

Clinical Allergy at the Interface of Sticky Dust Particles and Crystal-Clear Proteins



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Allergen extracts are currently the basic reagents of allergists, both for skin tests and for allergen-specific treatment. Their activity is largely due to the allergenic proteins (commonly referred to as “molecular allergens”), many of which are now available more than 95% pure, often even as crystalline substances. For several reasons, such as standardization, quantitation, and regulatory requirements, molecular allergens would be the logical allergic substances used for clinical applications. This does not imply that allergen extracts can be banned right now.

Is a complete ban on allergen extracts a real threat, or is it just science fiction? We want to argue that this depends on the field of application: therapeutic or diagnostic. For *therapeutic applications*, an optimistic ballpark number of fewer than 100 molecular allergens would be needed. This estimate is based on 2 assumptions: (1) allergen-specific immune therapy (AIT) would be needed for fewer than 20 allergen sources (grass pollen, tree pollen, weed pollen, dust mite, cockroach, moulds, mammalian pets, insect venoms, etc) and (2) from each of these allergen sources on average fewer than 5 molecular allergens will need to be included. Although most of these molecular allergens are not yet available for human use and would need extensive safety and efficacy testing, the gradual replacement of therapeutic extracts by molecular allergens would seem a realistic possibility. However, it is important to stress that even for therapeutic applications we are in the early phase of a transition in which allergenic proteins are being compared with currently available allergen extracts.

The situation is different for diagnostic applications (particularly skin testing). Allergy diagnosis involves hundreds of allergen sources, including, in addition to above-mentioned allergens, many foods and allergen sources with prevalences too low for a cost-effective development of AIT material. For diagnostic purposes, most of these allergen sources would require the production of more than 10 potentially relevant molecular allergen molecules. The actual validation of the sufficiency of a

molecular allergen panel as a potential replacement for a currently available diagnostic allergen extract has not been thoroughly studied for most allergen sources. Even for peanut, a relatively extensively studied allergen source, the validation of a panel of recombinant components proved to be problematic.¹ While these new pure allergen components are being validated, regulatory efforts to remove currently available extracts may lead to a situation where we have a severely deficient diagnostic arsenal.

In this theme issue we focus on molecular allergens, allergen extracts, and allergens in the environment. This covers a wide range of topics including the location and route of exposure of environmental and food allergens, testing methods, extracts, and differences between molecular allergens and allergens in the real world. As recombinant molecular allergens are becoming available, it is important to understand that natural allergens are much more complex. For example, after production in their natural host, allergen molecules are subjected to post-translational modifications, potentially including enzymatic cleavages, addition of sugars, and oxidation. After release into the environment, these proteins may bind to sticky particles, including textile fibers and skin scales, and may become airborne if these particles are dusty. These are the real triggers of allergic reactions. The goal of the articles in this theme issue is to review the complex information about allergens and allergen extracts that answers the questions that we need to know when seeing patients. These questions include what we know about allergens and allergen extracts. At this time many of the questions require more evidence before answering them. These questions are the ones we wonder ourselves, are asked by patients in clinic, or the ones patients are asking on social media. The questions whose answers we want to know in practice.

CLINICIAN QUESTION

Why Is It Important to Know About the Physical Properties of Allergens?

The challenge upon seeing any patient with an allergic reaction is to take a detailed history, which includes establishing the mechanism, dose, and timing of exposure in relation to the onset of symptoms. Part of writing the illness script is understanding what types of exposures are expected to lead to symptoms and what types are not known to cause symptoms. Establishing this history comes before doing testing, discussion of the diagnosis, and possibly prescribing immunotherapy. It highlights that understanding the various properties of allergens in our environment and then knowing the benefits and drawbacks of the individual extracts for diagnosis and treatment is essential for treating patients with allergies.

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Aeroallergens

Patient questions: *Why do I have trouble when I walk into a house with a cat, even if I do not see it or touch it? Are there places I can move so my allergies are better?*

The article by Martorano and Erwin² reviews evidence about where and when indoor and outdoor aeroallergens can be found. They highlight the fact that previous dogma about the location of and regions where these allergens are located have changed because of numerous potential factors. One of the more specific examples of shifting exposure is the regional location of dust mites. Dust mites are now found in homes with low annual temperatures and low relative humidity including homes in high alpine environments. They review studies from Grafetstätter et al³ who found no change in levels of house dust mite allergens with rising altitude in alpine regions when previous studies had found no dust mites in high altitude locations. They hypothesize that both climate change and improved construction methods have allowed dust mites to survive in areas that conventional wisdom thought they could not exist. Other studies suggest that synthetic pillows accumulate dust mites even faster than feather pillows and that most mite exposure occurs outside of the bed.^{4,5} Their review of the location and mode of exposure to aeroallergens allows clinicians to explain to patients how these allergens contribute to disease. Understanding these properties is not important solely to explain how to avoid the allergens, which was described in a recent theme issue of this journal.^{6,7} Many patients want to know why they are having symptoms just as much as how to make them better.

Food allergens in the environment

Patient question: *I am worried about introducing peanuts in my younger child because my oldest has peanut allergy. I am worried about peanuts being in the house, so I have always kept them out of the house. How do I prevent accidental exposure?*

In patients with environmental allergies, understanding the physical locations and routes of exposure to environmental allergens is important for us to be able to understand exposures leading to symptoms and to guide avoidance strategies. Similarly, our patients have a keen desire to understand the sources of hidden food allergen exposure. Sheehan et al⁸ explore the mechanisms by which food-allergic patients may be exposed to food allergens in the environment, on food preparation surfaces, through cross-contact in other foods, in pillows, in play areas throughout the house, in schools, and even on other people. Allergy providers should be able to explain the relative clinical relevance of these seemingly ubiquitous exposures. Fortunately, they review evidence that shows that systemic allergic reactions require the protein to be ingested, or to come in contact with mucosal surfaces to elicit systemic reactions. However, they speculate that food found in the environment may contribute to the development of food allergies, possibly through early or continued exposure through the skin. The clinical significance of food allergens in the environment on the development of food allergy is still being studied. Most of the available literature on this subject comes as yet from studies on peanut.

Recombinant allergens versus allergen extracts

Patient questions: *Will my allergy shots work? Why was my test result negative when I have severe symptoms around certain dogs?*

Clinician question: *Why was the skin test result to foods negative when the blood test result was positive?* Valenta et al⁹ discuss the potential advantages of the use of recombinant molecular allergens for diagnosis and treatment. They give an example where mixtures of recombinant timothy grass allergen components have been shown to be effective for AIT and could be a model on how to replace current therapeutic allergen extracts. They also highlight the many issues that are keeping currently available extracts from meeting the regulatory definitions for medicinal products. In reality, to date few recombinant allergen products have been approved for clinical use and any new product would need to fulfill the expensive clinical evaluation required of any other new medicinal product. Although these advances may produce more efficacious and safer extracts for therapeutic use, allergists in all countries need to understand how these regulations may affect the availability of not only therapeutic but also diagnostic extracts. Understanding the advantages of natural extracts will allow national and international allergy societies and individual allergists to plea with regulators to allow the continued diagnostic use (both *in vitro* and *in vivo*) of the naturally produced extracts, at least until validated superior products are available.

Hymenoptera venom extract

Patient question: *Why do I need shots to multiple insects when I was stung by only one?*

The case presentation of hymenoptera venom hypersensitivity by Tracy and Golden¹⁰ covers practical aspects of managing patients with anaphylaxis to venom. The review covers how to identify stinging insects and the clinical production and use of their venoms. Of all the naturally produced extracts that could be replaced by a recombinant, multiple-component alternative, the stinging insect venoms seem to be a relatively easy target.

Cross-reactivity between aeroallergens and food allergens

Patient questions: *Why don't you just test for all foods? I just want to make sure I don't miss any other unknown allergens?*

Faber et al¹¹ discuss the relevant pollens that can make food allergy testing results difficult to interpret. They review the specific foods to which different pollens can both cause symptoms and false positives when testing for foods with naturally derived extracts. Their article highlights the regional variability of certain food allergy syndromes and explains that this is likely related to the differences in regional flora. Their guide to the proteins found in pollen is an important reference as component testing for various foods becomes widely available. They reference studies showing interesting aeroallergen and food associations such as fig fruit syndrome and cat pork syndrome. The authors highlight that because of these potential cross-reactivities it is important to consider oral food challenges whenever the diagnosis for food allergy is not clear on the basis of a clinical history of a reaction.

Intradermal skin testing

Clinician question: *When should I do intradermal skin testing in patients who have negative skin prick testing results to environmental allergens?*

Patient question: *Do I really need all these tests?* In an article on controversies in allergy, Ledford and Lockey¹² dive into the debate about using intradermal skin testing (IDST) for aeroallergens when the skin prick test result is negative. They discuss both the efficiency and the efficacy of the skin prick test and highlight the clinical utility of using IDST to rule out allergy as a cause of symptoms. They discuss that high-dose single-challenge studies suggesting lack of utility of IDST do not represent all allergic patients and say that further research is needed to evaluate the efficacy of IDST in patients who have chronic exposure to allergens such as living with an animal. The major challenge in interpreting testing results in allergic patients is to differentiate between sensitization and clinical allergy. They argue that any test that allows the clinician to identify the true negatives remains a useful tool.

CONCLUSIONS

Allergenic extracts in their current form have been available for decades. The strengths and drawbacks of using these extracts for diagnosis have become a natural part of our practice. At this time, we have the potential to improve the naturally derived extracts to help reduce false negatives and improve the ability to avoid false positives when making a diagnosis and to make immunotherapy more effective with less side effects. However, replacement of allergen extracts by molecular allergens (either as a panel or as a mixture) needs to be validated before currently available extracts are taken away. Understanding the implications of these changes is important so that we can advocate for our patients and practice to be able to continue to use the currently available extracts until new and improved versions become available. Allergen extracts for skin testing are still a crucial component for optimal care of allergic patients. Regulations should distinguish between

diagnostic and therapeutic extracts, particularly in view of the more than 1,000-fold difference in cumulative dose.

In addition, long-held beliefs about the location and route of exposure of allergens have not been supported by recent studies. As the world becomes smaller and the climate changes, the locations and seasons of allergenic exposure will also change. As we study routes of allergen exposure, we need to integrate any changes in knowledge into clinical practice while advising patients on avoidance, diagnosis, and treatment.

REFERENCES

1. Aalberse JA, Meijer Y, Derksen N, van der Palen-Merkus T, Knol E, Aalberse RC. Moving from peanut extract to peanut components: towards validation of component-resolved IgE tests. *Allergy* 2013;68:748-56.
2. Martorano L, Erwin EA. Aeroallergen exposure and spread in the modern era. *J Allergy Clin Immunol Pract* 2018;6:1835-42.
3. Grafetstätter C, Proseger J, Braunschmid H, Sanovic R, Hahne P, Pichler C, et al. No concentration decrease of house dust mite allergens with rising altitude in alpine regions. *Allergy Asthma Immunol Res* 2016;8:312-8.
4. Rains N, Siebers R, Crane J, Fitzharris P. House dust mite allergen (Der p 1) accumulation on new synthetic and feather pillows. *Clin Exp Allergy* 1999;29:182-5.
5. Green WF, Marks GB, Tovey ER, Toelle BG, Woolcock AJ. House dust mites and mite allergens in public places. *J Allergy Clin Immunol* 2006;89:1196-7.
6. Wilson JM, Platts-Mills TAE. Home environmental interventions for house dust mite. *J Allergy Clin Immunol Pract* 2018;6:1-7.
7. Ahluwalia SK, Matsui EC. Indoor environmental interventions for furry pet allergens, pest allergens, and mold: looking to the future. *J Allergy Clin Immunol Pract* 2018;6:9-19.
8. Sheehan WJ, Taylor SL, Phipatanakul W, Brough HA. Environmental food exposure: what is the risk of clinical reactivity from cross-contact and what is the risk of sensitization. *J Allergy Clin Immunol Pract* 2018;6:1825-32.
9. Valenta R, Karaulov A, Niederberger V, Zhemov Y, Elisyutina O, Campana R, et al. Allergen extracts for *in vivo* diagnosis and treatment of allergy: is there a future? *J Allergy Clin Immunol Pract* 2018;6:1845-55.
10. Tracy J, Golden DBK. Hymenoptera venom extracts in clinical practice. *J Allergy Clin Immunol Pract* 2018;6:1856-62.
11. Faber MA, Van Gasse AL, Decuyper II, Sabato V, Hagendorens MM, Mertens C, et al. Cross-reactive aeroallergens: which need to cross our mind in food allergy diagnosis? *J Allergy Clin Immunol Pract* 2018;6:1813-23.
12. Ledford DK, Lockey RF. Controversies in allergy: intradermal aeroallergen skin testing. *J Allergy Clin Immunol Pract* 2018;6:1863-5.

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