HHS Public Access

Author manuscript

J Allergy Clin Immunol. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

J Allergy Clin Immunol. 2016 June ; 137(6): 1662–1670. doi:10.1016/j.jaci.2016.04.010.

IgE in the diagnosis and treatment of allergic disease

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Abstract

Traditionally, the concept of allergy implied an abnormal response to an otherwise benign agent (eg, pollen or food), with an easily identifiable relationship between exposure and disease. However, there are syndromes in which the relationship between exposure to the relevant allergen and the "allergic" disease is not clear. In these cases the presence of specific IgE antibodies can play an important role in identifying the relevant allergen and provide a guide to therapy. Good examples include chronic asthma and exposure to perennial indoor allergens and asthma related to fungal infection. Finally, we are increasingly aware of forms of food allergy in which the relationship between exposure and the disease is delayed by 3 to 6 hours or longer. Three forms of food allergy with distinct clinical features are now well recognized. These are (1) anaphylactic sensitivity to peanut, (2) eosinophilic esophagitis related to cow's milk, and (3) delayed anaphylaxis to red meat. In these syndromes the immunology of the response is dramatically different. Peanut and galactose α-1,3-galactose (alpha-gal) are characterized by high- or very high-titer IgE antibodies for Ara h 2 and alpha-gal, respectively. By contrast, eosinophilic esophagitis is characterized by low levels of IgE specific for milk proteins with high- or very high-titer IgG_4 to the same proteins. The recent finding is that patients with alpha-gal syndrome do not have detectable IgG_4 to the oligosaccharide. Thus the serum results not only identify relevant antigens but also provide a guide to the nature of the immune response.

Keywords

Asthma; allergen particles; IgE antibodies; eosinophilic esophagitis; alpha-gal; IgG_4

The first awareness of immediate hypersensitivity came from the separate investigations of seasonal hay fever over the period 1870–1910 by Blackley, Wymann, Noon, and Von

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Disclosure of potential conflict of interest: T. A. E. Platts-Mills has received a grant from ThermoFisher/Phadia. E. A. Erwin is employed by Nationwide Children's Hospital; has received royalties from UpToDate; and has received travel support from the American College of Allergy, Asthma, and Immunology. S. P. Commins has received personal fees from Genentech and UpToDate and has received a grant from the National Institutes of Health. J. A. Woodfolk has received grants from the National Institutes of Health/National Institute of Allergy and Infectious Diseases and the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases. A. J. Schuyler declares no relevant conflicts of interest.

Pirquet.[1] At that point, no evidence of an immune response to pollen could be detected in serum from these patients.[2] However, in 1921, Prausnitz and Kustner showed that serum of allergic subjects could transfer sensitivity locally in the skin.[3] This Prausnitz-Kustner test was used widely between 1921 and 1960 and played a major role in the discovery of IgE. Once IgE was established, it was possible to investigate many different aspects of allergic disease both in terms of diagnosis and in understanding the relevant treatment. Thus the discovery of IgE completely changed the investigation of these diseases because measurements were of a specific molecule measured in fully defined units (first in international units and then by absolute quantitation; ie, 2.4 ng/unit). The initial purification of Prausnitz-Kustner activity was primarily related to ragweed pollen.[4] Interestingly, Ishizaka et al[4] did not consider that the establishment of a new isotype of immunoglobulin, IgE, changed the argument about the causal role of pollen in hay fever. By contrast, measurement of IgE has now played a major role in the diagnosis of many allergic diseases other than hay fever. However, it has to be admitted that it is difficult to replicate the simple elegance of the evidence about the role of airborne pollen grains in hay fever.

Early in the 20th century, Coca[5] became Editor of the *Journal of Immunology* and proposed the concept of atopy or the hereditary tendency to become allergic to allergens in the environment. He included asthma, food allergy, and eczema, as well as hay fever, among the atopic diseases. Furthermore, he clearly implied that the sensitizing allergens had a causal role in these diseases. For the main forms of food allergy recognized at that time (eg, fish, nuts, egg, or milk), the rapid development of symptoms, including hives or angioedema, after exposure left little doubt about causality. By contrast, for chronic asthma in patients sensitized to 1 or more of the perennial allergens, the evidence of a relationship between allergens and disease is more difficult to establish. This is particularly true for allergens, such as dust mite or cockroach, where the allergens only become airborne during disturbance.[6,7] We would like to focus on the evidence for causality and the role of IgE in relation to 3 conditions:

1. chronic asthma in patients who are sensitized to 1 or more perennial allergens;
2. allergic symptoms in patients who are colonized with fungi in their lungs, sinuses, or nails; and
3. the different forms of food allergy, including those newly recognized syndromes in which the relationship between exposure and response is not “immediate.”

CHRONIC ASTHMA IN PATIENTS WITH SENSITIZATION TO 1 OR MORE PERENNIAL ALLERGENS

The opinion about the relevance of perennial allergen exposure to chronic asthma has differed from enthusiastic acceptance to denial or, worst of all, complete indifference.[8,9] In part, this reflects the failure of some important avoidance studies and the relentless pressure for treatment with pharmaceutical products. A more important cause is that the relationship between exposure and symptoms is not simple. Indeed, for mite, cockroach, “domestic” mice, and *Alternaria* species, patients often have very little sense that they are allergic and do not understand the role these allergens play in their asthma.[10] For cat and dog, it is not

unusual for the allergic patients to report that they have acute symptoms on entering a house with a relevant animal. However, in many communities the majority of patients with cat allergy do not live in a house with a cat, and nonetheless, sensitization is strongly associated with asthma.[11,12] In some studies there is clear evidence that children raised in a house with a cat are less likely to be sensitized.[12] However, for cat, the levels of this allergen in schools and homes without a cat increases with the prevalence of domestic cats in the community.[13] Statements of this kind are possible because the source of these allergens can be identified (ie, 4-legged animals) and because of the availability of sensitive assays for relevant allergens in dust or airborne allergens.[14] For cockroaches and mice, visual identification is possible but less reliable than measurement of specific allergens. For dust mites, there is no way of evaluating their presence or concentration in a house without microscopy or the use of an immunoassay.[6,15]

There are several major variables that have been used to understand the relationship of allergen exposure to IgE antibodies and asthma:

1. Many studies have been carried out in areas where dust mites flourish in all homes (eg, the United Kingdom, New Zealand, Australia, Costa Rica, and the Southeast or Northwest of the United States).[16–19]
2. Studies have been conducted in areas where, because of cold temperatures and low humidity, dust mites, cockroaches, and *Alternaria* species are either absent or at very low levels in homes.[12,20,21]
3. There are groups within the United States with dramatically different attitudes to animals, such that a large section of the population have much lower exposure and sensitization.[19,22]
4. Pollens and fungal spores, such as *Alternaria* species, have major seasonal and geographic differences in their outdoor particle counts. Since the 1950s, overall exposure to pollen allergens, particularly ragweed, has decreased considerably because of widespread use of home air conditioning, which started during the 1960s.

DIAGNOSTIC RELEVANCE OF IgE ANTIBODIES TO ASTHMA

In almost all clinical studies, IgE antibodies or skin tests are carried out with extracts derived from the relevant allergens, and these include multiple proteins. The relevance of the results can be assessed based on the prevalence of positive test results, the titer of IgE antibody, or the size of wheals or, alternatively, by tests using specific proteins.[13,23] Tests for sensitization to proteins can use purified or recombinant allergens, but these tests are carried out almost exclusively with *in vitro* assays.

There are many situations in which the significance of sensitization to certain specific proteins is different from that for the whole extract. A simple example is the tropomyosin Der p 10, which cross-reacts with both cockroach and shrimp and might not be a relevant inhalant allergen.[23] A more complex situation has developed with cat extracts. The major inhalant allergen was purified by Ohman et al[24] in 1974 as Cat 1, which subsequently

became Fel d 1. More recently, Fel d 4 has been recognized as a second major inhalant allergen.[25] However, cat extracts can produce positive skin test or IgE assay results because of IgE to 2 allergens that are not relevant to inhalant allergy. The first of these is Fel d 2 (or cat albumin), which cross-reacts with pork albumin, giving rise to the pork-cat syndrome.[26,27] The second is galactose α-1,3-galactose (alpha-gal), which has emerged as a major allergen related to red meat and is the main epitope on cat IgA.[28–30] A major cause of confusion comes from the difference between pelt extracts, which contain cat albumin and many proteins carrying alpha-gal, and dander extracts, which may only contain significant quantities of Fel d 1.

UNDERSTANDING THE ROLE OF ALLERGENS IN ASTHMATIC PATIENTS AND THE RELEVANCE OF IgE ANTIBODIES

We would like to focus on 3 observations about chronic allergic asthma: (1) the strongest association is with sensitization to common perennial inhalant allergens, which is true in particular for high-titer IgE antibodies to allergens that are prevalent in the patient's community; (2) the relevant allergens, such as dust mite, cat, dog, or cockroach, have been shown to become airborne on particles of 5 to 35 μm in diameter (Fig 1 and Table I); and (3) many or most acute episodes of wheezing cannot be related to increased or even high-level exposure to allergens. The implication of this last observation is that exacerbations are most likely occurring as a result of viral or other triggers in the context of underlying inflammation of the lungs and the associated bronchial hyperreactivity.[18,31,32]

In a simplistic view the fact that bronchial provocation of an allergic patient with nebulized allergen extract can induce both a decrease in FEV_1 and eosinophil-rich inflammation of the lungs could be taken as evidence that allergen exposure is causally related to asthma. However, the contrast between natural exposure of the lungs to particles, such as mite feces, and a bronchial challenge with nebulized allergen could hardly be more extreme (Fig 2).[33,34] Exposure to dust mite allergen is thought to consist of 5 to 100 fecal particles entering the lungs per day. Nebulized allergen is estimated to be 10 million droplets inhaled over 2 to 5 minutes, where each droplet is approximately 2 μm in diameter. Mite feces have been estimated to contain 0.2 ng of Der p 1, whereas the comparable figure for nebulized droplets is less than 10^{-7} ng (Table I).

We assume that deposition of a particle on the bronchial wall represents sufficient local allergen not only to activate mast cells but also to recruit eosinophils, basophils, and lymphocytes. What is not clear is how long such an inflammatory focus would last. Our view is that some consequences of local inflammation could persist for months or longer. These include persistence of changes in the vasculature that encourage local arrival of cells and persistence of allergen-specific T cells. It seems likely that allergen-specific T cells, as well as mast cells, could contribute to the long-term persistence of bronchial hyperreactivity. Taken together, the results could explain how IgE antibodies are relevant to the process and that locally accumulating T cells could be a target for peptide immunotherapy.[35]

SENSITIZATION TO FUNGI COLONIZING THE SKIN, NAILS, OR LUNGS AS A RISK FACTOR FOR ALLERGIC DISEASE

There are literally hundreds of pollinating plants or fungi that produce spores, which can act as a source of inhalant allergens. By contrast, there are only a limited number of fungi that induce the production of specific IgE by growing on patients. Fungi can be found growing on the skin, on mucosal surfaces, in the sinuses, or in the lungs. In many cases these fungi have specific properties that facilitate their growth. Thus dermatophytes have a specific ability to grow on keratinized surfaces (ie, skin and nails). By contrast, *Aspergillus* species are able to grow both at the temperature of the soil and also at 37°C in the lungs or sinuses. Although the significance of fungal sensitization was recognized in the 1930s, acceptance of their clinical importance fluctuated until allergic bronchopulmonary aspergillosis (ABPA) was established by Hinson; Pepys; and Patterson.[36,37] With the discovery of IgE, it became possible to define the diseases better and to show that many of these patients had IgE antibodies specific for fungal allergens. Although the primary focus of studies on fungal sensitization related to the lungs, it was recognized years ago that sensitization to both dermatophytes and *Candida* species can also be a cause of urticaria and angioedema.[38] Diagnostic criteria have been suggested for some fungal diseases; however, even with ABPA, a large proportion of patients who are growing either *Aspergillus* species or other fungi in their lungs do not fulfill the criteria for ABPA or allergic bronchopulmonary mycosis. These patients can be described as having *forme fruste* allergic broncho-pulmonary mycosis.

There is an important distinction between patients in whom the fungus is growing at the site of the inflammatory reaction, such as *Aspergillus* species or other fungi growing in the lungs or sinuses, and patients in whom fungi growing on the feet appear to be the cause of an inflammatory response elsewhere in the body.[39–41] The latter form can be described as an "ID" reaction (ie, comparable with those skin lesions associated with pulmonary tuberculosis but did not contain organisms that could infect a guinea pig). Historically, *Candida* and *Trichophyton* species were well recognized by dermatologists as causes of ID reactions in the hands or skin.[38,42] In Box 1 we present 3 cases that illustrate these differences.

Box 1

Three cases with severe allergic disease, documented fungal infection, sensitization, and response to antifungal treatment

- Case I: 43-year-old woman; repeated severe attacks of asthma; *Candida* species colonization of sinuses and lungs and full response to fluconazole; IgE to *Candida albicans* was 13.3 IU/mL.
- Case II: 62-year-old man; judge with almost continuous facial angioedema, taking 50 mg of prednisone per day; severe fungal infection of feet for "many years"; skin test *Trichophyton* ++ IgE antibody of 5.0 IU/mL; *Trichophyton* species grown from nail scrapings; no response to 3 months of fluconazole; full response to itraconazole over 1 year.

- Case III: 56-year-old man; diving instructor; increasingly severe late-onset asthma; continuous obstruction with FEV_1 of 45% of predicted value despite 40 mg of prednisone per day; culture of bronchoalveolar lavage fluid grew *Aspergillus* and *Nocardia* species; successful treatment with voriconazole and Augmentin for 1 year

Over the last 30 years, the field of fungal sensitivity has changed progressively because of the availability and widespread use of new oral antifungal drugs. In the early 1980s, the only oral drugs that were available were griseofulvin and ketoconazole; both of these drugs had severe side effects. The first new drug to arrive was fluconazole, and then came itraconazole, terbinafine, and voriconazole.[43–45] This means that there are not only better drugs that can be used to treat fungal infections associated with allergic disease but also there might be fewer cases of severe ony-chomycosis because of successful treatment in primary care. On the other hand, the use of antibiotics and steroids encourages growth of fungi, particularly yeasts. It is well recognized that many women need to take 2 or 3 doses of fluconazole when they are treated with antibiotics. It is a different question whether high-dose inhaled steroids can enhance yeast growth in the lungs. Our view is that all patients with severe asthma who produce sputum should be monitored for growth of aspergillus, yeasts, or other fungi in the lungs (see case I in Box 1).[46]

With all these fungal diseases, it is an open question whether it is necessary to obtain cultures before treatment. There is good evidence that patients with ABPA who are colonized with an *Aspergillus* species sensitive to itraconazole respond better to treatment with that drug.[44] The *in vitro* tests of sensitivity of cultured fungi to antifungals are improving and have become more readily available. We would argue that identifying the species improves the understanding of the condition and can contribute to the success of treatment. On the other hand, Denning et al[45] demonstrated that itraconazole could improve the outcome for patients with asthma who have skin sensitization to fungi without establishing the presence of a colonizing organism.[46]

ROLE OF IgE ASSAYS IN THE DIAGNOSIS OF DIFFERENT FORMS OF FOOD ALLERGY: PEANUT ANAPHYLAXIS, EOSINOPHILIC ESOPHAGITIS (EoE), AND DELAYED ANAPHYLAXIS TO RED MEAT (THE ALPHA-GAL SYNDROME)

Over the last 20 years, both the scientific investigation of allergic disease and the practice of allergy have moved progressively toward food allergy. In our practice in central Virginia, this has included major increases in 3 different forms of allergic reactions to food. The thing that is truly interesting about this is that these 3 forms of “allergy” appear to be distinct both in their clinical presentation and in their underlying immune response (Table II).[28,29,47,48] Peanut allergy is taken as the model for immediate and often anaphylactic reactions to food in children. This condition has been well recognized for many years but has increased rapidly during the period 1990–2010.[49] Initially, it was possible to argue that there was

increased awareness of the disease, but the prevalence of high-titer IgE antibody in random cohorts of children has increased.[50]

The second form of food allergy is EoE, which was hardly recognized at all before 1990 and has become progressively more common over the last 20 years so that today most academic centers in the United States have an EoE clinic. The disease is characterized by chronic inflammation of the esophagus, which gets better with a diet including avoidance of cow's milk.[51–53] Although many of the children have detectable IgE antibodies to cow's milk, wheat, egg, or soy proteins, the titers are consistently low (Fig 3).[47] Recent studies have shown that almost all children with EoE have high- or very high-titer IgG_4 antibodies to cow's milk proteins.[54,55] Clinically, patients with EoE continue eating cow's milk proteins because they are not aware of being allergic. Thus EoE does not have the features of an IgE-mediated disease and also does not improve during treatment with omalizumab. If EoE is a T cell–mediated disease, we should be able to focus on T cells that can recruit eosinophils, give rise to low levels of IgE, and strongly enhance IgG_4. In addition, these findings have major implications for the correct treatment.

The third group of patients present with anaphylaxis or urticaria to red meat, which is most common in adults.[29,56,57] Indeed, the typical case is a man older than 50 years with episodes of hives, angioedema, or anaphylaxis that start several hours after a meal including red meat. On skin testing, they have negative or weakly positive skin prick test responses to a commercial beef extract but strongly positive IgE assay results for the oligosaccha-ride alpha-gal.[28,29,57,58] Similar syndromes have now been described in many countries, including Australia, Sweden, France, Germany, and Japan.[57,59–61] In each of these countries, the reported reactions to meat have been delayed for several hours after eating, IgE antibody is directed at the same oligosaccharide, and there is reasonable or good evidence that tick bites are the primary cause of the sensitization.[59,61,62] In our practice the presence of alpha-gal–specific IgE that represents more than 1% of total IgE, a convincing report of bites from ticks (or chiggers), and a history of urticaria or anaphylaxis starting 2 to 6 hours after consuming red meat provide a high level of diagnostic certainty.

Evidence about these 3 forms of food allergy has provided a stronger basis for evaluating reactions to food in general, and several other syndromes have become much clearer. A simple example is the pork-cat syndrome, which was first recognized in Europe.[26,27] In evaluating cases of reactions attributed to red meat, we found patients with negative results to alpha-gal but positive results to pork, and weak results to beef. In these cases the pork response was explained by IgE specific for pork albumin. Absorption studies provided evidence that cat albumin was responsible for the initial sensitization and that food reactions were due to cross-reactivity.[27] Patients with IgE to alpha-gal can have delayed reactions to foods containing gelatin, such as marshmallows or jelly babies.[63] This occurs because gelatin made from mammals can carry alpha-gal; however, in addition, there are patients who are allergic to the protein epitopes on gelatin. The gelatins cross-react extensively, and this has given rise to anaphylactic reactions to vaccines containing gelatin.[64] Most recently, we have seen a case reporting delayed reactions to mammalian products, including cow's milk and beef, who was negative to alpha-gal. In this case the dominant assay result was to milk, and the specific protein was BSA.[65] What matters here is that testing IgE to specific

proteins and/or to the oligosaccharide alpha-gal makes it possible to identify the relevant allergens in many cases.

RELEVANCE OF THE ROUTE OF SENSITIZATION TO THE SPECIFICITY AND TITER OF IgE ANTIBODY RESPONSES

For many years, there have been questions about whether sensitization to allergens could occur through routes other than the inhaled or oral routes. The obvious example was atopic dermatitis, in which the skin is already damaged and IgE antibodies to inhalant allergens can reach high levels.[66,67] Furthermore, patients with severe atopic dermatitis often have IgE specific for foods, bacterial antigens, and also fungi, particularly yeasts, such as *Pityrosporum ovale*.[68,69] During the last 15 years, the evidence for sensitization through the skin has become much clearer. In relation to peanut allergy, it is well established that sensitization correlates with eczema and that use of topical treatments that incorporate peanut proteins increases the risk of sensitization. The success of early introduction of oral peanut in decreasing sensitization has added further evidence.[48,70] Perhaps equally striking is the outbreak of wheat sensitization among women in Japan who use a mildly abrasive face preparation that contains wheat proteins.[71–73]

Given that the oral route can be tolerogenic and that there are obvious advantages to not becoming allergic to food, the question arises whether the skin route can break tolerance induced through the oral route. This question became more complicated with the discovery that sensitization to alpha-gal was common in large areas of the United States.[28,56] It is now clear that tick bites are the dominant cause of this novel form of allergy in the United States and that this syndrome provides another example of high-titer IgE production in which the skin is the route of sensitization.[59,62]

Because we all make IgM and IgG_2 specific to alpha-gal as part of an innate response to gut bacteria, it could be argued that the IgE response to alpha-gal must have broken tolerance. However, we have remarkably little understanding of either the immunology of IgE responses to oligosaccharides or the relevance of T cells in the response to tick bites. Initial studies in collaboration with Dr Rispens in Amsterdam suggested that the response to alpha-gal does not include IgG_4.[74] Recently, we have extended those observations to confirm that neither the natural responses to this oligosaccharide nor the IgE-dominated response include IgG_4.[55] There is excellent evidence that oral desensitization of children with immediate hypersensitivity to milk or peanut can increase or induce IgG_4 antibodies.[48,70,75,76] Our current view is that the skin is an excellent route for inducing IgE to, for example, schistosomes, ticks, and peanut but in general is a poor route for inducing or boosting IgG_4 antibodies. The exception might be multiple bee stings. The early data on IgG_4 argued that this response required prolonged exposure. We would add that the oral route might be the best route for boosting high levels of IgG_4 in an already sensitized subject and that the esophagus might be an important route for this response (Fig 4).

CONCLUSIONS

The 3 areas on which we have focused here were chosen because they illustrate the difficulty of understanding the role of allergens in diseases in which the relationship between exposure and the disease is not obvious to the patient. In these studies the ability to measure IgE levels to allergen extracts, purified proteins, and novel allergens has been central to understanding the nature of the condition. Our first experience with this process came from investigating the epidemic of asthma in children in the United Kingdom at a time when it was already clear that many of these children were allergic to dust mites. The proof that Der p 1 was a major target for IgE was an essential part of the definition of this protein as a major mite allergen.[77] In turn, this was essential to proposing assays of Der p 1 in dust as a surrogate for microscopic counting of dust mites.[6,15]

Although sensitization to yeasts and dermatophytes was well known before the discovery of IgE, the level of scientific or clinical acceptance was “meager.” Purification of *Aspergillus* species allergens allowed measurements of IgG and IgE antibodies. Sensitization to *Trichophyton* species provides another example of the overall problem because very few of the patients have considered the possible relevance of the fungal infection on their feet to their disease. Purification of the relevant proteins was an important part of understanding the immune response that starts in the skin.[41] Clinically, the availability of the newer anti-fungals has completely changed the equation. We would stress that these cases continue to appear and that without considering fungal sensitization and using oral antifungal treatment, they will continue to be treated with high doses of steroids.

The 2 new syndromes of food allergy illustrate well the problems with diagnosis and treatment of allergic diseases in which allergen exposure does not give rise to immediate symptoms.

With EoE, the clearest guide to the relevance of foods comes from the response to diet and particularly from the exacerbations that can occur after reintroduction of specific foods. However, the esophageal symptoms do not reappear for 24 hours or more. Skin tests are generally not convincing in defining the important sensitivity. By using serum IgE assays, the presence of IgE to cow’s milk proteins is clear.[53] Nonetheless, it seems unlikely that IgE antibodies play a direct role in the disease. The most recent findings about IgG_4 antibodies to milk proteins add further evidence about the relevance of these proteins.

During the first years of the 21st century, many of the patients with alpha-gal syndrome presented to allergists and were consistently advised that their symptoms were not due to food allergy. This was because:

- **A.** the onset of allergic reactions to meat in adult life was considered rare;
- **B.** skin prick tests to meat showed 2- to 3-mm wheals at best (intradermal skin test results were positive); and
- **C.** the patients reported long delays after eating red meat before the symptoms started.

Without a specific assay for IgE antibodies to alpha-gal, it would have been very difficult to connect the dots.[78] Equally, establishing that the IgE binding to meat extracts was IgE specific for an oligosaccharide provided a further enigma until it became clear that sensitization was occurring through the skin.

Today it is clear that the skin is an important route for IgE responses, that a large proportion of allergic disease involves conditions in which the relationship of exposure to disease is not obvious, and that the ability to measure IgE and IgG_4 antibody levels to specific proteins can provide an important part of the diagnosis and management (Table III).

Acknowledgments

Supported by the National Institute of Allergy and Infectious Diseases (AI-20565 to T.A.E.P.-M. and AI-113095 to S.P.C.).

Abbreviations used

ABPA	Allergic bronchopulmonary aspergillosis
Alpha-gal	Galactose α-1,3-galactose
EoE	Eosinophilic esophagitis

References

1. Platts-Mills T. The allergy epidemics: 1870–2010. J Allergy Clin Immunol. 2015; 136:3–13. [PubMed: 26145982]
2. Von Pirquet, C. Translated version. In: Gell, PGH.Coombs, RRA., Lachmann, PJ., editors. Clinical aspects of immunology. Oxford: Blackwell Scientific Publications; 1906.
3. Prausnitz C, Kustner H. Studien uber die ueberempfinclichkeit. Zentralbl Bakteriol. 1921; 86:160.
4. Ishizaka K, Ishizaka T, Hornbrook M. Physicochemical properties of reaginic antibody. V. Correlation of reaginic activity with gamma-E-globulin antibody. J Immunol. 1966; 97:840–53. [PubMed: 4163008]
5. Coca A. Specific sensitiveness as a cause of symptoms in disease. Bull N Y Acad Med. 1930; 6:593–604. [PubMed: 19311744]
6. Tovey ER, Chapman MD, Wells CW, Platts-Mills TA. The distribution of dust mite allergen in the houses of patients with asthma. Am Rev Respir Dis. 1981; 124:630–5. [PubMed: 7305119]
7. de Blay F, Sanchez J, Hedelin G, Perez-Infante A, Verot A, Chapman MD, et al. Dust and airborne exposure to allergens derived from cockroah *(Blattella germanica)* in low-cost public housing in Strasbourg (France). J Allergy Clin Immunol. 1997; 99:107–12. [PubMed: 9003218]
8. Murray CS, Poletti G, Kebadze T, Morris J, Woodcock A, Johnston SL, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. Thorax. 2006; 61:376–82. [PubMed: 16384881]
9. von Hertzen LH, Haatela T. House dust mites in atopic diseases: accused for 45 years but not guilty? Am J Respir Crit Care Med. 2009; 180:113–9. [PubMed: 19395505]
10. Platts-Mills T, Erwin E, Heymann P, Woodfolk J. The evidence for a causal role of dust mites in asthma. Am J Respir Crit Care Med. 2009; 180:109–13. [PubMed: 19395504]
11. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. Lancet. 2001; 357:752–6. [PubMed: 11253969]

12. Perzanowski MS, Ronmark E, Platts-Mills TA, Lundback B. Effect of cat and dog ownership on sensitization and development of asthma among preteenage children. Am J Respir Crit Care Med. 2002; 166:696–702. [PubMed: 12204868]
13. Konradsen JR, Fujisawa T, van Hage M, Hedlin G, Hilger C, Kleine-Tebbe J, et al. Allergy to furry animals: new insights, diagnostic approaches, and challenges. J Allergy Clin Immunol. 2015; 135:616–25. [PubMed: 25282018]
14. Leaderer BP, Belanger K, Triche E, Holford T, Gold DR, Kim Y, et al. Dust mite, cockroach, cat, and dog allergen concentrations in homes of asthmatic children in the northeastern United States: impact of socioeconomic factors and population density. Environ Health Perspect. 2002; 110:419–25. [PubMed: 11940461]
15. Luczynska CM, Arruda LK, Platts-Mills TA, Miller JD, Lopez M, Chapman MD. A two-site monoclonal antibody ELISA for the quantification of the major *Dermatophagoide*s spp. allergens, Der p I and Der f I. J Immunol Methods. 1989; 118:227–35. [PubMed: 2926155]
16. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. N Engl J Med. 1990; 323:502–7. [PubMed: 2377175]
17. Erwin EA, Wickens K, Custis NJ, Siebers R, Woodfolk J, Barry D, et al. Cat and dust mite sensitivity and tolerance in relation to wheezing among children raised with high exposure to both allergens. J Allergy Clin Immunol. 2005; 115:74–9. [PubMed: 15637550]
18. Soto-Quiros M, Avila L, Platts-Mills T, Hunt J, Erdman D, Carper H, et al. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. J Allergy Clin Immunol. 2012; 129:1499–505. [PubMed: 22560151]
19. Gruchalla R, Pongracic J, Plaut M, Evans R, Visness C, Walter M, et al. Inner City Asthma Study: relationships among sensitivity, allergen exposure, and asthma morbidity. J Allergy Clin Immunol. 2005; 115:478–85. [PubMed: 15753892]
20. Ronmark E, Bjerg A, Perzanowski M, Platts-Mills T, Lundback B. Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. J Allergy Clin Immunol. 2009; 124:357–63. e1–15. [PubMed: 19577282]
21. Erwin EA, Ronmark E, Wickens K, Perzanowski MS, Barry D, Lundback B. Contribution of dust mite and cat specific IgE to total IgE: relevance to asthma prevalence. J Allergy Clin Immunol. 2007; 119:359–65. [PubMed: 17291853]
22. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011; 364:1005–15. [PubMed: 21410369]
23. Bronnert M, Mancini J, Birnbaum J, Agabriel C, Labeuf V, Porri F, et al. Component-resolved diagnosis with commercially available *D. pteronyssinus* Der p 1, Der p 2 and Der p 10: relevant markers for house dust mite allergy. Clin Exp Allergy. 2012; 42:1406–15. [PubMed: 22747483]
24. Ohman JL, Lowell FC, Bloch KJ. Allergens of mammalian origin: characterization of allergen extracted from cat pelts. J Allergy Clin Immunol. 1973; 52:231–41. [PubMed: 4742068]
25. Hales B, Chai L, Hazell L, Elliot C, Stone S, O'Neil S, et al. IgE and IgG binding patterns and T-cell recognition of Fel d 1 and non-Fel d 1 cat allergens. J Allergy Clin Immunol Pract. 2013; 1:656–65. [PubMed: 24565714]
26. Hilger C, Kohnen M, Grigioni F, Lehners C, Hentges F. Allergic cross-reactions between cat and pig serum albumin. Study at the protein and DNA levels. Allergy. 1997; 52:179–87. [PubMed: 9105522]
27. Posthumus J, James HR, Lane CJ, Matos LA, Platts-Mills TA, Commins SP. Initial description of pork-cat syndrome in the United States. J Allergy Clin Immunol. 2013; 131:923–5. [PubMed: 23352634]
28. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med. 2008; 358:1109–17. [PubMed: 18337601]
29. Commins SP, Satinover SM, Hosen J, Mozena J, Borish L, Lewis BD, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol. 2009; 123:426–33. [PubMed: 19070355]

30. Gronlund H, Adedoyin J, Commins SP, Platts-Mills TA, van Hage M. The carbohydrate galactose-alpha-1,3-galactose is a major IgE-binding epitope on cat IgA. J Allergy Clin Immunol. 2009; 123:1189–91. [PubMed: 19362358]
31. Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. Pediatr Infect Dis J. 2005; 24:S217–22. [PubMed: 16378049]
32. Zambrano JC, Carper HT, Rakes GP, Patrie J, Murphy DD, Platts-Mills TA, et al. Experimental rhinovirus challenges in adults with mild asthma: response to infection in relation to IgE. J Allergy Clin Immunol. 2003; 111:1008–16. [PubMed: 12743565]
33. Platts-Mills TA, Woodfolk JA. Allergens and their role in the allergic immune response. Immunol Rev. 2011; 242:51–68. [PubMed: 21682738]
34. Bates DV, Fish BR, Hatcxh TF, Mercer TT, Morrow PE. Deposition and retention models for internal dosimetry of the human respiratory tract. Task group on lung dynamics. Health Phys. 1966; 12:173–207. [PubMed: 5916786]
35. Larche M. Mechanisms of peptide immunotherapy in allergic airways disease. Ann Am Thorac Soc. 2014; 11(suppl 5):S292–6. [PubMed: 25525735]
36. Hinson K, Moon A, Plummer N. Broncho-pulmonary aspergillosis; a review and a report of eight new cases. Thorax. 1952; 7:317–33. [PubMed: 13015523]
37. Forman S, Fink J, Moore V, Wang J, Patterson R. Humoral and cellular immune responses in Aspergillus fumigatus pulmonary disease. J Allergy Clin Immunol. 1978; 62:131–6. [PubMed: 355293]
38. Champion RH, Roberts SO, Carpenter RG, Roger JH. Urticaria and angiooedema. A review of 554 patients. Br J Dermatol. 1969; 81:588–97. [PubMed: 5801331]
39. Ward GW Jr, Karlsson G, Rose G, Platts-Mills TA. *Trichophyton* asthma: sensitisation of bronchi and upper airways to dermatophyte antigen. Lancet. 1989; 1:859–62. [PubMed: 2564948]
40. Wise F, Sulzberger MB. Urticaria and hay fever due to *Trichophyton* (Epidermophyton interdigital). JAMA. 1930; 95:1504–8.
41. Woodfolk JA, Wheatley LM, Piyasena RV, Benjamin DC, Platts-Mills TA. *Trichophyton* antigens associated with IgE antibodies and delayed type hypersensitivity. Sequence homology to two families of serine proteinases. J Biol Chem. 1998; 273:29489–96. [PubMed: 9792655]
42. Weary P, Guerrant J. Chronic urticaria in association with dermatophytosis. Response to the administration of griseofulvin. Arch Dermatol. 1967; 95:400–1. [PubMed: 6024725]
43. Ward GW Jr, Woodfolk JA, Hayden ML, Jackson S, Platts-Mills TA. Treatment of late-onset asthma with fluconazole. J Allergy Clin Immunol. 1999; 104:541–6. [PubMed: 10482825]
44. Stevens DA, Schwartz HJ, Lee JY, Moskovitz BL, Jerome DC, Catanzaro A, et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med. 2000; 342:756–62. [PubMed: 10717010]
45. Denning DW, O'Driscoll BR, Powell G, Chew F, Atherton GT, Vyas A, et al. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: the Fungal Asthma Sensitization Trial (FAST) study. Am J Respir Crit Care Med. 2009; 179:11–8. [PubMed: 18948425]
46. Kennedy JL, Heymann PW, Platts-Mills TA. The role of allergy in severe asthma. Clin Exp Allergy. 2012; 42:659–69. [PubMed: 22515388]
47. Erwin E, Tripathi A, Ogbogu P, Commins S, Slack M, Cho C, et al. IgE antibody detection and component analysis in patients with eosinophilic esophagitis. J Allergy Clin Immunol Pract. 2015; 3:896–904. e3. [PubMed: 26099818]
48. Du Toit G, Roberts G, Sayre P, Bahnson H, Radulovic S, Santos A. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015; 372:803–13. [PubMed: 25705822]
49. Flinterman A, Knol E, Lencer D, Bardina L, den Hartog Jager C, Lin J, et al. Peanut epitopes for IgE and IgG4 in peanut-sensitized children in relation to severity of peanut allergy. J Allergy Clin Immunol. 2008; 121:737–43. [PubMed: 18234310]

50. Bunyavanich S, Rifas-Shiman SL, Platts-Mills T, Workman L, Sordillo JE, Gillman M, et al. Peanut allergy prevalence among school-age children in a US cohort not selected for any disease. J Allergy Clin Immunol. 2014; 134:753–5. [PubMed: 25086866]
51. Simon D, Cianferoni A, Spergel J, Aceves S, Holbreich M, Venter C, et al. Eosinophilic esophagitiis is characterized by a non-IgE-mediated food hypersensitivity. Allergy. 2016; 71:611–20. [PubMed: 26799684]
52. Kelly K, Lazenby A, Rowe P, Yardley J, Perman J, Sampson H. Eosinopohilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995; 109:1503–12. [PubMed: 7557132]
53. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol. 2012; 130:461–7. e5. [PubMed: 22743304]
54. Clayton F, Fang J, Gleich G, Lucendo A, Olalla J, Vinson L, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology. 2014; 147:602–9. [PubMed: 24907494]
55. Schuyler A, Tripathi A, Kruszewsi P, Russo J, Workman L, Platts-Mills T, et al. Serum IgG4 antibodies in Pediatric subjets with eosinophilic esophagitis treated with cow's milk elimination diet or swallowed fluticasone: high levels of specific IgG4 to cow's milk compoents despite low to negative IgE antibodies [abstract]. J Allergy Clin Immunol. 2016; 137:AB232.
56. Commins SP, Kelly LA, Ronmark E, James HR, Pochan SL, Peters EJ, et al. Galactose-alpha-1,3-galactose-specific IgE is associated with anaphylaxis but not asthma. Am J Respir Crit Care Med. 2012; 185:723–30. [PubMed: 22281828]
57. Hamsten C, Tran T, Starkhammar M, Brauner A, Commins SP, Platts-Mills TA, et al. Red meat allergy in Sweden: association with tick sensitization and B-negative blood groups. J Allergy Clin Immunol. 2013; 132:1431–4. [PubMed: 24094548]
58. Jappe U. Update on meat allergy. alpha-Gal: a new epitope, a new entity? Hautarzt. 2012; 63:299–306. [PubMed: 22418768]
59. Van Nunen SA, O'Connor KS, Clarke LR, Boyle RX, Fernando SL. An association between tick bite reactions and red meat allergy in humans. Med J Aust. 2009; 190:510–1. [PubMed: 19413526]
60. Mullins RJ, James H, Platts-Mills TA, Commins S. Relationship between red meat allergy and sensitization to gelatin and galactose-alpha-1,3-galactose. J Allergy Clin Immunol. 2012; 129:1334–42. e1. [PubMed: 22480538]
61. Chinuki Y, Ishiwata K, Yamaji K, Takahashi H, Morita E. *Haemaphysalis longicornis* tick bites are a possible cause of red meat allergy in Japan. Allergy. 2016; 71:421–5. [PubMed: 26551325]
62. Commins S, James H, Kelly E, Pochan S, Workman L, Perzanowski M, et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-α-1,3-galactose. J Allergy Clin Immunol. 2011; 127:1286–93. [PubMed: 21453959]
63. Hilger C, Fischer J, Swiontek K, Hentges F, Lehners C, Eberlein B, et al. Two galactose-alpha-1, 3-galactose carrying peptidases from pork kidney mediate anaphylactogenic responses in delayed meat allergy. Allergy. 2016; 71:711–9. [PubMed: 26728983]
64. Agarwal N, Spalding C, Nassef M. Life-threatening intraoperative anaphylaxis to gelatin in Floseal during pediatric spinal surgery. J Allergy Clin Immunol Pract. 2015; 3:110–1. [PubMed: 25577629]
65. Hoyt AEW, Schuyler A, Workman L, Platts-Mill TAE. Delayed-anaphylaxis to bovine serum albumin, mistaken for alpha-gal allergy and presenting clinically as chronic idiopathic urticaria. J Allergy Clin Immunol. 2016 in press.
66. Glatz M, Buchner M, von Bartenwerffer W, Schmid-Grendelmeier P, Worm M, Hedderich J, et al. *Malassezia* spp. -specific immunoglobulin E level is a marker for severity of atopoic dermatitis in adults. Acta Derm Venereol. 2015; 95:191–6. [PubMed: 24696225]
67. Sampson H. The evaluation and management of food allergy in atopic dermatitis. Clin Dermatol. 2003; 21:183–92. [PubMed: 12781436]
68. White T, Findley K, Dawson TJ, Scheynius A, Boekhout T, Cuomo C, et al. Fungi on the skin: dermatophytes and *Malassezia*. Cold Spring Harb Perspect Med. 2014; 4:019802.

69. Kekki O, Scheynius A, Poikonen S, Koskinen A, Kautiainen H, Turjanmaa K. Sensitization to *Malassezia* in children with atopic dermatitis combined with food allergy. Pediatr Allergy Immunol. 2013; 24:244–9. [PubMed: 23551180]

70. Du Toit G, Sayre P, Roberts G, Sever M, Lawson K, Bahnson H, et al. Effect of avoidance on peanut allergy after early peanut consumption. N Engl J Med. 2016; 374:1435–43. [PubMed: 26942922]

71. Yokooji T, Kurihara S, Murakami T, Chinuki Y, Takahashi H, Morita E. Characterization of causative allergens for wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat proteins in facial soap. Allergol Int. 2013; 64:435–45.

72. Dohi M, Suko M, Sugiyama H, Yamashita N, Tadokoro K, Juji F, et al. Food-dependent, exercise-induced anaphylaxis: a study of 11 Japanese cases. J Allergy Clin Immunol. 1991; 87:34–40. [PubMed: 1991921]

73. Brockow K, Kneissl D, Valentini L, Zelger O, Grosber M, Kugler C, et al. Using a gluten oral food challenge protocol to improve diagnosis of wheat-dependent exercise-induced anaphylaxis. J Allergy Clin Immunol. 2015; 134:977–84. e4.

74. Rispens T, Derksen NI, Commins SP, Platts-Mills TA, Aalberse RC. IgE production to alpha-gal is accompanied by elevated levels of specific IgG1 antibodies and low amounts of IgE to blood group B. PLoS One. 2013; 8:e55566. [PubMed: 23390540]

75. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008; 122:1154–60. [PubMed: 18951617]

76. Vickery B, Lin J, Kulis M, Fu Z, Steele P, Jones S, et al. Peanut oral immunotherapy modifies IgE and igG4 responses to major peanut allergens. J Allergy Clin Immunol. 2013; 131:128–34. [PubMed: 23199605]

77. Chapman MD, Platts-Mills TA. Purification and characterization of the major allergen from *Dermatophagoides pteronyssinus*-antigen P1. J Immunol. 1980; 125:587–92. [PubMed: 6771329]

78. Steinke J, Platts-Mills T, Commins S. The alpha-gal story: lessons learned from connecting the dots. J Allergy Clin Immunol. 2015; 135:589–96. [PubMed: 25747720]

79. Erwin EA, Kruszewski PG, Russo JM, Schuyler AJ, Platts-Mills TA. IgE antibodies and response to cow's milk elimination diet in pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2016 Apr 6. Epub ahead of print.

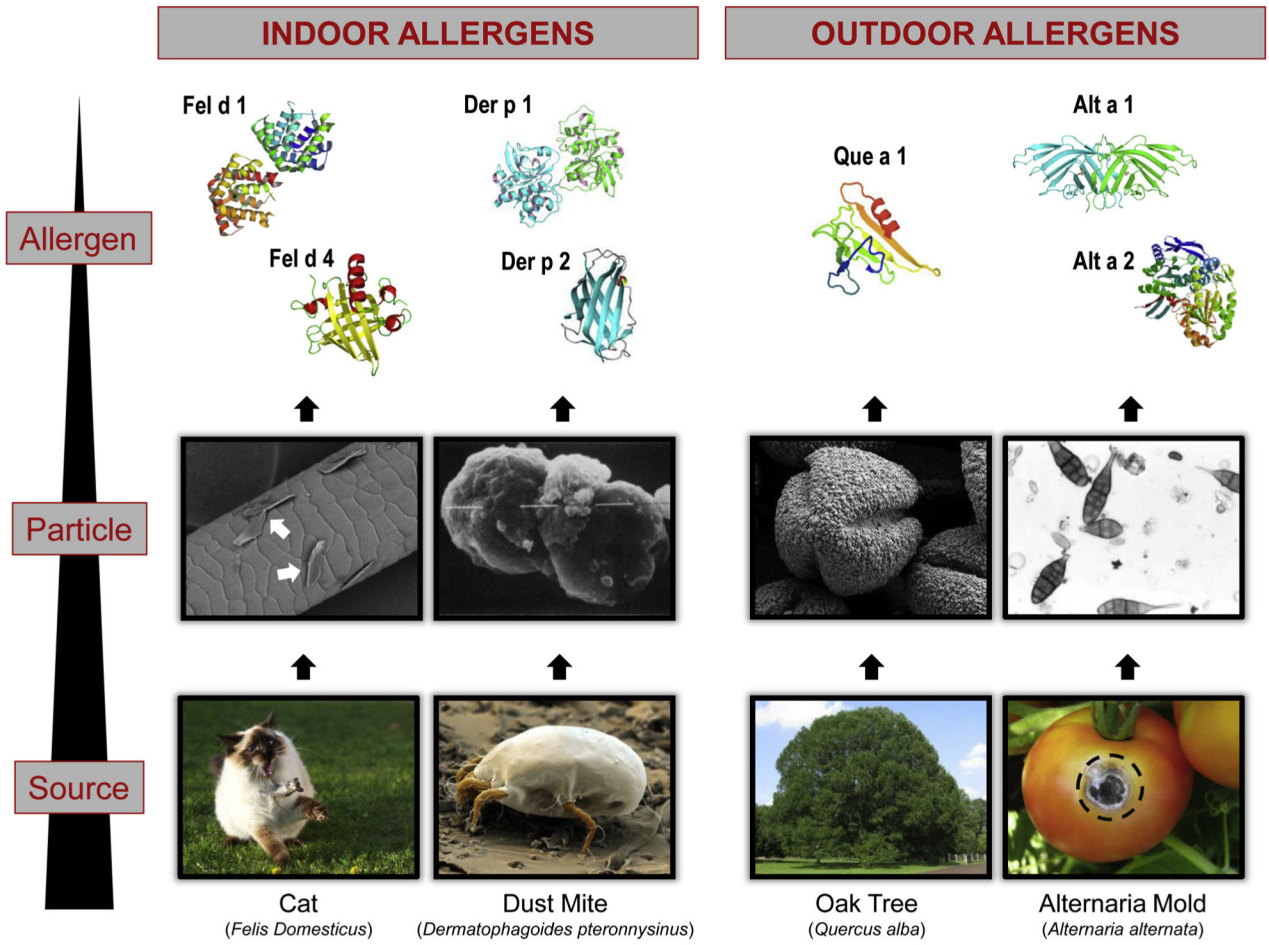


FIG 1.

Allergens become airborne and are inhaled in the form of particles, which range from 5 to 30 μm in diameter (Table I). The number of allergen molecules free in the air is essentially zero, and none of the source materials are inhaled.

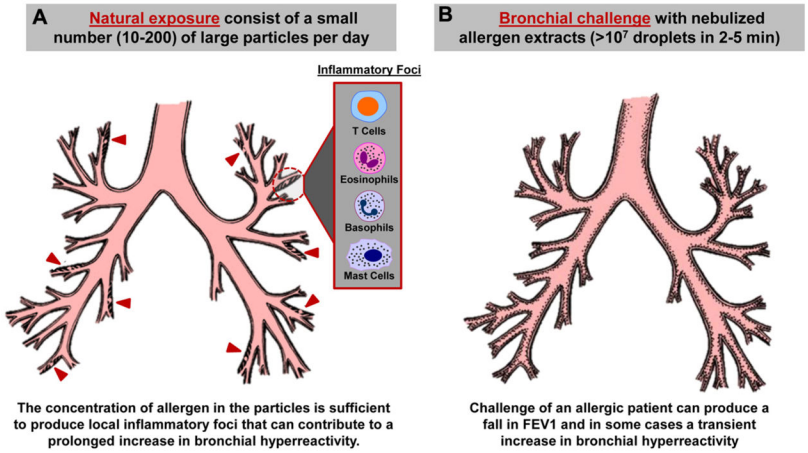
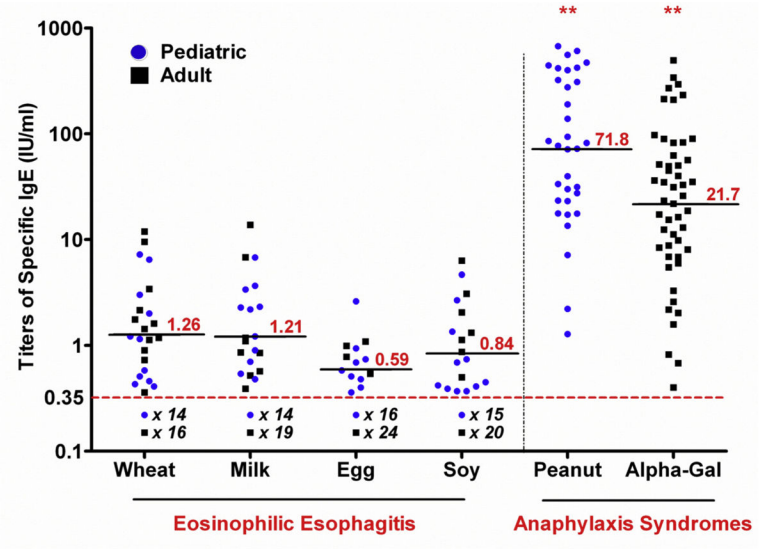


FIG 2.

Contrast between natural exposure to airborne allergen **(A)** and bronchial provocation with nebulized extract **(B)**. Natural exposure is to relatively large particles, which contain a wide range of allergens and adjuvants.



**p<0.001 compared to each of the EoE food allergens

FIG 3.

IgE antibodies in patients with EoE compared with those with 2 anaphylaxis syndromes: peanut and alpha-gal. Although IgE to milk, wheat, egg, and soy are common in children with EoE, the titers are generally low or very low.

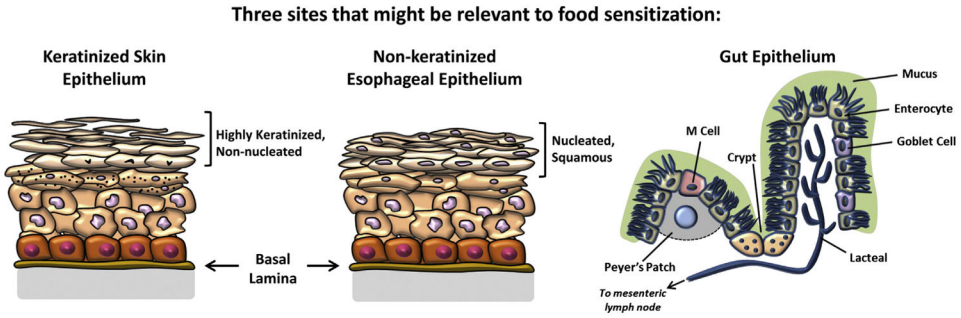


FIG 4.

Contrast between 3 body surfaces that are relevant to the induction and maintenance of immune responses for food allergens: skin (keratinized squamous epithelium), esophagus (nonkeratinized squamous epithelium), and columnar epithelium in the intestines. We recognize that the lymphoid tissues draining the upper airways and mouth are also important for response to food allergens.

TABLE I

Sizes of particles carrying some airborne allergens associated with asthma

	Diameter (μm)*	Allergen concentration	No. of particles		
			To deliver 20 ng	Entering the lung	Allergen per particle or droplet
Pollen grains	~20	~20 mg/mL†	~100	~5–100/d	0.1–0.3 ng
Mite fecal pellets	15–35	~20 mg/mL	~100	~5–100/d	0.1–0.3 ng
Alternaria species spores	14 × 10	Unknown	—	—	—
Rat allergen	7	1 mg/mL†	~27,000	~10,000/h	~0.001 ng
Nebulized allergen	2	1 μg/mL‡	$>10^8$	$\sim10^8$/2 min	$\sim10^{27}$ ng

*Sizes were determined from (1) direct microscopy, (2) distribution on a Cascade impactor, and (3) the theoretic behavior of a Wright nebulizer.

†Concentration of allergen in mite feces was calculated from quantity and diameter. Concentration of rat allergen was measured in whole rat urine.

‡Concentration of mite antigen P_1 or ragweed antigen E, which are commonly used for bronchial provocation.

J Allergy Clin Immunol. Author manuscript; available in PMC 2017 June 01.

TABLE II

Clinical and immunologic differences among 3 common forms of allergic disease

	Peanut-induced anaphylaxis	**EoE**	**Delayed anaphylaxis to mammalian meat (alpha-gal syndrome)**
Relevant allergens	Ara h 1, Ara h 2 (peanut)	Bos d 4, Bos d 5 (cow's milk) Wheat proteins	Alpha-gal [*]
Route of sensitization	Skin	Esophagus (?) Skin unlikely	Skin (Tick bites)
Risk factors	Eczema	Unknown	Outdoor activity Lipitor (?)
Serum IgE antibody	High-titer IgE to peanut proteins (5–500 IU/mL)	Low-titer or negative IgE to cow's milk proteins [†] (<0.1–2 IU/mL)	High-titer IgE to alpha-gal (often 10% to 30% of total IgE)
Treatment	Diet free of peanut Oral immunotherapy	Diet free of cow's milk with swallowed cromolyn 4 times daily [‡]	Diet free of mammalian products
Prevention	Prevent eczema Feed peanut from 3 mo	Not known	Avoid tick bites
Timing of reaction to foods	15–60 min to local and generalized swelling [§]	12–24 h	3–6 h after eating red meat

[*] Chung et al[28] and Commins et al.[29]

[†] Erwin et al.[47]

[‡] Erwin et al.[79]

[§] Du Toit et al.[48]

TABLE III

Relevance of specific IgE antibodies to the treatment of allergic disease

Disease	IgE assay and skin test	Role of IgE	Treatment*	Immunotherapyz
Hay fever	Seasonal allergens	Primary	Avoidance†	SCIT
Asthma	Indoor and outdoor allergens	Central	A. Avoidance†	SCIT
			B. Omalizumab†	
Late onset and severe asthma	AERD	Not clear		
	Vocal chord	Not relevant	Voice therapy, etc†	—
	Indoor allergens	Central	A. Avoidance†	SCIT
			B. Omalizumab†	
	Fungal	Mixed	Anti-fungal	?
Food allergy Immediate reactions	Peanut, etc	Primary	Avoidance	OIT
EoE	Cow's milk, wheat…	Probably none	Avoidance†	SCIT?
Alpha-gal Syndrome	Alpha-gal, beef…	Primary	Avoidance†	—

*Antihistamines and local steroids, for example, are asked for all these diseases.

†Dependent on identifying specific allergen or allergens.

‡*OIT*, Oral immunotherapy; *SCIT*, subcutaneous immunotherapy.