhinitis at 16 years.[85] It has been shown that asthma symptoms will likely persist into adolescence and adulthood if a child has a family history of atopy/asthma, genetics, impaired lung function, infections early in life, atopic sensitisation, allergic comorbidities, or smoking exposure.[20,73,86] In contrast, avoidance of tobacco smoke exposure during pregnancy, vaccinations in early childhood, and starting day care between 1.5 and 3 years of age might protect or delay the development of asthma.[28] Further, in terms of remission of asthma during school age and adolescence, it has been shown to occur more often in males and those with milder allergic disease.[20,73]

Several prediction models have been developed to predict asthma such as Supervised Machine Learning Models[87,88] and prediction scores—Stringent Asthma Predictive Index (API)[89] and Pediatric Asthma Risk Score (PARS).[90] They have good specificity but low sensitivity and consist of different components but related symptoms during first 3 years (wheezing and rash), atopy and parental history are common. A new Asthma Predictive Risk score (ASPIRE) was developed to predict asthma beyond childhood based on data from Isle of Wight Birth cohort of 1456 children.[91] The following risk factors included recurrent wheeze and positive SPT at 4 years predict asthma at 18 years (specificity = 0.80, sensitivity = 0.49, AUC = 0.65).[91] On another hand, predictors of asthma remission by adulthood were found to be combination of normal FEV1/FVC ratio, airway responsiveness, and serum eosinophil count at baseline (5–12 years).[92]

3.2 | Potential biomarkers for identification of children at risk of developing allergic diseases

DNA methylation (DNAm) has been considered as a pathway which may influence development of allergies. Results have shown that DNAm may be a cause or consequence of aeroallergen sensitization with different DNAm identified on blood as mediators of the

TABLE 1 Factors associated or suspected to be related to trajectories of allergic diseases.

Factors	Risk factors	Protective factors
Factors involved during prenatal period, birth, neonatal period and early life	Crucial time involved in all allergic diseases with opportunity for interventions	
	Tobacco smoke exposure Indoor and outdoor pollutants exposure Microbial dysbiosis Birth mode, birth weight Mother diet Skin impairement Psychological stress Perinatal antibiotics	Mother diet Microbial diversity
Factors involved during all childhood		
Exposure factors	Include all environment factors also called exposome Crucial role in asthma but also on all allergic diseases through epithelial barrier impairment	
	Tobacco smoke exposure Ambient pollution, « toxic air » Detergents Plastic Indoor pollutants: ventilation, cooking, heating, mold and dampness Outdoor pollutants: home, school, leisure activities Respiratory infections Antibiotics	Rural lifestyle Farm environment Presence of older siblings, day care center attendance Exposure to dogs
Diet factors	Involved in all allergic diseases	
	Delayed food introduction, poor diversity Ultraprocessed foods	Early and diverse food introduction Breastfeeding versus formula feeding[a] Immunonutrition strategies (fish, mediterranean diet, fiber-rich diet as ex)
Molecular and genetic factors	Gene–gene interactions Gene–environment interactions Polygenic risk of allergic diseases and multimorbidity Gene expression related to genetic variants and/or epigenetic mechanisms →*Towards risk or protection*	
Familial history (parents, siblings)	Asthma, allergic diseases	
Sex	Male (childhood), female (adolescence, adulthood)	
Genetics	Filaggrin deficiency mutation 17 q 12–21 (ORMDL3, GSMD) Genes associated to antiviral immunity/innate immunity deficiency (CDHR3, TLR-7, as ex) Network of genes associated to hyper T2 or T17 inflammation and epithelial barrier dysfunction (TSLP, IL33 as ex) Gene–environment interactions	
Epigenetics	DNA-methylation	
Child factors		
Sensitizations	Early and multiple sensitizations Early airborne allergens sensitizations	Late sensitizations (airborne allergens)
Severity of atopic diseases	Early and severe eczema Early and severe asthma	
Lung function	Neonatal impairment Early impairment High bronchial reactivity	
Growth	Obesity in childhood or low birth weight	
Lifestyle	Stressful environment	Physical activity
Other		Vaccinations Healthy diet

[a]Evidence is a bit mixed.

development of sensitization.[93] Others identified that nasal DNAm has better prediction in diagnoses of allergy outstanding blood DNAm, genetic risk and environmental factors.[94] A small study showed that nasal epithelial DNAm was able to differentiate between severe and non-severe asthma, which might be helpful in prediction of severity.[95] Thus, DNAm could be used as biomarkers and predictors of allergic diseases as well as severity but more validation is needed including appropriate time for measurement.[96] Many studies highlighted the need for considering genetics with family history, biomarkers, and comorbidities to predict development of allergies and asthma. This could be combined into polygenic risk scores to develop targeted therapeutic interventions.[7] While results seem promising, there are several methodological challenges which need to be considered while balancing diagnostic values and the feasibility of the procedure in routine practice.

Some potential "omic" biomarkers in early life including proteomics, metagenomics and metabolomics have been explored in eczema and FA but further research is needed to improve their identification and potential for prediction of trajectories and personalized medicine in early life.[97] Metabolomic profiling in atopic and/or asthmatic children identifies different pathways suggesting mechanisms such as modulation of host-pathogen and gut microbiota interactions, epigenetic changes in T-cell differentiation, and lower antioxidant properties of the airway epithelium underpinning the trajectories.[53]

Currently, we do not have data from large cohorts with repeated measurements of biomarkers and the optimal frequency of collection, which can be difficult in children. Further research is needed in asthma and allergic diseases in order to study biomarkers that can be used in daily practice to predict risk and trajectories.

4 | DISEASE MODIFICATION BY INTERVENTION AND PERSPECTIVES

Until recently, the goals of the maintenance treatment of asthma and allergic diseases were to control the symptoms and to prevent clinical events (exacerbations of asthma, flares-up of AD, for example) with a step-up/step-down strategy. The development of new strategies such as specific IT and biologicals has led to new treatment goals: not only to treat, but also to prevent the onset of a new allergic disease or to modify the course of the disease(s). From "one size fits all" treatments, the evolution is marked by precision-based approach and personalized strategies, considering the characteristics and all lifelong risks, including the development of any other allergic disease (e.g., asthma and rhinitis). We now have treatments that target mechanisms, enabling several allergic diseases to be treated or prevented simultaneously. The concept of disease modifying intervention or treatment has emerged and studies are underway to assess the impact of specific propositions on the course of the disease.[98] Early interventions are now recommended to target strategies including prevention of damage and complications associated both to allergic diseases (e.g., lung function impairment) and to their treatment (e.g., side effects of corticosteroids exposure). Today, a more holistic approach with actions on all the factors involved in the diseases (nutrition, environmental and behavioral factors, …) is emerging and underpinning the "One Health" concept.[99]

4.1 | Atopic dermatitis and food allergy

4.1.1 | Diet and skin interventions

It is well established that nutrition can influence the gut microbiome–immune system axis and the concept of immuno-nutrition has emerged.[100] A systematic review and meta-analysis including 23 randomized clinical trials (13,794 participants) found that introducing multiple allergenic foods between 2 and 12 months of age was associated with a reduced risk of FA, with a high-certainty evidence for egg or peanut.[101] Guidelines now provide recommendations regarding food introduction with details on timing and dose needed to prevent some food allergies, also highlighting that these interventions need to consider countries' and/or families' dietary habits and regional variations.[102] The effect of dietary intervention on the prevention or progression of other allergic diseases remains to be better demonstrated.[103]

Skin intervention with emollients in order to protect the epithelial barrier have also been studied. Some benefits have been recorded on skin conditions but not on the occurrence of FA or wheeze in the first years of life.[104,105] A trial conducted in Japan has shown that early treatment of AD with topical steroids to clinically affected and unaffected skin in high risk infants (7–13 weeks) was effective for egg allergy prevention evaluated at 28 weeks, but was associated with adverse effect on growth.[106] A longitudinal multicenter prospective trial (NCT03742414) is ongoing and aims to assess the impact of proactive treatment of infants with dry skin or AD between 0 and 12 weeks of age with petrolatum versus trilipid emollient and proactive topical steroid skin care on rates of FA and sensitization, postulating that earlier eczema/dry skin intervention including new generation emollients will reduce the incidence of FA.

Current data also suggest the link between gut microbiota and AD development. In particular, the subgenus composition of Bifidobacterium undergoes substantial changes in the first year of life.[107] The protective effect of Bifidobacterium depends on a specific microbiota composition at the respective age of the infant, highlighting the importance of timing in prevention strategies targeting infant-microbe interactions. Furthermore, there is evidence that infants with AD show decreased richness in members of the Lachnospiraceae family, as well as the genera Faecalibacterium and Dialister in stool samples of the first months of life.[108]

4.1.2 | Immunotherapy for food allergy

Allergen immunotherapy (AIT) is now supported by many guidelines in order to get mainly desensitization (i.e., an increase in the threshold of reactivity while on therapy).[109] However, the disease-modifying

effect of food AIT has been investigated. The long-term effect of peanut oral immunotherapy (OIT) has been studied in POISED phase 2 trial. The likelihood of maintaining tolerance (sustained unresponsiveness to repeated OFC) diminished if treatment was discontinued or reduced from 4000 to 300 mg peanut protein daily. Baseline blood markers were associated with better long-term outcomes, such as higher peanut-specific IgG4/IgE and lower Ara h 2 IgE and basophil activation responses.[110] The timing of intervention seems to be critical, with studies supporting the hypothesis that "the earlier, the better". Studies, such as the IMPACT trial (peanut OIT in children <4 years) have shown that younger age and lower baseline IgE levels are associated with higher probabilities of tolerance development, supporting window of opportunity for early interventions.[111] Similarly, data on epicutaneous allergen immunotherapy encourage this concept.[112]

4.2 | Allergic rhinitis/conjunctivitis and asthma

Identification of children at risk of persistent or severe allergic airway disease is now recognized as a priority.[113] Conventional treatment is effective on asthma symptoms but has no effect on trajectory, as illustrated by the CAMP study for inhaled corticosteroids in asthma.[114] A key question is whether early use of treatment such as AIT or biologicals may modify natural trajectories.

4.2.1 | Allergen immunotherapy

Allergen IT (AIT) is now recognized as a treatment strategy in asthma and AR management. Because of a better safety profile, sublingual (drops, tablets) rather than subcutaneous AIT (SCIT) is now recommended.[115] Up to now, SCIT has been the only treatment that has demonstrated a disease-modifying effect, showing long-term benefits that persist after discontinuation. There is some evidence of a reduced short-term risk (for up to 2 years post-AIT) of developing asthma in children and adolescents with moderate-to-severe AR triggered by grass/birch pollen, though long-term benefits remain to be better investigated, as well as for AR triggered by other allergens including mites.[116] Real-world retrospective database studies from Germany and France have shown a lower risk of asthma (assessed by treatment prescription) in children treated with sublingual (drops/tablets) IT (mainly pollen and mites) for AR.[117] Regarding primary prevention, a trend towards reduced asthma risk was observed in the Mite Allergy Prevention Study including 111 infants (age 5 months) with a high risk of atopy treated for 1 year with house dust mite sublingual AIT and followed up to the age of 6.5 years. Further studies are needed to confirm if AIT might be a preventive therapy for asthma in at-risk children.[118] The advent of molecular diagnostic platforms may allow early identification of one or more "initiator" allergens in at-risk children, before the onset of the first symptoms. Whether the use of early IT against such initiating allergens could have secondary preventive needs further investigation.[119]

4.2.2 | Bacterial lysates

Bacterial products may control the initiation and development of allergic asthma through several mechanisms of innate immune training.[120] The impact of bacterial oral mucosal IT (MV 130, 6 months) has been confirmed in a trial conducted in 120 infants younger than 36 months with ≥3 wheezing attacks during the previous 12 months and no allergic sensitizations.[121] In the year following treatment initiation, there was a significant effect on exacerbations and symptoms and no safety issues. The results of another trial (ORBEX, NCT02148796, 2 years of treatment, and 3 years follow-up) conducted in high-risk children (6–18 months) to assess the protective effect on the occurrence of the first episode of wheezing or lower respiratory tract illness are expected. These studies open new opportunities to prevent or treat a frequent condition in young children without effective treatment and possible long-term consequences such as lung function impairment and chronic obstructive pulmonary disease risk.[122]

Besides bacterial lysates, the farming environment and its components present intriguing options for potential primary and secondary prevention via innate immune system stimulation. Also, animals and plants from traditional farms produce proteins that transport hydrophobic microbial and plant metabolites.[123,124] When delivered to mucosal surfaces, these agents might regulate airway responses, which are relevant for preventive strategies.

4.2.3 | Biologicals: Allergic diseases modifying strategy for future?

The classic Th2 inflammatory pathway is associated with adaptive and innate immunity pathophysiological mechanisms. Epithelial barrier dysfunction is crucial in initiating an inflammatory cascade with alarmins (such as IL-25, IL-33, TSLP) production. All can be targets for intervention in allergic diseases. More than 20 biologicals have been developed, some of which are now approved or in clinical trials.[125] For instance, Bruton's tyrosine (BTK) and Janus kinase (JAK) inhibitors modulate intracellular signaling pathways crucial in type 2 inflammation. Others target molecules such as TSLP, IL-33, IL-5, and IgE, highlighting the potential of precision medicine in managing these diseases. Emerging therapies for type 2 diseases, such as IL-36 and IL-13 inhibitors, are continuously being developed and may become available soon. Biological treatments have so far demonstrated their efficacy and safety in various allergic diseases, including in children, even from a very young age, such as in severe AD in infants from the age of 6 months for dupilumab. However, data on their impact on the trajectory of allergic diseases remain very limited.

Multiple biologics such as omalizumab, mepolizumab, benralizumab, dupilumab, Tezepelumab, are now available for moderate to severe asthma treatment but not all have been studied in children less than 12 years. None is available for asthma in children under 6 years of age. The impact of biologicals on asthma trajectory remains a critical question. Some real-life studies have shown that treatment with omalizumab (anti-IgE treatment) can be discontinued in selected children with a history of severe allergic asthma and asthma that is well controlled on treatment without relapse.[126] Improvement of all asthma outcomes (severe exacerbation, control, lung function) has been recorded in children with moderate to severe T2 asthma included in the VOYAGE trial and treated with Dupilumab or placebo for 1 year.[99] This trial was followed by the EXCURSION study, a one-year active treatment open extension.[127] Sustained significant improvement of FEV1 may suggest an impact on bronchial remodeling associated with lung function decline and on asthma trajectory. The results of the PARK clinical trial (ClinicalTrials.gov identifier: NCT02570984) are expected. Its goal was to assess if the treatment by omalizumab can prevent asthma or modify its severity, as well as other allergic diseases. It has been conducted in children age 2–3 years at high-risk for developing asthma, treated with omalizumab or placebo for 2 years and then followed for an additional 2 years. Other targets such as TSLP or IL-33 may be particularly relevant in the pediatric landscape.

Dupilumab is a monoclonal antibody that inhibits the IL-4 receptor alpha and inhibits signaling by IL4 and IL-13. It is approved in patients as young as 6 months old with severe AD.[128] Tralokinumab is another approved biological treatment in patients as young as 12 years old, specifically targeting IL-13.[129] The efficacy and safety of these treatments have been demonstrated. Their disease-modifying effects are supported by some retrospective studies conducted in children treated with dupilumab for AD, compared to conventional treatments. Lin et al. showed a 40% and 31% reduction in the risk of asthma and of AR, respectively, over a 3-year observation period in a cohort of 2192 children treated with dupilumab (7 years of age at initiation) compared with children receiving conventional treatment.[109,130] The recent OUTMATCH trial has shown that omalizumab can be an effective monotherapy in multi-FA allergy management, which has already been suggested by other studies.[131–133] This biologic-based control of multiple food allergies seems attractive, but the effect on the longer-term control or suppression of clinical FA awaits results from food allergen exposure after cessation of treatment. A previous trial has shown the benefit of temporary add-on omalizumab to OIT with frequent persistent food tolerance after stopping, which may suggest some impact on FA trajectory.[134]

5 | CONCLUSION AND RESEARCH PRIORITIES

We know now that allergic diseases are characterized by complex (hyper)inflammatory conditions, that they often start in early life with multiple potential trajectories and that their consequences may be observed not only during childhood but also later in life. Knowledge on determinants associated to persistence, remission, relapse or severity are improving. The concept of multimorbidity with diseases underpinned by common pathways has overtaken that of the classic atopic march. Preventing diseases or their complications and modifying allergic diseases trajectories are new management goals. Remission has emerged as one goal but definitions remain to be agreed at a global level. In children, the priorities are early diagnosis, repeated response to treatment evaluation, and maintained control of the disease's activity. Many attractive disease-modifying treatment options remain reserved for children who have already developed severe disease. Long-term studies are now needed to accurately identify young patients before the onset of severe disease but who are at high risk of persistence or progression (biomarkers, omics research, genetics, etc.), for whom early use of treatments such as biologicals might be indicated, and to study the impact of these interventions on disease course and on the risk of developing new allergic diseases. Pharmacologic but also nonpharmacologic intervention are needed for developing a precision medicine and personalized approaches to control burden and risk associated to allergic diseases. All these propositions should be complemented by public health policies (e.g., environmental tobacco smoke exposure, indoor and outdoor air pollution, chemical exposure, weather and climate change consequences, nutrition, infection prophylaxis) which are also key priorities to control allergic diseases burden in a "one health concept" perspective.

AUTHOR CONTRIBUTIONS

Birgit Kalb: Writing – original draft. **Ekaterina Khaleva:** Writing – original draft. **Mattia Giovannini:** Writing – original draft. **Karine Adel-Patient:** Writing – review and editing. **Flore Amat:** Writing – review and editing. **Stefania Arasi:** Writing – review and editing; conceptualization. **Susanne Lau:** Conceptualization; writing – review and editing. **Antonio Nieto:** Conceptualization; writing – review and editing. **Bianca Schaub:** Writing – review and editing. **Marie Standl:** Writing – review and editing. **Jonathan O'B Hourihane:** Writing – review and editing; conceptualization; funding acquisition; supervision. **Philippe Eigenmann:** Conceptualization; writing – review and editing; funding acquisition; supervision. **Antoine Deschildre:** Conceptualization; writing – original draft; writing – review and editing; supervision; methodology.

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