Clinical Commentary Review

The Role of Aeroallergen Sensitization Testing in Asthma Management

Thomas B. Casale, MD[a,b], Soren Pedersen, MD, DMSc[c], Pablo Rodriguez del Rio, MD, PhD[d], Andrew H. Liu, MD[e,f,g], Pascal Demoly, MD, PhD[h], and David Price, MD[i,j] *McLean, Va; Tampa, Fla; Kolding, Denmark; Madrid, Spain; Aurora and Denver, Colo; Montpellier, France; Aberdeen, UK; and Singapore*

Asthma is a global disease affecting almost 400 million people. Simultaneously, the overall burden of allergies is increasing. Although allergies are frequent and commonly recognized triggers of asthma severity and exacerbations, the majority of patients with asthma are not investigated for their underlying aeroallergen sensitizations, despite the potentially preventable consequences and therapeutic options. This review summarizes the current state of aeroallergen sensitization testing for people with asthma. We describe who should be tested and why, how testing can be used to optimize asthma management, list barriers to implementation of effective asthma management strategies, and make recommendations for improving asthma/allergy management by aeroallergen testing. Establishing a diagnosis of asthma and determining whether there is an allergic component is fundamental to an effective treatment plan. Moreover, moving from severity-based to phenotype-based asthma care can improve the care of asthma and allergic diseases. Timely diagnosis of aeroallergen sensitizations forms the basis for individualized treatment plans, which may include allergen remediation strategies when appropriate, and allergen immunotherapy, the only immunomodulating therapy for allergic asthma. Finally, the advent of biologics will expand the number of patients who can benefit from treatment, with decreased symptoms and disease remission a possibility for the first time. **(J Allergy Clin Immunol Pract 2020;8:2526-32)**

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Asthma is a global disease affecting almost 400 million people (Table I).[1,2] Simultaneously, the prevalence of allergic diseases has continued to rise in the industrialized world for more than 50 years.[3] Although allergies are frequent and commonly recognized triggers of asthma exacerbations, the majority of patients with asthma are not investigated for their underlying allergic triggers[4] despite the potentially preventable consequences. Given this

[a]Food Allergy Research and Education (FARE), McLean, Va
[b]Department of Medicine, University of South Florida, Tampa, Fla
[c]Departmet of Pediatrics, Kolding Hospital, Kolding, Denmark
[d]Department of Pediatrics, University Children's Hospital, Niño Jesús, Madrid, Spain
[e]Breathing Institute, Section of Pediatric Pulmonary & Sleep Medicine, Children's Hospital Colorado, Aurora, Colo
[f]Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colo
[g]Department of Pediatrics, National Jewish Health, Denver, Colo
[h]Division of Allergy, Department of Pulmonology, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France
[i]Department of Primary Care Respiratory Medicine, University of Aberdeen, Aberdeen, UK
[j]Observational and Pragmatic Research Institute, Singapore

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Corresponding author: Thomas B. Casale, MD, University of South Florida, 12901 Bruce B Downs Blvd, MDC19, Tampa, FL 33612. E-mail: tbcasale@usf.edu.

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Abbreviations used
AIT- Allergen immunotherapy
AR- Allergic rhinitis
EAACI- European Academy of Allergy and Clinical Immunology
GINA- Global Initiative for Asthma
HDM- House dust mite
ICS- Inhaled corticosteroid
mAPI- Modified Asthma Predictive Index
sIgE- Specific IgE
NICE- National Institute for Health and Care Excellence
PARSE- Perennial allergic rhinitis with seasonal exacerbations
SPT- Skin prick testing

reality, a group of asthma and allergy specialists were convened by Thermo Fisher (a manufacturer of medical equipment to measure IgE) to explore the clinical challenges and unmet needs in diagnosing and managing asthma. Asthma guidelines or algorithms generally recommend specific IgE (sIgE) or skin prick testing (SPT) for aeroallergen sensitization in subpopulations of patients with asthma. The recommendations for testing suggested 4 main objectives for discussion by the specialists: (1) to determine current recommendations for aeroallergen sensitization testing for patients with asthma; (2) to define which patients with asthma would be candidates for allergy testing, and what added value test results would provide in improving asthma care; (3) to identify the challenges preventing allergy diagnostics and the missed opportunities for allergic trigger control, and to recommend practical strategies for overcoming them; and (4) to offer guidance on integrating allergy evaluation into asthma management.

WHAT IS THE CURRENT PRACTICE IN TESTING FOR AEROALLERGENS?

Asthma guidelines recommendations

Although testing criteria may differ among guidelines, they often describe at-risk patients as having a complicated diagnosis,[5] chronic or recurring symptoms,[6] difficult-to-control or treat asthma,[7] or those being considered for allergen immunotherapy (AIT), anti-IgE, or other biologic therapy.[7-10] None of the guidelines address the value of testing wheezing children for prediction of developing persistent asthma, response to therapies, or phenotype-directed care. One hindrance to guideline-recommended testing is that most patients with asthma present in primary care settings,[4] where busy clinicians may not be aware of the guidelines, lack knowledge about or do not believe in the relevance of evaluating aeroallergen sensitization in asthmatic patients, and may need help to interpret results. Adherence to guideline recommendations was studied among 1176 patients with persistent asthma aged 5 to 65 years seen in family medicine or pediatric practices.[4] Only 32.5% had an allergy evaluation, and only 2% had documented allergy test results. A European primary care survey conducted by the European Academy of Allergy and Clinical Immunology (EAACI) and the International Primary Care Respiratory Group found that 20.6% of practices had no access to allergy tests.[11] A shortage of allergy and asthma specialists in the vicinity of general practices may further hinder appropriate testing and referral. In addition, some guidelines have not kept pace with current evidence and practices.

TABLE I. A global perspective on asthma from the World Health Organization[1,2]

- 338,000 asthma deaths were reported in 2015,[1] and asthma affects almost 400 million people worldwide.[2] Asthma deaths will increase in the next 10 years if urgent action is not taken.
- Asthma is the most common chronic disease among children.
- Asthma attacks can be fatal but are largely preventable.
- Asthma is often underdiagnosed and undertreated.
- Strong risk factors for developing asthma are exposure to indoor allergens (eg, dust mites, pet dander), outdoor allergens such as pollens, molds, and irritants such as tobacco smoke, ambient pollutants, and chemicals in the workplace.
- Avoiding asthma triggers can reduce the severity of asthma.
- Treatment and vigilance and regular medical checks are crucial. Patients can live rewarding, fulfilling lives with the right treatment. Asthma is often treated using an inhaler to breathe in medicines. People with ongoing symptoms will need to take daily medication for the long term. It is also important for people living with asthma to avoid triggers.

Global Initiative for Asthma. The Global Initiative for Asthma (GINA) strategy is not a guideline per se, but rather "an integrated evidence-based strategy focusing on translation into clinical practice."[12] The GINA strategy emphasizes stepwise medication therapy; however, its Implementation Toolbox notes that "it is useful to know if somebody is allergic to specific airborne allergens"[13] and advises, "Avoid or reduce contact with relevant substances to which one is allergic." Since 2017, GINA notes that AIT is indicated for patients with mild asthma and allergic rhinitis (AR) due to house dust mite (HDM) who have flare-ups despite using regular controller medication. Furthermore, "most people with asthma also have rhinitis… either of allergic origin or not. It should ideally be well treated to avoid its influence on asthma control." Another recent change in the GINA strategy is to update guidance on management of asthma in preschool children (≤5 years old).[12] GINA also recommends SPT or sIgE testing for relevant allergens if not already done as part of the assessment of comorbidities and phenotyping for those with severe asthma.

National Institute for Health and Care Excellence (UK). National Institute for Health and Care Excellence (NICE) recommends using sIgE testing for aeroallergens to identify triggers after a diagnosis of asthma has been made.[14]

ERS/ATS (Severe) Asthma Guidelines. The European Respiratory Society/American Thoracic Society guidelines on severe asthma recommend, "in all patients, determining whether there is an association between sIgE (as measured by skin prick testing or serum testing), on-going exposures and symptoms may help identify factors which contribute to asthma symptoms and exacerbations."[15] However, it should be noted that patients with severe asthma are not appropriate candidates for AIT due to the risks of AIT-induced anaphylaxis. Nonetheless, identification of allergic status can help phenotype severe asthma patients and thereby aid in the use of appropriate biologics.

National Asthma Education and Prevention Program (USA). These guidelines recommend evaluating the potential role of allergens, particularly indoor inhalant allergens in patients

with persistent asthma.[5] This recommendation is based on strong evidence from randomized controlled trials with a rich body of supportive data (Evidence Category A). Using the modified Asthma Predictive Index (mAPI) is advised for identifying children from birth to age 4 at high risk of developing asthma. A National Institutes of Health update conditionally recommends that in adults and children with symptoms and/or sensitization to identified indoor allergens, including pets, a multicomponent allergen-specific mitigation intervention be initiated. They also conditionally recommend AIT in adults and children with mild-to-moderate allergic asthma as an adjunct treatment to standard pharmacotherapy when there is a clear connection between symptoms and exposure to an allergen to which the patient is sensitive.[16]

European Academy of Allergy and Clinical Immunology. EAACI stresses the importance of recognizing and treating the allergic components of asthma.[17] Sensitization, defined as detectable sIgE antibodies, serves as the basis for recommending AIT as a disease-modifying therapy for prevention of the development of asthma in children with AR and grass/birch pollen allergy. Questions remain regarding the optimal age at which to introduce AIT for prevention, the optimal therapy duration, the optimal product, dose and administration, and whether AIT can prevent asthma in children with AR due to HDM and other allergens.

Current allergy testing practices for patients with asthma

Rates of specific allergen testing vary from country to country, influenced by the availability of testing and specialists, and broader health system support. As noted previously, 20.6% of European practices had no access to allergy tests.[11] The greatest unmet need was for access to allergy and asthma specialists. In public health services that had specialists, delays for appointments often exceeded 6 weeks. The lack of specialists limits access to SPT, although most primary care respondents to the survey reported having access to serum sIgE testing. Still, they cited achieving sufficient competence at the appropriate level of care with allergy testing as an issue.[11] Indeed, even expert opinion differs on the number and types of inhalant allergens that should be tested. Furthermore, it is critical to perform these tests using validated and reproducible methodology.

Some underserved populations suffer more asthma morbidity and mortality than would be predicted by disease prevalence alone.[18] Many factors contribute to this disparity, including genetic, environmental, access to reimbursement of care, and social influences. Some have high numbers of aeroallergen sensitizations associated with asthma severity and exacerbation.[19-21] However, several studies have found that underserved populations are also less likely to receive guideline-directed care.[22,23]

The utility of aeroallergen sensitization testing in asthma phenotyping

The management approach to asthma currently includes a phenotyping step[24] for the identification of allergic and eosinophilic and non-T2 phenotypes based on measurement of biomarkers such as eosinophils in blood or sputum, fractional exhaled nitric oxide, and sIgE.[25] GINA currently recommends this mainly for more severe asthma, but others have called for much earlier phenotyping to define the specific asthma that a patient has[26] or to guide earlier interventions including earlier biologics use.[27] Patients with an allergic phenotype respond better to corticosteroids[28] and in severe cases to omalizumab. Allergic asthma patients might also improve with allergen remediation and/or AIT as discussed previously. Furthermore, recent evidence suggests that sIgE bound to dendritic cells results in impaired antiviral effects. Blocking IgE with omalizumab decreases susceptibility to respiratory viral illnesses through enhanced IFN-α responses in plasmacytoid dendritic cells.[29] These data provide further support for the utility of identifying sIgE to better provide a personalized and more effective therapeutic regimen.

WHO WOULD BENEFIT MOST FROM TESTING FOR AEROALLERGEN SENSITIZATION?

Children

In early childhood, sensitization to multiple inhalant allergens and sensitization combined with perennial exposure in the home predict asthma persistence, exacerbation, and lung dysfunction.[30] Preschool children with persistent wheeze and inhalant allergies are more likely to develop persistent asthma.[21] Transient early wheezing and nonallergic wheezing generally subside by 3 years of age as the airways enlarge in a growing child. But approximately 50% of children with wheezing and atopic asthma continue to be symptomatic at age 12.

Aeroallergen sensitization testing increases the ability to predict asthma development, drug response, and risk for future asthma exacerbations.[31] In predictive models of childhood asthma development, indices identifying preschool children who are more likely to develop asthma include the mAPI (Table II),[32] which highlights the role of allergic sensitization to at least 1 aeroallergen.[32-34] In a high-risk cohort, a positive mAPI greatly increased future asthma probability (eg, 30% pretest probability to 90% posttest probability).[32] In addition, allergy testing may help identify common comorbid conditions such as AR, which when treated appropriately can improve asthma control.

Testing for aeroallergen sensitization may be particularly helpful in confirming 2 or more coexisting sensitizations (polysensitization). Subjects with polysensitized phenotypes have frequent multimorbidity, with severe and persistent disease, and therefore require more health care resources.[35] In the 3-year TENOR study of children aged 6 to 12 years, there was a direct relationship between the number of allergens to which participants were sensitized and rates and severity of exacerbations, and associated deterioration in quality of life.[36] Children with a higher number of allergic triggers had a longer duration of asthma and a higher prevalence of atopic dermatitis and AR. A study of moderate-to-severe, exacerbation-prone asthma found that the average number of inhalant sensitizations for school-age children was 14 positive results of the 22 allergens tested (68%).[19]

Identifying sensitizations in allergic phenotypes may also help guide AIT for asthma prevention.[37] Published longitudinal studies suggest that children with AR are at high risk of becoming asthmatic and AIT may prevent the development of asthma.[38] Early referral has positive outcomes for the patient.[39] Yet most allergic children are not receiving AIT because of lack of awareness at the primary care level, a lack of testing for aeroallergen sensitization, and no referral to an asthma/allergy specialist.

TABLE II. The modified Asthma Predictive Index (mAPI)[32]

Stringent API: ≥4 episodes of wheezing per year during the first 3 y of life and	
• At least 1 major criterion or	
•At least 2 minor criteria	
Major criteria	**Minor criteria**
1. Parental physician-diagnosed asthma	1. Wheezing unrelated to colds, reported by the parents
2. Physician-diagnosed atopic dermatitis	2. Peripheral eosinophilia ≥4% in circulation
3. Allergic sensitization to at least 1 aeroallergen	3. Allergic sensitizations to milk, egg, or peanuts

TABLE III. Barriers to implementing asthma management strategies[47]

Health care providers
• Insufficient knowledge of guideline recommendations
• Lack of agreement with or confidence in recommendations
• Resistance to change
• External barriers (organizational, policies, cost)
• Lack of time and resources
• Medical-legal issues
People with asthma
• Low health literacy
• Insufficient understanding of asthma and its management
• Lack of agreement with recommendations
• Cultural and economic barriers
• Peer influence
• Attitudes, beliefs, preferences, fears, and misconceptions

Patients with severe or poorly controlled asthma

GINA and the European Respiratory Society/American Thoracic Society guidelines on severe asthma specifically recommend sIgE or SPT for relevant allergens if not already done as part of the assessment of comorbidities and phenotyping for those with severe asthma.[13,15] The NICE guidelines call for specific allergy testing for patients with difficult-to-control asthma, and the recently published EAACI guidelines on the management of severe asthma with biologics recommend as a first step characterization of the patients with biomarkers including sIgE.[25]

Patients with mild-to-moderate asthma

Changes in GINA for 2019 included a call for renewed vigilance in managing patients with mild-to-moderate asthma.[12] Although exhibiting less severe symptoms, this population still experiences severe exacerbations (0.12-0.77 per patient-year), represents 30% to 40% of emergency consultations, and accounts for 15% to 20% of asthma deaths per year.[40] Symptom control and risk reduction are long-term goals of asthma treatment and certainly apply to this subpopulation. One concern is that patients who feel good may discontinue their controller medication. GINA cautions that stopping controller medication increases the risk of serious flare-ups.[12] The causes of these exacerbations in this patient population are not all well known but certainly include aeroallergen sensitization and sudden massive exposure to allergens, as evidenced by thunderstorm asthma in Australia.[41]

The European Community Respiratory Health Survey group recently reported that atopy modifies the association between inhaled corticosteroid (ICS) use and lung function in adults aged 20 to 44 years with asthma.[42] As stated above, they also found that biomarkers of atopy can predict a more favorable long-term response to ICS and concluded that allergy tests could be useful T2 phenotype biomarkers for clinical decisions regarding asthma therapy.

HOW DOES sIgE TESTING FIT INTO WORKFLOW?

The rationale for using inhalant aeroallergen sensitization testing

sIgE testing can be a valuable tool in primary care especially when done in consultation with a specialist, whereas allergy skin testing might be better performed by an allergist. Compelling reasons to incorporate specific allergy testing into asthma management include:

- Patterns of aeroallergen sensitization help in defining asthma phenotypes.
- Allergy test results can guide clinical precision medicine for chronic airway disease in individual patients, including AIT.
- Negative allergy test results prompt a search for other causes of symptoms.
- Known aeroallergen sensitizations stimulate recommendation of environmental remediation advice and AIT when appropriate.
- Testing will address common patient concerns about allergy, predicting exacerbations and response to therapies, and possibly increase compliance with therapy.
- Positive allergy test results can be considered as one of the referral criteria for specialist care.

Value of negative results for aeroallergen sensitizations

Negative sIgE test results are useful in developing personalized treatment plans, not least because they spare patients the inconvenience of attempts at avoiding allergens to which they are not sensitized, of taking medications that are ineffective (eg, antihistamines), and spending money unnecessarily. For example, the pet owner with asthma who is not sensitized to pet allergens may have fewer symptoms than pet-sensitized patients who have more severe symptoms but no immediate exposure. Moreover, negative test results should lead to additional investigation of the underlying causes of symptoms and might help better define the asthma phenotype, thereby providing a more rational therapeutic plan.

Recommendations for personalized asthma treatment

A personalized asthma treatment plan is foundational to addressing the patient's individual conditions according to NICE.[14] As an incurable disease, asthma should be managed by "reducing exposure to known triggers if possible, relief of symptoms if there is airway narrowing, and reduction in airway inflammation by regular preventive treatment."

Except in occupational asthma, environmental allergen avoidance for sensitized patients is difficult to achieve and often not completely effective; however, exposure for known aeroallergen sensitizations can sometimes be mitigated. For example,

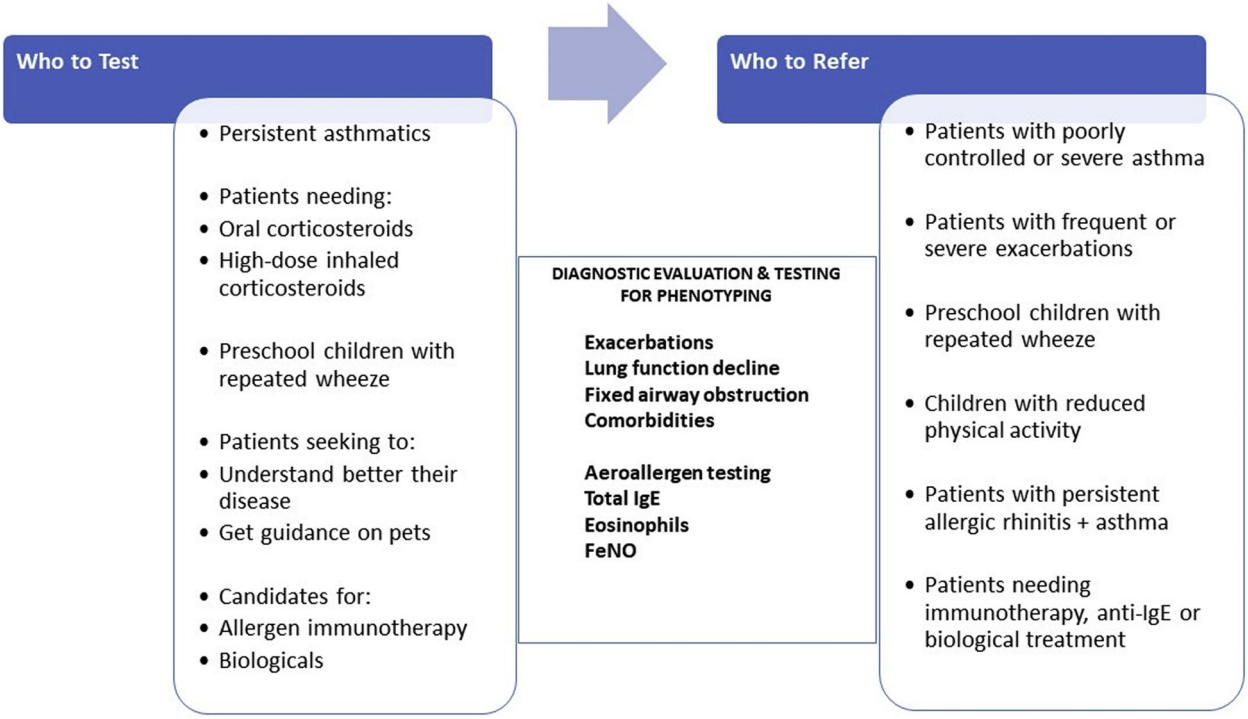

FIGURE 1. Pragmatic approach to aeroallergen testing and referral to asthma specialists. *FeNO,* Fractional exhaled nitric oxide.

thunderstorm grass pollen asthma can be managed by grass pollen immunotherapy,[43] and GINA recommends AIT for patients with mild asthma and AR due to HDM.[13] Similarly, a patient allergic to cats may elect not to have one in the house, or at least not to allow the animal to enter the bedroom. Strict hygiene measures can also be taken (including washing clothes that have been near the animal), although asthma severity can still be affected by continuing allergen exposure over time.[13]

A recent review from the Agency for Healthcare Research and Quality that was used to inform updated National Asthma Education and Prevention Program clinical practice guidelines drew the following conclusions about allergen avoidance and asthma: evidence for single interventions designed to reduce indoor allergen exposure on asthma outcomes is lacking; multicomponent interventions may improve some asthma outcomes, but it is unclear if specific combinations are more effective than others; and multicomponent interventions that include high-efficiency particulate air-filtration vacuums or pest control reduce exacerbations and improve quality of life. However, the authors concluded that the evidence for both single and multicomponent interventions does not address many other important outcomes, including asthma-related health care utilization, pulmonary physiology, and asthma-related quality of life.[44,45]

HOW CAN OPTIMIZED ASTHMA/ALLERGY MANAGEMENT BE IMPLEMENTED?

The increasing prevalence of allergy and the complexity of managing asthma complicate plans to implement best practices in caring for asthmatic patients in primary care.[46] Table III lists some of the barriers to implementing optimal asthma management.[47] Awareness about the relevance of evaluating aeroallergen sensitizations in asthmatic patients is a key step in improving asthma/allergy care. Knowing which patients to test and which aeroallergens to test for is also vital (Figure 1). Interpreting test results and applying them clinically is more challenging. To that end, asthma and allergy specialists have created helpful algorithms[6,14] and provided guidance on appropriate referral criteria.[48] These recommendations and tools make asthma management more efficient, given the time constraints in crowded primary settings and the more intensive management available in asthma.

CONCLUSIONS

Establishing a diagnosis of asthma and determining whether there is an allergic component are fundamental to an effective asthma clinical management plan. Blind reliance on escalating doses of ICS or bronchodilators ignores the underlying pathophysiology of asthma and the importance of aeroallergen sensitization in inflammation and susceptibility to respiratory viruses that underlie disease persistence, exacerbation, and poor control. Instead, more precise and effective individualized treatment relies on systematic investigation of a patient's history of exposure and symptoms, combined with physical examination and appropriate testing (Figure 1).

Moreover, moving from severity-based to phenotype-based asthma care can change the trajectory of asthma and allergic diseases, as demonstrated with timely diagnosis of aeroallergen sensitizations and intervention in very young children. Most importantly, optimal asthma/allergy management can improve patient outcomes. AIT, the only immunomodulating therapy for allergic asthma, requires sIgE testing. Biologics that are now under development may expand the number of patients who can benefit from treatment.[27] In moving beyond a control-based

treatment plan for asthma, the Lancet Commissions call for "at least one primary prevention strategy for high-risk children and one disease-modifying intervention for children and adults to be identified."[26]

The barriers to adopting guideline-recommended diagnosis and management of allergic asthma are mostly logistical. Many primary care clinicians lack knowledge of the value of sIgE testing in determining asthma phenotype and tailoring an individualized treatment plan. Thus, the need for generalist education is pressing, especially as new diagnostic tools and medications become available. Aeroallergen sensitization testing by nonspecialists requires an understanding of the clinical relevance of positive and negatives tests, knowledge of effective environmental control measures, and referral to a specialist when AIT is considered. Therefore, clinical guidance and support by asthma/allergy specialists remain vital, especially in sIgE test interpretation and providing AIT. Other barriers, such as cost, lack of time, and medical system resources, deserve attention in light of the improved outcomes for patients. Testing in some places has been driven by patients, who want to understand their condition and find relief from their allergy/asthma symptoms.

Finally, an area of future study is to define whether molecular component diagnostics will improve the accuracy of identifying clinically significant allergy for asthmatics as well as better guide therapeutic choices (ie, component-directed AIT).

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REFERENCES

1. World Health Organization (WHO). Asthma Q&A. 2019. Available from: https://www.who.int/news-room/q-a-detail/asthma. Accessed March 19, 2020.
2. Global Burden of Disease 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1211-59.
3. The American Academy of Asthma, Allergy, and Immunology (AAAAI). Allergy statistics: general allergy. Available from: https://www.aaaai.org/about-aaaai/newsroom/allergy-statistics. Accessed July 7, 2020.
4. Yawn BP, Rank MA, Cabana MD, Wollan PC, Juhn YJ. Adherence to asthma guidelines in children, tweens, and adults in primary care settings: a practice-based work assessment. Mayo Clinic Proc 2016;91:411-21.
5. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. J Allergy Clin Immunol 2007;120(Suppl): S94-138.
6. Demoly P, Chabane H, Fontaine JF, Boissieu D, Ryan D, Angier E, et al. Development of algorithms for the diagnosis and management of acute allergy in primary practice. World Allergy Organ J 2019;12:100022.
7. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, et al. Practical guide to skin prick tests in allergy to aeroallergens. Allergy 2012;67:18-24.
8. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2020. Available from: https://ginasthma.org/gina-reports/. Accessed July 9, 2020.
9. British Thoracic Society. BTS/SIGN British guideline on the management of asthma. 2016. Available from: https://www.brit-thoracic.org.uk/document-library/guidelines/asthma/btssign-guideline-for-the-management-of-asthma-2019/. Accessed January 18, 2017.
10. Lougheed MD, Leniere C, Ducharme FM, Dell SD, Rowe BH, FitzGerald M, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults: executive summary. Can Respir J 2012;19:e81-8.
11. Agache I, Ryan D, Rodriguez MR, Yusuf O, Angier E, Jutel M. Allergy management in primary care across European countries—actual status. Allergy 2013;68:836-43.
12. Global Initiative for Asthma (GINA). What's new in GINA 2019? [slide program]. 2019. Available from: www.ginasthma.org. Accessed March 19, 2020.
13. Global Initiative for Asthma (GINA). GINA implementation toolbox. 2018. Available from: www.ginasthma.org. Accessed March 14, 2020.
14. National Institute for Health and Care Excellence (NICE). Asthma: diagnosis, monitoring and chronic asthma management (NG80). 2017. Available from: https://www.nice.org.uk/guidance/ng80. Assessed March 13, 2020.
15. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
16. National Institutes of Health (NIH). Guidelines from the National Asthma Education and Prevention Program (EPR-3). Asthma Care Quick Reference. Bethesda, MD: National Institutes of Health; 2012.
17. European Academy of Allergy and Clinical Immunology. AIT guidelines. Available from: https://medialibrary.eaaci.org/mediatheque/media.aspx?mediaId=60223&channel=8518. Accessed June 9, 2020.
18. Mushtaq A. Asthma in the USA: the good, the bad, and the disparity. Lancet Respir Med 2018;6:335-6.
19. Pongracic JA, Krouse RZ, Babineau DC, Zoratti EM, Cohen RT, Wood RA, et al. Distinguishing characteristics of difficult-to-control asthma in inner-city children and adolescents. J Allergy Clin Immunol 2016;138: 1030-41.
20. Zoratti EM, Krouse RZ, Babineau DC, Pongracic JA, O'Connor GT, Wood RA, et al. Asthma phenotypes in inner-city children. J Allergy Clin Immunol 2016; 138:1016-29.
21. Liu AH, Martinez FD. Natural history of allergic diseases and asthma. In: Szefler SJ, Bonilla FA, Akdis CA, Sampson H, Leung DYM, editors. Pediatric Allergy: Principles and Practice. 3rd ed. Philadelphia, PA: Elsevier, Inc.; 2016.
22. Patel MR, Song PXK, Bruzzese JM, Hao W, Evans D, Thomas LJ, et al. Does cross-cultural communication training for physicians improve pediatric asthma outcomes? A randomized trial. J Asthma 2019;56:273-84.
23. Mitchell SJ, Bilderback AL, Okelo SO. Racial disparities in asthma morbidity among pediatric patients seeking asthma specialist care. Acad Pediatr 2016;16:64-7.
24. Fitzpatrick AM, Bacharier LB, Jackson DJ, Szefler SJ, Beigelman A, Cabana M, et al. Heterogeneity of mild to moderate persistent asthma in children: confirmation by latent class analysis and association with 1-year outcomes. J Allergy Clin Immunol Pract 2020;8:2617-27.
25. Agache I, Akdis C, Akdis M, Canonica GW, Casale T, Chivato T, et al. EAACI Biologicals Guidelines—recommendations for severe asthma [published online ahead of print June 2, 2020]. Allergy. https://doi.org/10.1111/all.14425.
26. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet 2018;391:350-400.
27. Bardin PG, Price D, Chanez P, Humbert M, Bourdin A. Managing asthma in the era of biological therapies. Lancet Respir Med 2017;5:376-8.
28. Wu W, Bang S, Bleecker ER, Castro M, Denlinger L, Erzurum SC, et al. Multiview cluster analysis identifies variable corticosteroid response phenotypes in severe asthma. Am J Respir Crit Care Med 2019;199:1358-67.
29. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ Jr, Calatroni A, et al. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. J Allergy Clin immunol 2015;136: 1476-85.
30. Liu A, Luskin A, Brown R, Cabana MD, Emanuel I, Fromer L, et al. The practical application of allergic trigger management to improve asthma outcomes: step 1: identify patients with allergic components of asthma. J Fam Pract 2018;Sept:S5-13.
31. Global Initiative for Asthma (GINA). GINA 2018 Update. Available from: http://www.ginasthma.org/. Accessed June 9, 2020.
32. Chang TS, Lemanske RF Jr, Guilbert TW, Gern JE, Coen MH, Evans MD, et al. Evaluation of the modified Asthma Predictive Index in high-risk preschool children. J Allergy Clin Immunol Pract 2013;1:152-6.
33. Iordanidou M, Loukides S, Paraskakis E. Asthma phenotypes in children and stratified pharmacological treatment regimens. Expert Rev Clin Pharmacol 2017;10:293-303.
34. Guilbert TW, Morgan WJ, Krawiec M, Lemanske RF Jr, Sorkness C, Szefler SJ, et al. The Prevention of Early Asthma in Kids study: design, rationale and

methods for the Childhood Asthma Research and Education network. Control Clin Trials 2004;25:286-310.
35. Anto JM, Bousquet J, Akdis M, Auffray C, Keil T, Momas I, et al. Mechanisms of the development of allergy (MeDALL): introducing novel concepts in allergy phenotypes. J Allergy Clin Immunol 2017;139:388-99.
36. Chipps BE, Haselkorn T, Rosen K, Mink DR, Trzaskoma BL, Luskin AT. Asthma exacerbations and triggers in children in TENOR: impact on quality of life. J Allergy Clin Immunol Pract 2018;6:169-176.e2.
37. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sørensen HF, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. J Allergy Clin Immunol 2018;141:529-38.
38. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, et al. EAACI guidelines on allergen immunotherapy: prevention of allergy. Pediatr Allergy Immunol 2017;28:728-45.
39. Humbert M, Bourdin A, Papadopoulos NG, Holgate ST, Hanania NA, Halpin DMG, et al. Reducing the hidden burden of severe asthma: recognition and referrals from primary practice [published online ahead of print May 13, 2020]. J Asthma. https://doi.org/10.1080/02770903.2020.1759084.
40. Dusser D, Montani D, Chanez P, de Blic J, Delacourt C, Deschildre A, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy 2007;62:591-604.
41. Thien F, Beggs PJ, Csutoros D, Darvall J, Hew M, Davies JM, et al. The Melbourne epidemic thunderstorm asthma event 2016: an investigation of environmental triggers, effect on health services, and patient risk factors. Lancet Planet Health 2018;2:e255-63.
42. Marcon A, Marchetti P, Antó JM, Cazzoletti L, Cerveri I, Corsico A, et al. Atopy modifies the association between inhaled corticosteroid use and lung function decline in patients with asthma. J Allergy Clin Immunol Pract 2020;8:980-988.e10.
43. O'Hehir RE, Varese NP, Deckert K, Zubrinich CM, van Zelm MC, Rolland JM, et al. Epidemic thunderstorm asthma protection with five-grass pollen tablet sublingual immunotherapy: a clinical trial. Am J Respir Crit Care Med 2018; 198:126-8.
44. Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Lynch MP, Kaczmarek JL, et al. Effectiveness of indoor allergen reduction in asthma management: a systematic review. J Allergy Clin Immunol 2018;141:1854-69.
45. Leas BF, D'Anci KE, Apter AJ, Bryant-Stephens T, Schoelles K, Umscheid CA. Effectiveness of indoor allergen reduction in management of asthma. Rockville, MD: Agency for Healthcare Research and Quality (US); 2018.
46. Flokstra-de Blok BM, van der Molen T, Christoffers WA, Kocks JW, Oei RL, Oude Elberink JN, et al. Development of an allergy management support system in primary care. J Asthma Allergy 2017;10:57-65.
47. Global Initiative for Asthma (GINA). Pocket guide for implementing asthma management strategies into health care 2018. Available from: https://ginasthma.org/wp-content/uploads/2019/02/GINA-Implementation-Pocket-Guide-2019.pdf. Accessed March 13, 2020.
48. Price D, Bjermer L, Bergin DA, Martinez R. Asthma referrals: a key component of asthma management that needs to be addressed. J Asthma Allergy 2017;10:209-23.