

Clinical Importance of Identifying Immunoglobulin E-Mediated Disease in Patients With Asthma

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The strong association between allergy and asthma is well documented; however, few practitioners—even asthma specialists—accurately estimate the percentage of patients with asthma who have clinically relevant allergies. Because allergen exposure can prompt airway inflammation, trigger asthma exacerbations, and possibly lead to negative health outcomes for patients with asthma, identifying allergies and immunoglobulin E (IgE)-mediated disease in patients with persistent asthma is crucial. Updated Expert Panel 3 asthma guidelines from the National Asthma Education and Prevention Program reinforce the need for clinicians to identify allergic sensitivities in patients with persistent asthma and determine their clinical relevance. Allergy testing can be useful in educating the patient with IgE-mediated asthma about the need for allergic trigger avoidance and can help determine optimal therapy for patients with concomitant asthma and allergy. Implementing this guideline recommendation, however, requires active clinical engagement. Data from a recent observational study indicate that there may be a substantial gap between guideline recommendations and actual clinical practice. These data also suggest that when clinicians participate in education about the role of IgE in asthma and begin testing their patients for allergy, the recognition of allergies among patients with asthma dramatically increases. (*Clinical Cornerstone*. 2009;9[4]:20–29) © 2009 Elsevier. All rights reserved.

ATOPY, ALLERGY, AND ASTHMA: AN INTRODUCTION

For patients, and even for many clinicians, the term “allergy” has been most strongly associated with symptoms of the nose and eyes. Perhaps this can be attributed to the immediately recognizable effects of the allergic process on the ocular surface and upper respiratory tract. Allergic processes mediated by immunoglobulin E (IgE) also play a fundamental role in the development and persistence of lower airway inflammation and asthma,¹ a role that is increasingly recognized and supported by clinical evidence and treatment guidelines. Because the presence of allergy has been linked to negative health outcomes for many patients with asthma, successful long-term management of asthma requires that clinicians be able to identify and address allergic disease in patients with persistent asthma. In this article, the role of IgE-mediated disease

in asthma will be considered, and practical guidance on how to incorporate allergy testing in the management of persistent asthma will be provided. We will also review the results of a recent study conducted by the Respiratory & Allergic Disease (RAD) Foundation that underscore the importance of allergy testing for patients with persistent asthma.

Atopy and atopic disease represent an increasingly significant public health problem in the United States and other Western countries. The World Allergy Organization defines atopy as “a personal and/or familial tendency, usually expressed in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens.”² As a consequence of this tendency, atopic individuals are at risk for developing IgE-mediated allergic diseases, including asthma, rhinoconjunctivitis, and eczema.

IgE-MEDIATED ASTHMA IS HIGHLY PREVALENT

The prevalence of atopy and asthma is quite high, both in the United States and around the world. In the United States, allergic diseases affect 40 to 50 million individuals,³ and the worldwide incidence of allergic diseases such as asthma has about doubled in the past 2 to 3 decades.⁴ Asthma alone affects >22 million individuals in the United States, or approximately 7% of the US population.⁵ The prevalence of asthma increased by 74% from 1980 to 1996 and it continues to rise.⁶

The high prevalence of asthma and allergy is not surprising to clinicians who routinely treat patients with allergic and respiratory diseases. The strong association between asthma and allergy and its clinical implications, though, also must be considered. Patients with asthma are more likely to have relevant allergies than are individuals without asthma: approximately 60% of patients with asthma have IgE-mediated disease, and among children with asthma, a staggering 90% are atopic.^{4,7}

KEY POINT

Approximately 60% of patients with asthma have IgE-mediated disease, and among children with asthma, a staggering 90% are atopic.

The substantial prevalence of concomitant asthma and allergy has clinical implications that are stressed in the 2007 Expert Panel 3 (EPR-3) asthma guidelines from the National Asthma Education and Prevention Program (NAEPP).⁸ For example, symptoms of IgE-mediated asthma can be exacerbated by exposure to an allergen to which the patient has been sensitized. Moreover, the presence of allergy also has been linked to increased airway hyperresponsiveness, exacerbations, and health care costs for patients with asthma.^{8,9} Therefore, successful long-term management of persistent allergic asthma requires clinicians to both identify and address atopy in patients and help them reduce their exposure to relevant allergens.⁸ Because almost half of patients with asthma are cared for by primary care physicians,¹⁰ it is important that the primary care community understand the basics of aller-

gy testing and how to integrate allergy detection and management into the treatment of persistent allergic asthma.

IgE Plays an Important Clinical Role in Asthma

IgE is the antibody that mediates allergic reactions (see sidebar). Human IgE is a highly complex molecule, with a variable region that contains infinitely variable amino acid sequences. These hypervariable regions are known as complementary determining regions. The variable region is designed to bind to specific components (or epitopes) of the allergen after exposure to an allergen. Upon reexposure to the allergen, the IgE antibody will bind, and if bound to the mast cell, cause release of inflammatory mediators.¹ The Fc region of the IgE molecule cannot bind to the antigen, but it determines the biologic function because it binds to receptors on various cells via the region known as Cε3 (**Figure 1**).

Epidemiologic studies have confirmed the role of atopy and IgE in the development of airway inflammation and asthma by demonstrating a clear association between IgE and the pathogenesis and symptoms of respiratory disease.^{11,12} Evidence suggests that increased serum IgE is associated with an increased incidence of asthma, persistent wheezing in children, and airway hyperresponsiveness during in vivo challenges and in vitro studies.¹³ Moreover, the prevalence of IgE-associated asthma increases with age, whereas the prevalence of nonatopic wheezing tends to decline.¹⁴

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ASTHMA GUIDELINES: WHO SHOULD BE TESTED FOR ALLERGIES?

Because allergen exposure can increase asthma severity and precipitate exacerbations, it is important to identify

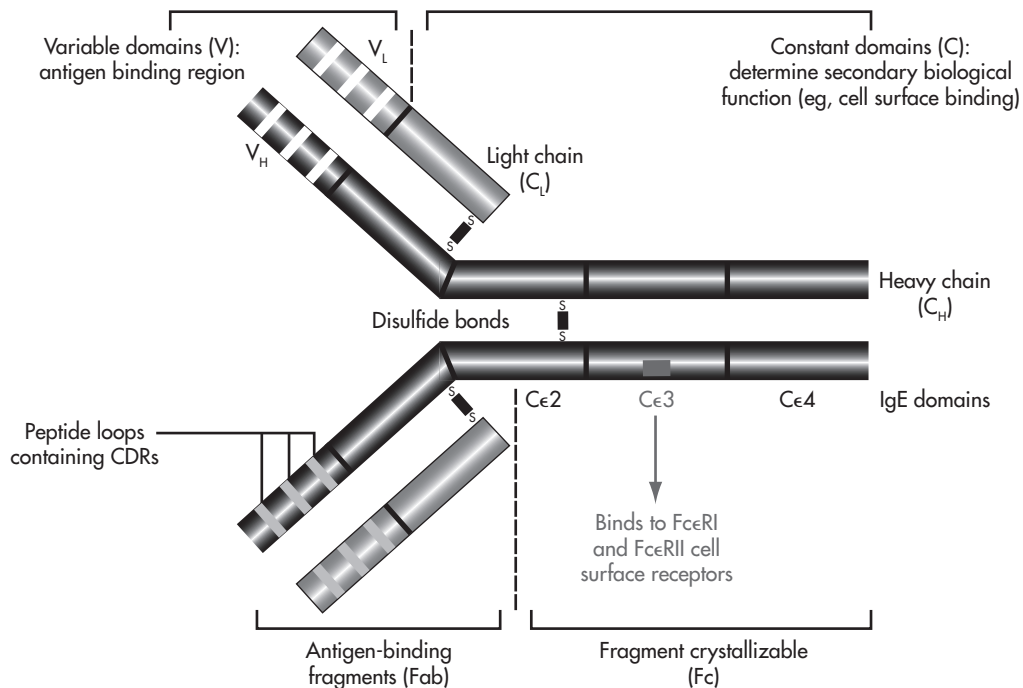


Figure 1. Human immunoglobulin E (IgE). CDR = complementary-determining regions. Reprinted with permission from the Respiratory & Allergic Disease Foundation. © 2007.

IgE: The Antibody That Mediates Allergic Reactions

IgE is produced by IgE-secreting plasma cells and β cells subsequent to initial allergen exposure, sensitization, and reexposure. IgE is normally present in the serum at very low levels, but it can be significantly elevated in atopic patients.¹⁵ Despite its low concentration, IgE is very biologically active, binding to high-affinity receptors found on mast cells and basophils. When IgE binds to these receptors, it triggers the release of inflammatory mediators involved in the allergic response.

Patients with asthma typically have higher levels of IgE than do individuals without asthma, as demonstrated in a study by Wittig et al.¹⁶ These investigators found that mean IgE levels were nearly 10 times higher in patients with asthma and >30 times higher in patients with asthma and eczema than in the healthy population.¹⁶ In addition, a landmark study by Burrows et al.¹¹ evaluating the relationship between asthma and serum IgE (N = 2657) demonstrated that the risk of asthma increased in a linear fashion with IgE levels (**Figure 2**). Finally, it is important to recognize that even with normal total IgE levels, allergen-specific IgE levels can be very high and contribute to the pathogenesis of allergic diseases.

patients with allergic asthma and the allergens to which they are sensitized to optimize asthma control. Identifying and controlling asthma triggers is a critical component of asthma management. According to the EPR-3 guidelines, clinicians should evaluate the potential role of allergens in all patients with persistent asthma.⁸ The role of indoor inhalant allergens is particularly important to consider. This recommendation is one of the Expert Guidelines Implementation Panel's 6 core recommenda-

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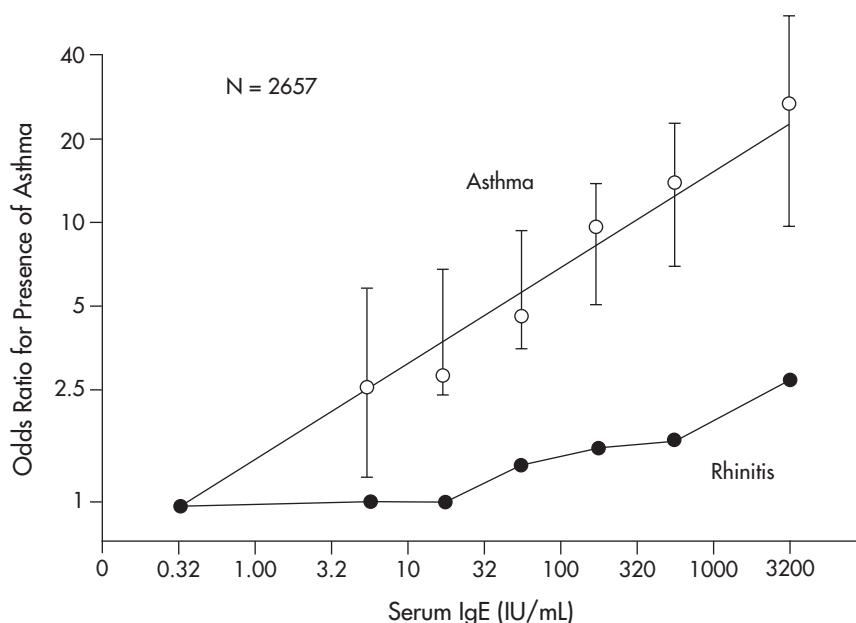


Figure 2. Association between serum immunoglobulin E (IgE) level and the risk of asthma and rhinitis (N = 2657). Reprinted with permission from Burrows B, Martinez FD, Halonen M, et al. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med.* 1989;320:271–277. © 2008 Massachusetts Medical Society. All rights reserved.

tions, which emphasizes the fundamental role of investigating these potential triggers in clinical practice.

To evaluate the impact of allergens on a patient's asthma, the clinician should first take a detailed medical history to identify the triggers that may exacerbate the patient's asthma. Determining sensitivity to a specific allergen usually is not possible by medical history alone, however. For example, patients may not be aware that a cat dander allergy is exacerbated when they come in contact with schoolmates or colleagues who have cats at home. For this reason, the EPR-3 guidelines stress that allergy testing is the only reliable way to determine a patient's sensitivity to perennial indoor allergens.⁸

If an allergy is suspected, objective measures such as IgE skin testing or specific IgE in vitro assays should be used to determine a patient's sensitivity to the relevant inhalant allergens.⁸ About 80% of the US population is exposed to household dust mites and 60% to cat or dog dander.^{17,18} For patients living in inner cities or in the southern parts of the United States, cockroach sensitivity also may be a common issue.

Allergy skin or in vitro tests can reliably determine the presence of specific IgE, but they cannot determine whether the sensitivity is responsible for a patient's symptoms.⁸ Therefore, clinicians should only test patients for sensitivi-

ty to the allergens to which the patients may be exposed. If patients are sensitive to an allergen, clinicians must determine the clinical relevance of the sensitivity. In other words, clinicians should assess whether and to what extent exposure to the allergen actually triggers or exacerbates symptoms and manage exposure to clinically relevant allergens as appropriate.

What Type of Allergy Testing Is Appropriate?

Although it is strongly recommended that all patients with persistent asthma be tested for allergies, many clinicians who treat asthma are not equipped to conduct allergy testing themselves. Skin testing is usually the best method for identifying allergies (**Table I**); however, it is not always possible to perform skin testing, for several reasons. First, it must be performed by an appropriately trained specialist and generally involves an allergy consultation. Second, because skin testing carries a small risk of anaphylaxis, it must be performed in a medical setting equipped for the treatment of such a reaction. Third, skin testing is not appropriate for patients who are taking antihistamines or other antiallergy medications, those with certain dermatologic diseases, or very young infants. Skin testing also requires considerable time to

TABLE 1. IN VITRO VERSUS IN VIVO TESTING.

	In Vitro High-Quality Test	In Vivo Skin Test
High sensitivity	Yes	Yes
High specificity	Yes	Yes/No
High reproducibility	Yes	No
Quantitative results	Yes	No
WHO calibrated	Yes	No
Quality-assured test program	Yes	No
Can be used independently of pharmaceutical treatment	Yes	No
Can be used independently of patient skin status	Yes	No
Time factor	Weeks	Minutes
Cost factor	Expensive	Inexpensive
Patient understanding	Obscure	Dramatic

WHO = World Health Organization.
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perform—30 to 60 minutes. When the testing is completed, however, results are available immediately.

In contrast, in vitro testing (ie, RadioAllergoSorbent Test [RAST] or CAP RAST) takes very little in-office time—no more than does standard phlebotomy—but its results are usually not available for 1 to 2 weeks. It can be used for patients taking any medication other than anti-IgE therapy, including antihistamines, and it can be used regardless of evident dermatologic disease or patient age. Although it is generally more expensive than skin testing and only available for certain allergens, in vitro testing carries no risk of anaphylaxis and can be performed by nearly all medical personnel. Moreover, assessment of total serum IgE, which is necessary when anti-IgE therapy is being initiated, can be accomplished with in vitro testing; correct interpretation of results, however, is essential to accurate determination of clinical relevance.

If anti-IgE therapy is not being considered, total IgE assessment is of little practical value without specific IgE assessments (Figure 3). Total IgE levels are rarely high when specific IgE titers are not; however, total IgE levels can be low even when a specific IgE level is significantly high. Consequently, total IgE assessments cannot be used to exclude the presence of allergy.

Clinicians should consider how best to implement screening for allergies for patients with persistent asthma. Possible strategies include a referral to an allergist for consultation, implementing in-office in vitro testing,

or some combination of both options. The critical component of this process is taking action to ensure that appropriate patients are screened.

Despite the importance of allergy testing in patients with persistent asthma, some clinicians may resist testing. There may be multiple reasons for this resistance. For example, some clinicians may not be aware of the critical links between IgE-mediated allergic processes and lower airway disease processes. Others may be deterred by perceived logistic barriers. Knowing that a patient with asthma has allergies has significant clinical implications, however, and allergy testing strategies can be implemented efficiently in a wide range of clinical settings.

Why Is Allergy Testing Clinically Important?

Demonstrating a patient’s sensitivity to allergens will allow the clinician to recommend specific environmental

KEY POINT

Although skin testing is considered the best method for identifying allergens, analysis of serum allergen-specific IgE is warranted in many situations.

		Total IgE Reading	
		Negative (normal)	Positive (abnormal, elevated)
Specific IgE Reading	Negative (normal)	Nonallergic Patient	Rare ¹
	Positive (abnormal, elevated)	Allergic Patient	Allergic Patient

Figure 3. Understanding total immunoglobulin E (IgE). ¹American Academy of Allergy, Asthma, & Immunology. *The Allergy Report*. 2000;1:35. Reprinted with permission from the Respiratory & Allergic Disease Foundation. © 2007.

controls to minimize allergen exposure.⁸ Skin or in vitro testing can be particularly useful to educate patients about the role of allergens in their disease and to demonstrate the need for patients to avoid specific allergens. Because recommendations for avoidance are commonly allergen-specific, it is usually possible to convince patients to practice allergen avoidance only after they know which allergens to avoid through the use of skin or in vitro testing.¹⁹

KEY POINT

Skin or in vitro testing can be particularly useful to educate patients about the role of allergens in their disease and to demonstrate the need for patients to avoid specific allergens.

Knowing that a patient with asthma has allergies may help the clinician manage concomitant diseases in that patient. For example, patients with asthma and seasonal allergic rhinitis may benefit from using a leukotriene receptor antagonist alone or in combination with inhaled corticosteroids. Moreover, there is some evidence that the ability of rhinitis to trigger or exacerbate asthma may be alleviated by treating allergic rhinitis.²⁰

Current asthma treatment guidelines stress the need for a multifaceted, comprehensive approach to allergen

avoidance, suggesting that individual steps to avoid allergens are usually ineffective.⁸ If there is clear evidence of a relationship between symptoms and allergen exposure, allergen immunotherapy can be considered. Because there is a risk of anaphylaxis with immunotherapy, the allergen extracts used in immunotherapy should be administered only in a setting in which potentially life-threatening reactions can be treated. Immunotherapy has the added benefit of being the only treatment modality that may halt the progression of rhinitis to asthma.^{21–23}

Immunomodulation as an asthma treatment has been integrated into the EPR-3 guidelines.⁷ Therapies that modulate the effects of IgE in atopic patients have been shown to control asthma symptoms.⁸ For patients whose asthma is inadequately controlled despite a medium dose of inhaled corticosteroid (ICS) and a long-acting inhaled β_2 -agonist or leukotriene receptor antagonist, or those whose asthma is adequately controlled but who are using high-dose ICSs or regularly using oral steroids, anti-IgE therapy with omalizumab may be an effective choice. When given as an add-on therapy with an ICS to patients with moderate to severe allergic asthma, omalizumab significantly reduces asthma exacerbations and can facilitate ICS dose reductions.^{24–27}

RESPIRATORY & ALLERGIC DISEASE FOUNDATION

Because of the importance of IgE-mediated mechanisms in the development and persistence of airway inflammation and asthma symptoms, RAD conducted a study designed under the guidance of Richard Martin, MD, to determine whether a gap exists between evidence-based

recommendations for allergy testing of patients with asthma and actual clinical practice. In this 3-phase observational study involving 100 pulmonary physicians in the United States, RAD evaluated 3 dimensions of practice: the current attitudes and behaviors of pulmonary physicians regarding the observed role of allergy in asthma, the role of allergy in patients with asthma treated in these pulmonary office-based practices, and the potential impact of physician education on clinical practice.

STUDY DESIGN

The first phase of this study, known as the “pretesting phase,” included a survey assessing the practice habits and opinions of the pulmonologists enrolled in the study. Next, enrolled physicians completed a CD-ROM–based educational course and postprogram examination developed by RAD focusing on the role of allergy and IgE in asthma and an examination evaluating their knowledge of the material presented in the educational program.

The second phase of the study involved the testing of adult patients with persistent asthma seen in the participating physicians’ offices. Patients included in the study were either sequentially or randomly chosen and those with histories of past IgE/allergy testing were not excluded. In this phase, patients underwent a kit-based, finger-prick blood test for total serum IgE, as well as for specific allergies to cats, dogs, dust mites, and ragweed; notable exclusions to the allergy panel used in the study included mold, grass, tree pollen, and foods. The physician participants then reviewed the results of the blood tests (which were conducted by a central laboratory) and completed patient history reports for the population who underwent allergy testing.

Finally, in the third phase of the study, after a 60- to 90-day waiting period, physician participants completed a postprogram survey on their current practice habits and opinions. This survey was designed to determine if and how the physician participants’ practice habits had changed after they participated in the educational activity and performed allergy testing.

RESULTS OF PHASE I: BASELINE SURVEY OF PULMONOLOGISTS

Thirty-two pulmonologists completed all phases of the study. Information regarding the patients and practices of the participating physicians was collected using an online survey and results are shown in **Table II**.

TABLE II. RAD STUDY: PARTICIPATING PHYSICIANS’ PATIENTS.

Mean number of outpatients seen on weekly basis	111
Mean percentage of patients with persistent asthma seen weekly	~27%
Mean number of new patients with persistent asthma seen per week	7
Percentage of patients with persistent asthma tested for a specific allergy by history	42%
Percentage of patients with persistent asthma tested for serum IgE level by history	47%
Percentage of patients with persistent asthma thought to have clinically relevant allergy/IgE-mediated disease	27%
Physicians who routinely test all or most patients with persistent asthma for allergy	19%

RAD = Respiratory & Allergic Disease Foundation; IgE = immunoglobulin E. Data courtesy of the Respiratory & Allergic Disease Foundation. © 2007.

Notably, only 20% of all patients seen by participating pulmonologists had received allergy testing. When the physicians were asked what percentage of their patients with persistent asthma they thought had clinically relevant allergy or IgE-mediated disease, the mean response was ~27%.

RESULTS OF PHASE II: SPECIFIC ALLERGY RESULTS

Results from 279 patients were obtained for the 5 common allergens tested. Only 44% of these patients had histories of prior allergy testing, consistent with the results of the physician survey conducted in Phase I of the study. More than half (53%) of these patients tested positive for at least 1 of the allergens that exhibited an allergy of Class 1* or higher; 29% of patients had at least 1 result that indicated a Class 3 allergy or higher.

The mean total serum IgE level among the 283 patients who were tested was 125 kU/L, with a range of <0.1 to 941 kU/L (**Figure 4**). More than half (58.7%) had serum IgE levels >30 kU/L and more than one third (33.9%) had serum IgE levels >100 kU/L.

*The class refers to the severity of the allergy during RAST testing in which Class 0 represents no allergy and Class 5 or higher represents severe allergy.

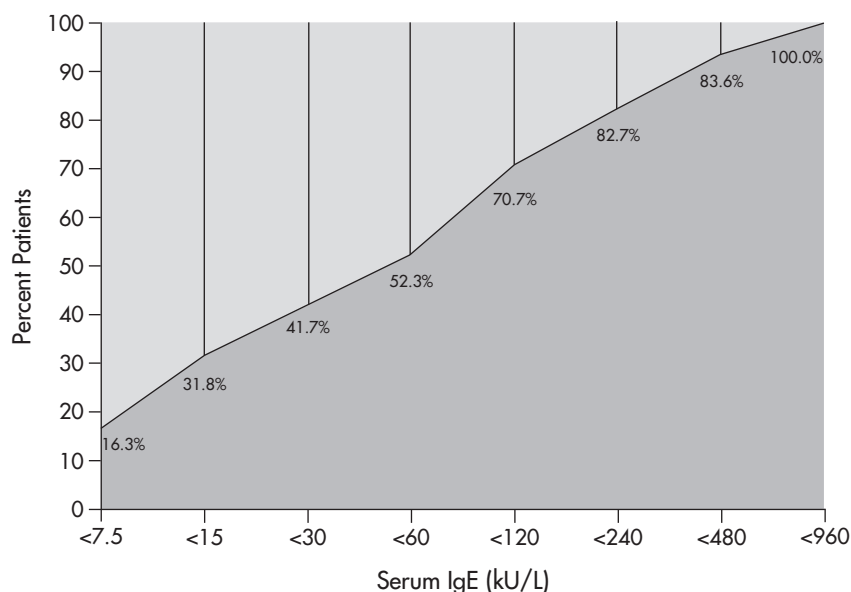


Figure 4. Distribution of serum immunoglobulin E (IgE) levels among patients participating in the Respiratory & Allergic Disease study (N = 283). Reprinted with permission from the Respiratory & Allergic Disease Foundation. © 2007.

After the allergy-testing phase of the study, clinicians were asked to complete patient history and profile reports for the same population who underwent allergy/IgE testing. Once the clinicians completed testing, they suspected that 54% of their patients had 1 or more clinically relevant allergies or elevated total IgE levels (compared with ~27% before the educational intervention and allergy testing). The presence of relevant allergy was associated with negative health outcomes, including hospitalizations in the past 12 months and poor asthma control, and 2 were outcomes associated with reduced quality of life and increased health care costs. Interestingly, poor asthma control and presence of allergy were the only 2 variables that were strongly associated with hospitalization.

These results surprised more than half of the participating pulmonologists: 54% felt that more patients than they expected tested positive for the specific allergens in question, and 52% felt that elevated IgE levels correlated more closely with poor asthma control than they expected.

RESULTS OF PHASE III: THE POSTINITIATIVE PULMONOLOGIST SURVEY

Table III shows the results of the postinitiative survey, which the pulmonologists completed 60 to 90 days after their patients underwent allergy testing. Responses were

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Once the clinicians completed testing, they suspected that 54% of their patients had 1 or more clinically relevant allergies or elevated total IgE levels (compared with about 27% before the educational intervention and allergy testing). The presence of a relevant allergy was associated with negative health outcomes, including hospitalizations in the past 12 months and poor asthma control, and 2 were outcomes associated with reduced quality of life and increased health care costs.

compared with the results from the baseline survey. After participating in the program, pulmonologists were significantly more likely ($P < 0.05$) to order allergy testing, order serum IgE tests, and initiate anti-IgE therapy for patients with asthma. In addition, physician participants

TABLE III. RESULTS OF PREINITIATIVE AND POSTINITIATIVE SURVEY: CHANGES IN CLINICAL PRACTICE AND OPINION.

Question	Preprogram	Postprogram	Relative Change	Significant ($P < 0.05$)
In the past 30 days, for how many patients have you...				
Hospitalized a patient for asthma*	7.6	6.6	-13.2%	NS
Initiated oral systemic steroids*	10.4	10.7	2.9%	NS
Addressed adherence with an asthma patient*	19.8	18.8	-5.1%	NS
Ordered allergy testing for an asthma patient	10.4	12.5	20.2%	$P < 0.05$
Ordered serum IgE test for an asthma patient	10.6	15.6	47.2%	$P < 0.05$
Started a patient on anti-IgE therapy	1.8	2.2	22.2%	$P < 0.05$
Open-ended questions				
If you tested all of your persistent asthma patients for allergies, what percentage would you estimate would have clinically relevant allergies?	26.5%	54.1%	96%	$P < 0.05$
What percentage of your persistent asthma patients do you anticipate testing for allergies at some point in their care?		72.7%	NA	Did not ask before the study

*Control questions; no change was anticipated.

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KEY POINT

After participating in the program, pulmonologists were significantly more likely ($P < 0.05$) to order allergy testing, order serum IgE tests, and initiate anti-IgE therapy for patients with asthma.

estimated that a significantly greater percentage of their patients would have clinically relevant allergies (54.1% vs 26.5%; $P < 0.05$).

Participants were asked to rank their level of agreement or disagreement with several clinical assertions on a scale of 1 (strongly disagree) to 5 (strongly agree) before and after the initiative. Significantly more physicians agreed that nasal symptoms often contribute significantly to asthma (4.1 vs 4.6; $P < 0.05$) and that it is important that patients with persistent asthma be tested for allergies (3.8 vs 4.6; $P < 0.05$).

This study has several limitations. First, much of the data collected were either observational or self-reported.

Further, because of privacy and logistic restrictions, we were unable to link chart and medical information to allergy and IgE tests of individual patients. Finally, there was significant attrition among the participating clinicians, which might be explained either by low baseline interest in the topic among those who did not complete the study and/or a preexisting interest in the topic area among those who did complete the study.

CLINICAL IMPLICATIONS AND CONCLUSIONS

Although the asthma guidelines developed by the NAEPP clearly indicate that IgE and IgE-mediated airway inflammation play a critical role in the development of allergic asthma, the RAD study suggested that the importance of IgE in asthma persistence and control is not always truly accepted by physicians, even among asthma-treating specialists. For example, rates of allergy testing and estimates of the prevalence of allergy among patients with persistent asthma treated by pulmonologists may be low. Once these physicians began conducting allergy testing and, presumably, discussing the results with their patients, however, the importance of allergies seemed to be reinforced, and this continued well past the intervention period. An educational approach that includes a trial of

allergy testing may be a viable behavioral modification technique.

Because of the role of allergies in persistent asthma, all patients with chronic persistent asthma should be questioned thoroughly regarding any history of allergies, undergo specific testing to identify relevant allergies, be educated about how to avoid allergens, and, if indicated, receive allergen immunotherapy or anti-IgE therapy to help control the IgE-driven process.

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