

Advancements and Dilemmas in the Management of Allergy

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KEYWORDS

- Allergy • Allergic rhinitis • Prevention • Allergy testing • Sublingual immunotherapy • Desensitization

KEY POINTS

- Prevention of peanut allergy has been demonstrated through intentional oral exposure to peanut protein to promote tolerance.
- The diagnosis of inhalant allergy has not changed substantially, but continued research into component (or molecular) immunoglobulin E testing and research on local allergy may improve the accuracy of allergy testing in the future.
- Efficacious immunotherapy has expanded to include sublingual drops, sublingual tablets, and subcutaneous immunotherapy.
- With a wider variety of immunotherapy options, clinical decisions on allergen selection, such as the efficacy of sublingual tablets in polyallergic patients, have become more relevant.
- More humanized immunoglobulins targeting specific receptors and mediators of allergic inflammation (biologics) are now available, providing new options for patients with severe asthma and atopic conditions.

INTRODUCTION

The options for diagnosing and managing allergic disease have broadened over the last several years, creating new considerations for clinical allergists. This article provides a cursory synopsis of issues that have arisen in the literature and how clinical practitioners might alter their assessment and management of allergic patients.

PREVENTION

The prevalence of allergic rhinitis and other atopic conditions (specifically food allergies) has increased in the United States and other developed countries.¹ The

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reasons for this are not clear, and several theories have been offered including fewer childhood infections,^{2,3} lower vitamin D levels,⁴ changes in diets,⁵ and exposures to a greater array of chemicals.⁶ Studies that have tried to prevent inhalant allergic disease through decreased exposure to allergen sources such as dust mites or animal dander have often failed to show benefit or had conflicting results.^{7,8}

The LEAP study advanced understanding by successfully preventing the development of peanut allergy in high-risk infants by intentional oral exposure to peanut proteins.⁹ The paradigm shift of prevention through exposure to allergen rather than avoidance of allergen may lead to other successful prevention strategies that are certain to be investigated. The prevention of allergic rhinitis or allergic asthma has not been robustly demonstrated at this time.

DIAGNOSIS

The false-positive rate of sIgE testing (whether in sera or by skin testing) has been problematically high in the general population.¹ Fifty-four percent of the US population was skin prick test (SPT) positive per a Centers for Disease Control and Prevention survey.¹⁰ As such, the clinical assessment of allergic rhinitis is central for making the correct diagnosis. Although the symptoms caused by intermittent and seasonal rhinitis, including itching, sneezing, rhinorrhea, and nasal congestion provide an identifiable pattern, the dominance of nasal congestion in perennial allergies has a broader differential diagnosis, including nonallergic rhinitis, mixed rhinitis, anatomic contributions, and chronic rhino-sinusitis. Clinically, selecting allergens for testing and knowing which positive tests are clinically relevant is challenging. Although major advances in the diagnosis of inhalant allergic disease have not gained wide-spread clinical use, there are some new technologies on the horizon.

Component or molecular diagnosis of allergy refers to delineating the IgE reactivity by the protein the allergen binds rather than the source material alone.^{11,12} For example, component results for the dust mite *Dermatophagoides pteronyssinus* could be provided as Der p1 and Der p2. Potentially, component testing would better identify which allergens were more clinically important and identify cross-reactivity across different allergic sources.¹¹ However, the relationship between clinical allergic symptoms and component testing results may be complicated and require more research and population-specific data to be interpretable. Complex test results may lead to either computer-assisted interpretation of component testing or isolating a few clinical scenarios where certain component tests are clinically meaningful.

Local IgE in allergic rhinitis refers to presence of allergen-specific IgE in nasal secretions or tissues that can be detected when skin or sera-specific IgE testing is negative.^{13–15} Standardized methods for collection and testing have not yet been established. If a standard method is agreed upon, identifying the clinical significance will remain a research goal. Adding to the confusion, nasal polyps also stain positive for polyclonal IgE; however, the relevance to specific allergic disease remains unclear, as the available literature shows that nasal polyposis and allergic rhinitis are not closely correlated.¹⁶

MANAGEMENT OF ALLERGIC DISEASE

For inhalant allergy, management of disease is classically discussed in terms of avoidance (or reduction of exposure through environmental control), pharmacotherapy, and immunotherapy.¹ Management with biologics, which refers to using humanized antibodies targeted against elements of the allergic inflammatory network, is also in use clinically.¹⁷

Avoidance

One of the main tenants of allergy therapy is education on what sources are causing an individual's symptoms and trying to reduce symptoms by limiting exposure. However, strategies to reduce symptoms through use of dehumidifiers, air filters, dust mite covers, pet washing, and other interventions have rarely shown a significant decrease in symptoms, although reduction of antigen is often demonstrated.¹ Reducing allergen exposure enough to reduce symptoms in an already sensitized individual seems to be difficult to achieve in most situations. Evidence-based counseling would suggest that resources would be better utilized on more proven management options.

Pharmacology

Nonsedating antihistamines and intranasal corticosteroid sprays are now over the counter in the United States. Still, professional medical providers remain the trusted source of information on how to best select medications to manage allergic symptoms. There are likely several areas where the use of medications for allergic rhinitis could be optimized. Four suggestions based on the literature stand out.

Oral forms of sedating antihistamines may be overused by the allergic population. Less-sedating and nonsedating antihistamines clearly have a better benefit/adverse effect profile and should be advocated in most situations.^{1,18}

Studies show limited benefit of adding an oral antihistamine to an intranasal corticosteroid; however, this combination seems commonly utilized.^{1,19,20} There may be specific cases where patient preference or poor symptom control with INCS alone make this combination reasonable.²¹

Montelukast has been identified as a poor first-line choice in allergic rhinitis and perhaps overprescribed for this indication in patients without asthma.¹

Consideration of the high rate of concomitant allergic conjunctivitis with allergic rhinitis should influence pharmacologic choices more.²²

For patients with severe disease, especially steroid-dependent asthma commonly encountered by otolaryngologists in aspirin exacerbated respiratory disease (AERD) and other chronic sinusitis with polyps patients, monoclonal antibodies targeting the workings of inflammatory mediators such as interleukin (IL-5) and IgE are available.¹⁷ These seem especially suited for severe disease that is refractory to other measures due their expense and are further discussed in other articles in this issue.

Desensitization

The role of sublingual immunotherapy (SLIT) continues to be source of debate among allergy specialists.^{23,24} Although multiple trials have shown efficacy,²⁴ the optimal regimen and dosage are not known.²⁵ There is also not a clear understanding of why some trials show efficacy, and others do not.²⁵

SLIT is provided as sublingual drops prepared by allergy specialists and as commercially available tablets. Tablets are available for grass and ragweed, and a tablet for dust mite allergy was recently approved by the US Food and Drug Administration.

Many otolaryngologists employ sublingual therapy, and there seems to be enthusiasm from patients for a form of immunotherapy that does not require as many office visits, waiting periods, and needle sticks.

Traditionally, allergen-specific immunotherapy has targeted multiple allergens in the polyallergic patient. However, the scientific support for treating multiple allergens compared with fewer allergens is minimal.²⁶⁻²⁸ In SLIT, effective doses may be 30 times higher the monthly totals used in subcutaneous immunotherapy.²⁵ Providers

are faced with cost and logistical realities that have led to questions about whether fewer allergens can be used to treat polysensitized patients. Currently there is some scientific uncertainty about the relative efficacy between SLIT and subcutaneous immunotherapy, as well as uncertainty about the number of allergens to treat. The clinician's role now involves helping patients make an informed decision in selecting sublingual drops, sublingual tablets, or subcutaneous immunotherapy in terms of efficacy, time, costs, and convenience.

Another form of desensitization that has received attention in the literature is aspirin desensitization. Research into AERD suggests a higher identification rate when aspirin challenges are employed with some advocating for a larger role of aspirin desensitization.²⁹ Despite newer biologics and aspirin desensitization, AERD patients remain difficult to manage.

Gene Therapy

In a recent animal study, gene therapy was successfully employed to silence the Th2 immune response to a specific allergen-provoked inflammation.³⁰ Gene therapy for allergic disease has not been demonstrated in people, and application in a clinical setting is not expected soon. However, the genetic understanding of allergic disease and the ability to manipulate genes continue to improve.

SUMMARY

The diagnosis and treatment of allergic disease continue to advance and challenge clinicians with increasing complexity and new opportunities. For decades, the foundation of treating severe inhalant allergies relied on skin testing and subcutaneous immunotherapy, but component testing, prevention through exposure, local allergy, biologics, and sublingual immunotherapy are among the advances that have entered the literature and are finding clinical application. The next generation of providers who treat allergic diseases will have new tools and treatment options, but also will face greater complexities. In addition to more research, mechanisms to deal with the increasing complexity may also need to coevolve.

REFERENCES

1. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. *Otolaryngol Head Neck Surg* 2015;152:S1–43.
2. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259–60.
3. Daley D. The evolution of the hygiene hypothesis: the role of early-life exposures to viruses and microbes and their relationship to asthma and allergic diseases. *Curr Opin Allergy Clin Immunol* 2014;14:390–6.
4. Kim YH, Kim KW, Kim MJ, et al. Vitamin D levels in allergic rhinitis: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2016;27:580–90.
5. Saadeh D, Salameh P, Baldi I, et al. Diet and allergic diseases among population aged 0 to 18 years: myth or reality? *Nutrients* 2013;5:3399–423.
6. Baldacci S, Maio S, Cerrai S, et al. Allergy and asthma: Effects of the exposure to particulate matter and biological allergens. *Respir Med* 2015;109:1089–104.
7. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003;58:489–93.
8. Custovic A, Simpson BM, Simpson A, et al. Effect of environmental manipulation in pregnancy and early life on respiratory symptoms and atopy during first year of life: a randomised trial. *Lancet* 2001;358:188–93.

9. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803–13.
10. Arbes SJ Jr, Gergen PJ, Elliott L, et al. Prevalences of positive skin test responses to 10 common allergens in the US population: results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2005;116:377–83.
11. Ciprandi G, Incorvaia C, Frati F, Italian Study Group on Polysensitization. Management of polysensitized patient: from molecular diagnostics to biomolecular immunotherapy. *Expert Rev Clin Immunol* 2015;11:973–6.
12. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ, et al. EAACI molecular allergology user's guide. *Pediatr Allergy Immunol* 2016;27(Suppl 23):1–250.
13. Cheng KJ, Zhou ML, Xu YY, et al. The role of local allergy in the nasal inflammation. *Eur Arch Otorhinolaryngol* 2017;274(9):3275–81.
14. Reisacher WR, Suurna MV, Rochlin K, et al. Oral mucosal immunotherapy for allergic rhinitis: A pilot study. *Allergy Rhinol (Providence)* 2016;7:21–8.
15. Wise SK, Ahn CN, Schlosser RJ. Localized immunoglobulin E expression in allergic rhinitis and nasal polyposis. *Curr Opin Otolaryngol Head Neck Surg* 2009;17:216–22.
16. Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *Int Forum Allergy Rhinol* 2016;6(Suppl 1):S22–209.
17. Lam K, Kern RC, Luong A. Is there a future for biologics in the management of chronic rhinosinusitis? *Int Forum Allergy Rhinol* 2016;6:935–42.
18. Church MK, Maurer M, Simons FE, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy* 2010;65:459–66.
19. Anolik R, Mometasone Furoate Nasal Spray With Loratadine Study Group. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2008;100:264–71.
20. Di Lorenzo G, Pacor ML, Pellitteri ME, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. *Clin Exp Allergy* 2004;34:259–67.
21. Brozek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol* 2017. [Epub ahead of print].
22. Cingi C, Gevaert P, Mosges R, et al. Multi-morbidities of allergic rhinitis in adults: European Academy of Allergy and Clinical Immunology Task Force report. *Clin Transl Allergy* 2017;7:17.
23. Greenhawt M, Oppenheimer J, Nelson M, et al. Sublingual immunotherapy: a focused allergen immunotherapy practice parameter update. *Ann Allergy Asthma Immunol* 2017;118:276–82.e272.
24. Lin SY, Ereksom N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA* 2013;309:1278–88.
25. Leatherman BD, Khalid A, Lee S, et al. Dosing of sublingual immunotherapy for allergic rhinitis: evidence-based review with recommendations. *Int Forum Allergy Rhinol* 2015;5:773–83.
26. Lowell FC, Franklin W. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. *N Engl J Med* 1965;273:675–9.

27. Franklin W, Lowell FC. Comparison of two dosages of ragweed extract in the treatment of pollenosis. *JAMA* 1967;201:915–7.
28. Nelson HS. Multiallergen immunotherapy for allergic rhinitis and asthma. *J Allergy Clin Immunol* 2009;123:763–9.
29. Stevenson DD, White AA. Clinical characteristics of aspirin-exacerbated respiratory disease. *Immunol Allergy Clin N Am* 2016;36:643–55.
30. Al-Kouba J, Wilkinson AN, Starkey MR, et al. Allergen-encoding bone marrow transfer inactivates allergic T cell responses, alleviating airway inflammation. *JCI Insight* 2017;2 [pii:85742].