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Natural Evolution of IgE Responses to Mite Allergens and Relationship to Progression of Allergic Disease: a Review

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Abstract
Purpose of Review Allergenic molecules of the house dust mite (HDM) are crucially important indoor allergens, contributing to allergic rhinitis and asthma around the globe. In the past years, recombinant molecules for diagnostics opened new pathways to investigate individual sensitization profiles and new chances for the prevention and treatment of HDM allergy. This review summarizes the latest findings on the evolution of IgE responses towards mite allergens.
Recent Findings Several cross-sectional and longitudinal studies confirmed the role of Der p 1 and Der p 2 as major allergenic proteins of the HDM. A newly identified player is the major allergen Der p 23. Apart from identifying the early sensitization towards this molecule as a risk factor for asthma in school age, a recent longitudinal study described sensitization patterns showing that the production of IgE usually starts towards a group of initiator proteins and may stay monomolecular or expand to an oligo- or even polymolecular stage. This phenomenon also correlates to clinical symptoms. A relation between a broad sensitization pattern and symptom severity has also been shown cross-sectionally.
Summary Individual sensitization profiles towards HDM allergens provide important information to evaluate a patient's current stage and risk for clinical symptoms. This knowledge paves the way for an early and adequate prevention and/or treatment.

Keywords Allergic rhinitis · Asthma · House dust mite · IgE response · Molecular allergology · Specific immunotherapy

Abbreviations

AD	Atopic dermatitis
AIT	Allergen-specific immunotherapy
CRD	Component-resolved diagnostics
D. pteronyssinus	*Dermatophagoides pteronyssinus*
EAACI	European Academy of Allergy and Clinical Immunology
HDM	House dust mite
IgE	Immunoglobulin E
ISAAC	International Study of Allergy and Asthma in Childhood
MAAS	Manchester Asthma and Allergy Study
MAS	Multicenter Allergy Study

Introduction

House dust mites (HDM) are cosmopolitan pyroglyphids tenanting human habitats around the globe. As the contact to these minuscule cohabitants is perennial, different proteins of the mite itself as well as its feces became crucially important indoor allergens [1] contributing to and co-causing allergic rhinitis and asthma worldwide. Although the prevalence of house dust mite allergy shows a wide range of geographic variation [2–4], its overall significance is prominent with numbers suggesting that 65 to 130 million people might be affected [5•]. This equals 1–2% of the world's population and turns a tiny animal into the cause of a major burden for

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international health care systems [6•]. A continuous increase in prevalence of allergic airway diseases, especially in childhood, has been observed in a multitude of studies, including the global surveillance study International Study of Asthma and Allergy in Childhood (ISAAC) [7] and its extension the Global Asthma Network (GAN) [8]. Nevertheless, a clear association between HDM exposure and allergic airway inflammation is difficult to establish [9] due to methodological variations in the performed studies. For the same reason, prevention guidelines are a delicate matter, as especially the results on allergen avoidance have been contradictory [10–13]. Still, allergen avoidance and the alleviation of symptoms by pharmacotherapy represent the main treatment strategies, as the efficacy of allergen-specific immunotherapy (AIT) is still debated [14, 15]. Another reason for relatively low prescription numbers [15] may be a lack of accuracy in the routine diagnostic procedures as skin tests and immunoglobulin E (IgE) measurements are often performed with HDM extracts. Component-resolved diagnostics (CRD) using recombinant and/or purified allergenic proteins can improve the diagnostic precision, but the correct interpretation of these results as well as related therapeutic consequences need to be implemented as guidance for physicians. The crucial basis for this implementation is a deep understanding of the natural evolution of IgE responses to HDM allergens, especially set into relationship with disease progression, which will be the topic of the following paragraphs.

Molecular Allergology: the Concept

During the past two decades, diagnostic procedures in allergology have significantly gained precision through the production of recombinant and purified allergenic molecules for serological, as well as skin test diagnostics [16]. This follows a worldwide trend coined "Precision Medicine," which is aimed at providing personalized treatment strategies on the base of individual geno- as well as phenotyping of the disease [17]. While commercial extracts often contain a varying allergen composition and concentration [18, 19], the use of recombinant/purified single proteins allows to choose the specific molecules of interest according to the clinical history of the patient. By this, false negative results are less likely and the identification of cross-reactivity is facilitated [20]. In addition, false positive results due to the presence of cross-reactive carbohydrate side chains in extracts and in native molecules are prevented by the use of recombinant proteins. Last, an IgE reactivity towards certain marker molecules may help to evaluate the risk of severe reactions [21].

Serological analysis on the base of biotechnologically engineered allergens can be performed in singleplex assays testing one allergen at a time or in a multiplex set which allows the IgE determination towards a multitude of (up to 112 molecules; ©ImmunoCAP ISAC, Thermo Fisher Scientific) molecules within one test run. Especially for pediatric patients, a multiplex assay seems tempting as it provides a wide set of information, while only requiring as little as 20 μl of serum [22]. While the evaluation of a possible cross-reactivity is facilitated by this large amount of serological data, the results obtained by a multiplex test may also uncover sensitizations of unclear clinical relevance. Therefore, clear guidelines for the physician are essential, considering that CRD is not yet broadly accessible for routine diagnostics. This fact has already been taken into account by the World Allergy Organization [23] as well as the European Academy of Allergy and Clinical Immunology (EAACI) [24••], who published a consensus document and a user's guide on molecular allergology. In these, the authors underline the impact of molecular allergy diagnosis on clinical decisions [25••]. As shown in various studies, the knowledge of the individual sensitization profile clearly affects the physicians' decision for or against the prescription of an allergen-specific immunotherapy [26, 27]. Once the decision has been taken in favor of an immunotherapy, the knowledge of the patient's individual sensitization profile allows the composition of a personalized treatment, omitting those proteins to which the patient shows no IgE reaction and by this avoiding a possible induction of new sensitizations as a treatment side effect [16, 28]. Unfortunately, this kind of accurate therapy is not yet commercially available for the treatment of HDM allergy, but promising research is being performed including the plan of designing of a house dust mite vaccine on the base of recombinant hypoallergenic proteins [29–31].

The "Classical" House Dust Mite Molecules

Although several species of storage and house dust mites are known as allergenic sources Table 1, the most important ones are *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* [32••, 33]. In subtropical and tropical regions, the storage mite *Blomia tropicalis* has been added to the list of most important mite allergen sources [34]. As *D. pteronyssinus* is significantly distributed worldwide, most studies are related to this species and its allergenic molecules. In order to keep a universal structure in the nomenclature of allergenic proteins, molecules from different sources but with a similar structure and function belong to the same group (1, 2, 3, 4,…) Table 2.

The most important allergenic proteins of *D. pteronyssinus* are the cysteine protease and primary activator of other proteolytic mite allergens Der p 1 and the epidermal secretory protein Der p 2 [35, 36]. These molecules can also be found in high concentrations (between 20 and 100 μg/ml) in extracts of *D. pteronyssinus* [37, 38]. A Spanish study among 384 HDM-allergic patients, which was able to reproduce the strong correlation between serum levels of IgE to crude extract

Table 1 The most commonly found house dust mite species

Mite species	Defined molecules
House dust mites	
Dermatophagoides pteronyssinus	20
Dermatophagoides farinae	31
Euroglyphus maynei	5
Blomia tropicalis	13
Storage mites	
Acarus siro	1
Glycyphagus domesticus	1
Lepidoglyphus destructor	5
Tyrophagus putrescentiae	8

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and to the components Der p 1/Der p 2, observed a higher risk of developing asthma among subjects being sensitized to these major allergens [39]. In order to further investigate individual sensitization schemes, the IgE profiles of 461 children taking part in the Manchester Asthma and Allergy Study (MAAS) have been grouped according to certain clusters of allergen components [40]. Within the component group 2, which contained almost exclusively house dust mite allergens, all children were sensitized to Der p 1 and most also to the group 2 allergens at age 11 years. This observation went along with an approximately threefold increase in asthma and a significant increase in airway hyperresponsiveness in patients sensitized to Der p 1 and Der p 2.

Another well-known, although clinically less significant, allergen is the protein Der p 10, which belongs to the group of tropomyosins. The amino acid sequence of this protein shows a 98% homology to the tropomyosin of *D. farinae* and 75–80% to the tropomyosins from shrimp and fruit fly [41], which makes Der p 10 the main cause of cross-reactivity in HDM allergy. A sensitization rate of 15.2% to Der p 10 was observed among 1322 HDM-allergic patients randomly selected in an Austrian allergy clinic [42]. Although this prevalence is quite low, the Der p 10-positive group stood out by exhibiting significantly higher total and mite-specific IgE levels than those patients without IgE towards Der p 10. This phenomenon could also be observed in grass pollen allergic patients indicating a close connection between broader sensitization profiles and higher IgE levels. Therefore, a sensitization to Der p 10 may be taken as a marker for broad sensitization. Nevertheless, the serological data of each patient need to be interpreted considering the clinical history and also other tests like skin or provocation tests. A comprehensive algorithm for clinical decision-making has been provided by the expert team editing the EAACI Molecular Allergology User's Guide [24••] based on IgE responses to Der p 1, Der p 2, and Der p 10.

Although not yet available for most patients in clinical daily life, the longitudinal evolution of IgE responses is of special interest to monitor and possibly predict the course of disease. Birth cohorts especially deliver valuable information in this area as they give insight to serological evolutions in early life. The IgE profiles of 235 children of the Manchester Asthma and Allergy Study birth cohort were recently analyzed towards grass pollen and mite allergens [43•].

They identified three different sensitization trajectories related to mite allergy between the ages 5 and 11 years: group 1 sensitization (to Der f 1 and Der p 1), group 2 sensitization (to Der f 2 and Der p 2), and complete mite sensitization (to both groups plus Der p 10, Blo t 5 from *B. tropicalis* and Lep d 2

Table 2 Major and minor mite allergens

Species	Allergenic molecule	Biochemical name	Prevalence among patients (%)	Molecular weight (kDa)
D. pteronyssinus	**Der p 1, Der f 1, Blo t 1**	Cysteine protease	70–100	24–27
D. farinae	**Der p 2, Der f 2, Blo t 2**	NPC2 protein family (epidermal secretory proteins)	80–100	15–26
B. tropicalis	**Der p 3, Der f 3, Blo t 3**	Trypsin-like protein	16–100	29–31
	Der p 4, Blo t 4	Alpha-amylase	25–46	60
	Der p 5, Blo t 5		50–70	14
	Der p 7, Der f 7	Lipid-binding protein	50	26–31
	Der p 8, Der f 8, Blo t 8	Glutathione *S*-transferase	40	27
	Der p 10, Der f 10, Blo t 10	Tropomyosin	5–18, 50–95	36
	Der p 11	Paramyosin	80	103
	Blo t 12	Chitin-binding protein	50	14
	Der p 21, Blo t 21			13.2
	Der p 23	Peritrophin-like protein	74	8

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from *Lepidoglyphus destructor*). Both children from the group 1 and complete mite sensitization trajectory had a significantly increased risk for asthma, eczema, and rhinitis, but the highest odds ratio (OR, 7.15; 95% CI, 3.80–13.44) for asthma could be observed among children in the complete mite sensitization group. Further, those children belonging to the group 2 allergens trajectory generally had lower odds of clinical symptoms, except for a significant association with asthma. In contrast to the grass allergic children, no specific role of the longitudinal IgE evolution could be observed among HDM-sensitized subjects. [43•].

New House Dust Mite Molecules

Apart from the "classical" house dust mite allergens described above, a large number of other mite allergenic proteins have been described and sequenced over the past decades. Additionally to their individual protein function, their allergenicity may be based on a complex interaction between allergens from various groups [44]. Still, the evidence on the role in disease of many allergens is often rather weak [24••]. Special interest should be given to two rather recently discovered molecules.

One of them, Der p 23, has been unknown until 2013, when it was discovered as a peritrophin-like protein forming part of the midgut and dung ball membranes. [45]. Although this allergen is present only in low amounts in HDM extracts, it is apparently capable of inducing high IgE titers. [46••]. In a European study, Der p 23 has been described to be a major allergenic protein of *D. pteronyssinus* reacting with IgE antibodies from 74% of the 347 house dust mite allergic patients and exhibiting a high in vitro allergenic activity [45]. A similarly high prevalence of 74.5% could also be confirmed among 47 North American patients. In contrast to previous observations, the specific IgE levels elicited by Der p 23 among this study population were rather low, while the major HDM allergens Der p 1 and Der p 2 accounted for 85% of the specific IgE [47]. This observation underlines the importance of the known major allergenic molecules, while suggesting that the newly discovered allergen Der p 23 also represents a possibly essential component for the diagnosis and maybe even immunotherapy of house dust mite allergy.

The other recently described house dust mite allergen belongs to the group 11 from *D. pteronyssinus* (Der p 11) and is distinctive because of its high molecular weight of ~95–100 kDa [48•]. When testing the sera of patients from Europe and Africa, the frequency of IgE reactivity to Der p 11 was relatively low among European subjects (between 7 and 16% according to varying geographic regions), especially when compared to patients from Zimbabwe (44% IgE reactivity). Interestingly, these numbers changed significantly when selecting the patients according to their symptoms. Among the group of patients affected by atopic dermatitis (AD), sensitization rates to Der p 11 increased up to 67% and made the protein a marker allergen for AD in house dust mite allergic patients. This may reflect the fact that high molecular weight allergens easily penetrate the eczematous skin.

Other potentially important allergens showing a high frequency of IgE binding in sera of allergic patients are Der p 5 [49], Der p 15, Der p 18 [50, 51], Der p 21 [52], and other allergens from groups 4 and 7 (please see [32••, 46••] for a comprehensive review on the molecular properties of house dust mite allergens).

A cross-sectional study investigating the sensitization to a broad panel of HDM allergens in 1302 HDM-allergic patients from Europe, the USA, Canada, and Japan found that a HDM allergy may be revealed in over 70 and 80% of the cases by measuring IgE antibody levels towards the major allergens Der p 1 and/or Der f 1 and Der p 2 and/or Der f 2, respectively [53]. Similar numbers have been observed in different European populations. Over 97% of the patients in this study presented IgE antibodies towards the major allergens Der p 1 and Der p 2. With the addition of Der p 5 and Der p 7, the percentage of diagnosed patients could be increased to almost 100% [54]. When assessing the serological data of 105 HDM-allergic asthmatic and 53 non-atopic non-asthmatic children, it was discovered an interesting setting underlining also the role of minor allergens as diagnostic indicators [55••]. As expected, the asthmatic children showed higher IgE levels to a panel of seven HDM allergens than the control group, but interestingly their IgE repertoire was not only higher in concentrations but also directed to a greater variety of allergenic molecules. This goes along with the "molecular spreading" phenomenon previously described for grass pollen sensitization [56].

The Evolution of the IgE Response: the "ABC" of Mite Allergy

Taking up the idea of a "mite molecular spreading," the sera of 722 participants to the German Multicentre Allergy Study (MAS), a birth cohort started in 1990, were examined for IgE to a comprehensive panel of 12 recombinant *D. pteronyssinus* allergens [57••]. The results offered a broad view of the longitudinal evolution of mite-specific IgE responses throughout childhood and youth up to age 20 years and seemed similar to those found by Hatzler et al. when assessing *Phleum pratense* allergenic proteins [56]. The "initiator molecules" most frequently triggering an IgE response were found to be Der p 2, Der p 1, and the recently identified major allergen Der p 23. Interestingly, the mean age at first detection correlated inversely with the frequency of detection of each molecule, i.e., the strongest initiator of the IgE response elicited the earliest response. In order to generate a strategic overview of the multitude of IgE responses observed over time, the researchers generated a group system according to the prevalence ranking

at age 20 years. Group A summarized the molecules most frequently eliciting an IgE response at this age (Der p 2, Der p 1, Der p 23), followed by group B (Der p 5, Der p 4, Der p 7, Der p 21), and finally the less frequent molecules of group C (Der p 11, Der p 14, Der p 15, Der p 18, and Clone 16). An IgE sensitization started almost invariably with molecules belonging to group A and expanded sequentially first to group B and finally to group C molecules Fig. 1.

Nevertheless, the individual sensitization profiles were extremely heterogenous at age 20 years with 27 children responding to only one molecule (monomolecular profile), 50 responding to 2–4 (oligomolecular profile), and 42 children producing IgE to 5 or more of the 12 molecules (polymolecular profile) Fig. 2.

As the birth cohort also included clinical data, as well as an assessment of the Der p 1 load in the house dust collected at the patients' homes at age 6 and 18 months, the authors were able to evaluate the role of exposure and other possible risk factors for the clinical evolution of the disease. This analysis showed that an early IgE sensitization onset, parental hay fever, and higher exposure to mites were associated with a broader polymolecular IgE sensitization pattern. Participants who reached the broadest sensitization stage (i.e., A → B → C) had a significantly higher risk of mite-related allergic rhinitis (OR 5.5, 95% CI 2.9–10.8, $p < 0.001$) and asthma (OR 6.1, 95% CI 3.2–11.5, $p < 0.001$) or both (OR 6.9, 95% CI 3.4–13.6, $p < 0.001$) than not sensitized participants. Another predictive outcome of this study showed that the presence of IgE to Der p 1 or Der p 23 at age 5 years or earlier predicted a higher risk of developing asthma at school age (i.e., 6–20 years). This study therefore expands the knowledge about the natural course of IgE responses in mite allergic children/youth. This novel information leads to a more precise and earlier diagnosis of HDM allergy, which consequently should speed up the clinical decision-making for allergen avoidance and immunotherapy. The study also opens new avenues to secondary allergen-specific immunoprophylaxis, defined as "the administration of an allergen preparation to prevent the onset of allergic symptoms in healthy children with IgE antibodies against the corresponding allergenic source" [58], although this field still requires wide-ranging investigations.

Conclusions and Future Perspective

Considering the fact that a broad sensitization profile to HDM is linked to high levels of HDM exposure and an increase in

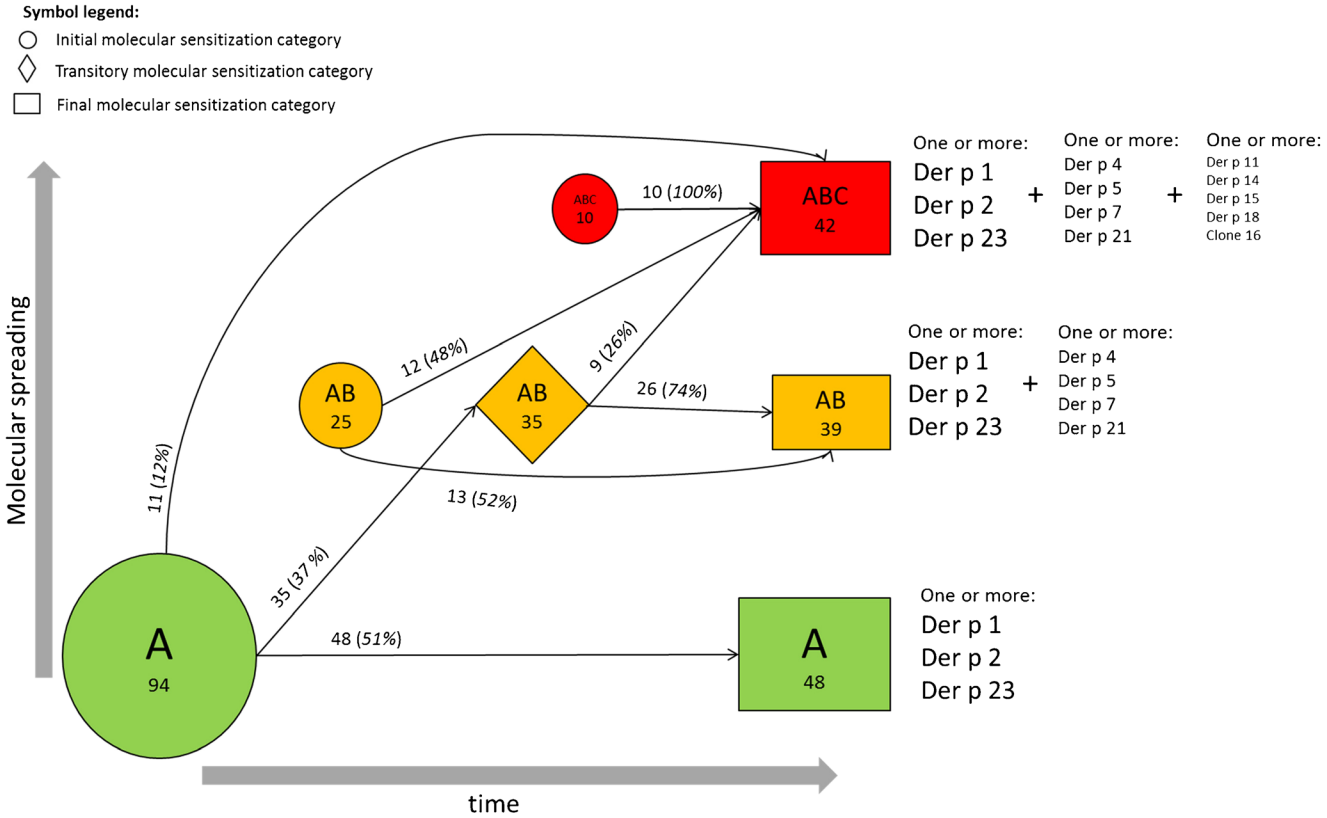

Fig. 1 Trajectories of IgE sensitization in mite-sensitized subjects (n = 129). Evolution of the IgE responses to 12 *D. pteronyssinus* allergen molecules according to the "A," "AB," or "ABC" classification, in participants sensitized at two or more follow-up points. The *round*, *rhombus*, and *rectangular boxes* represent the initial, intermediate, and final sensitization stage, respectively. Numbers (percentages) refer to participants and areas are proportional to their frequency. Figure 1 is reused with kind permission (License Number 4067591172012): Posa et al. [57••]

Number of molecules	Der p 1	Der p 2	Der p 4	Der p 5	Der p 7	Der p 11	Der p 14	Der p 15	Clone 16	Der p 18	Der p 21	Der p 23	n	%
1		•											15	12.6
2	•	•											10	8.4
0													10	8.4
3	•	•										•	7	5.9
1												•	7	5.9
3	•	•		•									5	4.2
3	•	•	•										4	3.4
2		•										•	4	3.4
1	•												4	3.4
7	•	•	•	•	•						•	•	3	2.5
4	•	•	•									•	3	2.5
4	•	•		•							•		3	2.5
2	•											•	3	2.5
10	•	•	•	•	•	•	•		•		•	•	2	1.7
6	•	•	•	•	•							•	2	1.7
6	•	•	•		•						•	•	2	1.7
5	•	•	•		•							•	2	1.7
5	•	•		•							•	•	2	1.7
4	•	•			•							•	2	1.7
11	•	•	•	•	•	•	•	•	•	•		•	1	0.8
10	•	•	•	•	•	•	•			•	•	•	1	0.8
10	•	•	•	•	•	•	•	•		•		•	1	0.8
9	•	•	•	•	•	•				•	•	•	1	0.8
9	•	•	•	•	•	•	•		•			•	1	0.8
9	•	•	•	•	•	•	•	•				•	1	0.8
8	•	•	•	•	•	•					•	•	1	0.8
8	•	•	•	•	•					•	•	•	1	0.8
8	•	•	•	•	•				•		•	•	1	0.8
8	•	•	•	•	•	•				•		•	1	0.8
7	•	•	•	•	•					•		•	1	0.8
6	•	•	•	•		•						•	1	0.8
6	•	•		•	•						•	•	1	0.8
6	•	•		•	•					•		•	1	0.8
6	•	•		•	•				•			•	1	0.8
6	•	•	•	•	•						•		1	0.8
5	•	•							•	•		•	1	0.8
5	•	•		•	•				•				1	0.8
5	•	•		•					•		•		1	0.8
4	•	•		•								•	1	0.8
4	•	•				•						•	1	0.8
4	•	•		•	•								1	0.8
4	•	•			•	•							1	0.8
4		•		•	•							•	1	0.8
4		•		•							•	•	1	0.8
3		•		•								•	1	0.8
3		•			•							•	1	0.8
3		•									•	•	1	0.8
1				•									1	0.8
													119	100

Fig. 2 IgE profiles to 12 *D. pteronyssinus* molecules in 119 subjects with an IgE reaction to *D. pteronyssinus* at 20 years of age tested with microarray and the complete data set. Absolute frequencies are shown. Profiles are ordered by decreasing frequency. Figure 2 is reused with kind permission (License Number 4067671235830): Posa et al. [57••]

disease severity [43•, 57••], it is reasonable to hypothesize that a dramatic decrease of exposure to HDM allergens may prevent and/or improve the clinical condition of asthma and rhinitis related to HDM. Although this approach has been endorsed by a wide range of controlled trials performed in different countries [59, 60, 43•, 61, 62], showing that the avoidance of HDM allergens may not only reduce acute clinical symptoms but also improve the condition of bronchial hyperresponsiveness. Following this prevention line, education and allergen avoidance are pivotal topics, requiring extra care due to the complex biology of dust mites and their invisibility in daily life, which make an accurate avoidance often difficult for patients. Because of this reason and the need for better-targeted recommendations, the concept of avoidance as a prevention measure is still debated [63]. But not only environmental measures play an important role in modifying the allergic disease.

Also AIT, as the only disease-modifying treatment for IgE-mediated allergic diseases [64] with an acceptable side effect profile [65••], may play an important role in its immunological and clinical evolution. A recent systematic review and meta-analysis from the EAACI AIT-Task Force has assessed the current evidence of AIT for the prevention of allergy [65••] and found an AIT-related

reduction in the short-term risk of developing asthma in subjects with allergic rhinitis as well as a diminution of new sensitizations in allergic patients [66–67, 68•]. In regards to the risk of developing a first allergic disease, a recent randomized controlled trial by Zolkipli [68•] proved the disease-modifying potential of allergen immunotherapy when applied early enough in previously healthy subjects [69]. These data are in line with previous postulations in regard to grass pollen allergy [58]: the immune response is more susceptible to be modified in the first, weaker, asymptomatic, mono-/oligomolecular stages, rather than in advanced, stronger and polymolecular, clinical conditions. Therefore, early monitoring of the IgE response at a molecular level may be helpful to start an allergen-specific treatment as soon as possible. Moreover, given the higher simplicity of the preclinical IgE response (mono- or oligomolecular stage), a prophylactic intervention tailored on the child's molecular sensitization profile (often one or more among Der p 1, Der p2, or Der p 23) would be more feasible [16] than at later stages [70].

However, further well-designed, large studies are needed to assess the efficacy of a tailored immunotherapy designed to fit the individual sensitization profile of the patient. This is the case for applying individual therapeutic allergen compositions in order to prevent the first onset of an allergic disease in healthy but already sensitized children ("component-resolved prophylaxis") but also for an early treatment during the first months after the commencement of allergic symptoms ("early component-resolved immunotherapy") [58]. A justified objection to the approach of early serological monitoring as a base for early treatment or even prevention is the fact that invasive methods such as blood-drawing should be avoided especially in children. In order to develop a more careful way of obtaining test material which still delivers reliable diagnostic data, the reliability of mite-specific IgE detection in nasal secretions has been recently tested with promising results [71•]. This may open up new ways for a gentle and early monitoring in order to prevent one of the biggest health challenges worldwide.

Compliance with Ethical Standards

Conflict of Interest Dr. Matricardi reports materials and personal fees from Thermo Fisher Scientific and personal fees from Euroimmun AG and HYCOR Biomedical. Drs. Posa, Hofmaier, and Arasi declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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