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Using Specific IgE Testing To Optimize Management of Allergic Diseases in the Primary Care Setting

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INTRODUCTION

On a typical mid-winter day, patients with upper respiratory symptoms fill waiting rooms. Viral infections (colds and flu) are immediate suspects, but for some patients, underlying allergy may be adding to the misery. The overlapping signs and symptoms of respiratory and allergic diseases complicate the diagnosis. Moreover, both viral infections and allergies can exacerbate chronic co-existing respiratory conditions, such as asthma. Virtually all patients with allergy-like symptoms see a primary care practitioner first, where identifying atopic patients may not be considered a necessary diagnostic step. In addition, the majority of patients with asthma, regardless of asthma severity or control, are managed in primary care settings. Thus, frontline physicians face the daunting challenge of making a precise diagnosis, which then lays the foundation for appropriate management.[1,2] The increasing specificity of treatments and the current concerns about health care utilization and cost underscore the importance of an accurate diagnosis.

The basic diagnostic and management paradigm for disease has often been overlooked in the case of allergic illness. In diabetes or hypercholesterolemia, for example, the history and physical examination are followed by laboratory testing, which helps confirm the diagnosis and also guides treatment. With respiratory and allergy-like symptoms, laboratory testing is often skipped in favor of pharmacotherapy. However, empiric management seldom uncovers the cause of the patient's symptoms, and may result in overtreatment, ineffective treatment, repeat office visits, and high medication costs.[3] This scenario is unfortunate because diagnostic evidence for immunoglobulin E (IgE)-mediated antibody formation (sensitization) is readily available in the primary care setting in the form of specific IgE (s-IgE) blood testing. Positive results can identify the allergen(s) and quantify the extent of sensitization. Combined with a patient's history and clinical symptoms, s-IgE testing can help confirm the diagnosis. This information, in turn, can be used to individualize treatment, instituting avoidance and control measures when allergic disease exists, and avoiding unnecessary lifestyle

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restrictions, medication, and referrals when it does not.

This article presents the natural history of allergic diseases, explores the rationale for s-IgE testing, and examines how guideline-based treatment of allergy can improve asthma management.

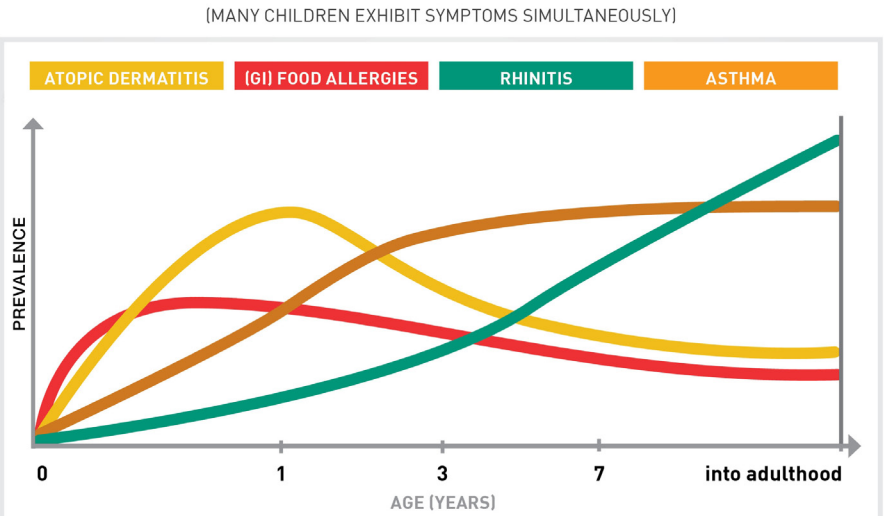
THE NATURAL HISTORY OF ALLERGIC DISEASES

Family physicians manage patients with allergic disease or conditions exacerbated by allergy triggers over the course of a patient's lifetime. During that time, allergic disease can manifest in a variety of ways.[4] The prevalence of IgE-mediated allergic disease at different ages has been captured in a model called the allergic march (**FIGURE 1**).[5]

Formation of IgE antibodies can start early in life, and these antibodies may be detected in the form of sensitivity before any clinical symptoms appear. Food antigens typically have the earliest sensitization, in part because exposure to foods occurs early in life. Babies may develop eczema, specifically atopic dermatitis, as the first sign of sensitization, and this may be followed by gastrointestinal and respiratory symptoms. Sensitization to food antigens frequently precedes problems with inhalant allergens.[6] Eczema and food-related symptoms may actually fade as respiratory symptoms develop.[5] However, young children with atopic dermatitis and a positive family history of asthma have a greater than 40% risk of developing asthma.[6] Indeed, sensitization to food and airborne allergens may foreshadow the development of allergic airway disease.

Not all sensitized children will join the allergic march; 70% of young children with wheeze will have no symptoms at age 10 years.[7] Children who wheeze, but are not sensitized, go into remission more often than those who wheeze and are sensitized.[8,9] Still, once-sensitized children appear to have a greater risk of developing allergic symptoms as adults.[5] Children with high levels of IgE antibodies to specific allergens have a poorer prognosis and greater risk of clinically relevant reactions to those allergens after exposure.

FIGURE 1. Relative Prevalence of Symptoms According to Age[4]



The "allergic march" depicts the prevalence and progression of sensitization and IgE-mediated disease. Atopic dermatitis typically appears first, often the result of sensitization to food allergens. Exposure and sensitization to airborne allergens in early childhood increases the risk of allergic diseases in adulthood.[5] Young children with asthma who are sensitized to food or airborne allergens face increased risk for serious disease compared with children who are not sensitized.

Abbreviations: GI, gastrointestinal; IgE, immunoglobulin E.
Adapted from the World Allergy Organization.[4]
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THE DIAGNOSTIC CHALLENGE—IS IT REALLY ALLERGY?

The risks associated with early sensitization and emergence of clinical symptoms make early diagnosis and management of IgE-mediated disease desirable. Yet allergy-like symptoms are widely mislabeled by patients as well as professionals. A meta-analysis of literature that addressed the prevalence of food allergy found that approximately 75% of children with self-reported food allergy may not have IgE-mediated disease.[10] This misperception frequently results in unnecessary and burdensome dietary restrictions. For physicians, distin-

guishing allergic from nonallergic disease using history and physical examination alone is also imprecise.[3] As many as two-thirds of patients with upper respiratory, allergy-like symptoms may be misdiagnosed, according to a well-designed study in a managed care population.[11] Specific IgE testing facilitates diagnosis and management of allergic or nonallergic diseases in accordance with guideline-based recommendations.

The National Institutes of Health *Guidelines for the Diagnosis and Management of Food Allergy in the United States*[12] and *Guidelines for the Diagnosis and Management of Asthma*[13] support the use of s-IgE blood testing, along with a detailed clinical history and physical examination, to confirm an allergy diagnosis. Patients with clinical symptoms, a suggestive history, and known exposure to potential allergens may be candidates for s-IgE testing. The American College of Allergy, Asthma and Immunology/American Academy of Allergy, Asthma and Immunoogy Joint Task Force provides an overview of allergic diagnostic testing that may also be helpful.[14] For example, in patients whose rhinosinusitis lasts 12 weeks or longer or in patients who fail to improve or whose symptoms are consistent with both allergy and rhinosinusitis, further studies inclusive of s-IgE testing or skin prick testing (SPT) are recommended to differentiate symptom etiology.[15,16] For asthma patients requiring regular medication and whose treatment includes allergen avoidance, confirmation of s-IgE sensitization can be used to provide education about the role of allergens in their symptoms, targeted exposure reduction, prescribed medications, potential referral recommendations, and immunotherapy when indicated.[16]

Strong evidence exists that identifying and reducing exposure to allergic triggers helps relieve symptoms and improve control in rhinitis, asthma, and other allergic diseases, such as eczema.[17-19] Because the negative predictive value of s-IgE testing is high, negative results suggest that nonallergic causes are responsible for the patient's clinical symptoms.[20] Symptom management and selection of efficacious pharmacotherapy depends upon several factors, including the type of rhinitis present. Therapies that are effective for allergic rhinitis may be less effective for other types of rhinitis. Without confirmation of symptom etiology, the patient may bear the expense of medication(s) from which he or she derives no symptom relief. A retrospective study highlights this point: Welsh et al[21] evaluated the medication records of patients who tested negative for allergic rhinitis by s-IgE. More than 50 percent had been prescribed second-generation antihistamines and montelukast sodium, including refills. In cases of suspected food allergy, negative results lower the risk of a supervised food challenge, depending on patient history, and may allow a wider variety of foods in the diet. It is important to note that elevated total serum s-IgE levels in the absence of specific allergen sensitization may also be associated with nonatopic conditions, such as immunodeficiencies, IgE myeloma, drug-induced interstitial nephritis, graft versus host disease, parasitic diseases, and hyper-IgE syndrome.

THE RATIONALE FOR IgE TESTING

In vivo SPT and in vitro blood testing can both detect the presence of s-IgE antibodies (sensitization). Specific IgE test results must be interpreted in the light of allergen exposure, the manifestation and duration of clinical symptoms, and the technical capabilities of the test method.

For more than 100 years allergy specialists have relied on SPT, which exposes mast cells in the skin to potential allergens. In a sensitized patient, this exposure can initiate a complex IgE-mediated inflammatory response within minutes, with histamine released from the exposed mast cells quickly producing a wheal and erythema. The longest diameter of the wheal is measured and its size compared to negative (saline) and positive (histamine) control reactions. SPT came first and no other test was then available, and it became the gold standard for diagnostic allergy testing. However, SPT is not practical in most primary care settings as it requires high-quality, standardized extracts, personnel trained in test administration and interpretation, and carries a small though significant risk of life-threatening anaphylaxis.

The discovery of IgE antibodies more than 40 years ago led to the development of tests that could detect s-IgE antibodies circulating in the blood.[22] Contemporary s-IgE blood testing can be easily accessed and is effective in diagnosing allergy,[23] with relative clinical sensitivity, specificity, positive and negative predictive values, and efficiency comparable to SPT.[24,25] Today, 3 types of s-IgE laboratory assays predominate in the United States, all demonstrating acceptable linearity between their total s-IgE calibration curve and dilution of test sera. The assays differ in format, reagents, and analytic performance, yielding results that may vary by >20% from one another.[25] Of the 3, ImmunoCAP® (Phadia AB Corporation, Thermo Scientific) has been

the most extensively studied and is considered the reference standard for s-IgE measurement.[26,27] As long as physicians are aware of the differences between assays and careful not to generalize test results, s-IgE blood testing is a practical tool for confirming allergic sensitization in the primary care setting.[14]

ImmunoCAP® (Phadia AB Corporation, Thermo Scientific) s-IgE testing uses a single blood sample and evaluates a spectrum of allergic triggers using preselected food and inhalant (indoor/outdoor) antigen profiles. These profiles simplify allergen selection based on typical patterns of clinical allergy. Each profile contains multiple allergens, including grasses, weeds, molds, and trees relevant to a given geographical area, as well as cat and dog dander, 2 types of dust mites, and cockroach. Some of the outdoor allergens exhibit high cross-reactivity, so sensitivity to a selected allergen predicts a high likelihood of clinical reaction to others in the same botanical class.[28] The profiles have been designed to produce high negative and positive predictive value with limited numbers of tested allergens.

A single positive s-IgE result seldom correlates with clinical disease, but the probability of clinically significant disease rises to 75% with 4 or more positive s-IgE tests from a total of 14 common allergens, or a sum of s-IgE >34 kilouints of antibody per liter (kUA/L) to the same allergens.[5] The results of s-IgE testing are reported quantitatively in kUA/L, with the probability of symptoms increasing as s-IgE levels increase.[29]

Of course, the most compelling reason to use s-IgE testing is that it can improve treatment outcomes and the quality of care. That is amply illustrated in the management of patients with asthma who also have allergic triggers.

KNOW MORE…MANAGE ASTHMA BETTER

Asthma currently affects 26 million Americans and costs an estimated $25.6 billion annually, while millions more suffer from undiagnosed asthma.[30] Perhaps just as problematic, approximately 86% of asthmatic patients on medication continue to experience symptoms.[31] Uncontrolled asthma exacts a personal toll on patients, but also comes with a hefty price tag.

Sullivan et al[32] compared the economic burden of severe or difficult-to-treat asthma in patients with uncontrolled or controlled asthma. Eighty-three percent of the study population had uncontrolled asthma, and their medical costs (medications, physician visits, and hospitalization) were more than double those of patients with controlled asthma over a 2-year period. The mean annual cost for an uncontrolled case was $4046 vs $2194 for a controlled case at 2 years. Cisternas et al[33] reported similar findings for disease severity: $2646 for patients with mild asthma and $12,813 for those with severe asthma. The largest direct costs for asthma management are for prescription medicines and office-based visits, amounting to approximately 38% of total expenditure for children and 49% for adults.[34]

Fifty-nine percent of asthmatic adults and up to 90% of asthmatic children have allergic triggers.[35,36] In addition, many patients are polysensitized and unaware of their specific allergic triggers. Specific IgE testing to identify allergic triggers, combined with simple, targeted avoidance measures, can lead to improved outcomes for patients with asthma. This is true because allergic sensitization is cumulative and clinical symptoms only appear after the allergen load exceeds a patient's threshold of tolerance.

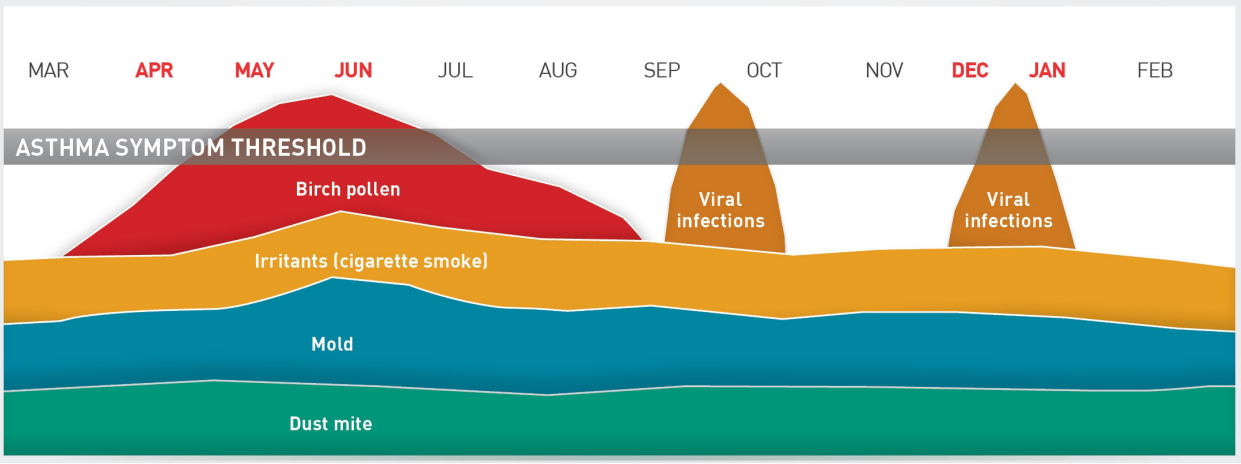
Boner et al proposed the allergic threshold after studying asthmatic children who moved back and forth between a low-altitude, allergen-rich environment and a high-altitude, allergen-free environment.[37,38] At high altitudes their serum levels of total IgE fell, eosinophil activation abated, pulmonary function improved, and they required less medication. The allergen load is dynamic; perennial allergens, irritants (eg, smoking or perfume), and viral infections (colds and flu) can all push patients beyond their asymptomatic threshold. Usually the most recent allergen is blamed and thought to be the sole cause for symptoms. **FIGURE 2** illustrates how birch pollen and viral infections can precipitate clinical symptoms in an asthmatic patient affected by cigarette smoke, mold, and dust mite sensitization.

Numerous studies have documented the benefits of targeted reduction in the cumulative allergen load. Eggelston[39] summarized the evidence for control of environmental allergens (eg, dust mite, animal, cockroach, and fungi) and recommended practical reduction methods over a decade ago. One study demonstrated that targeted reduction compared favorably with use of low-dose inhaled corticosteroids or leukotriene modifiers.[40]

In 2003, Halken et al[41] conducted a prospective, double-blind, placebo-controlled study to determine whether mattress and pillow casings could effectively control dust-mite allergen levels and reduce the need for asthma medication in children diagnosed with asthma and house dust mite allergy. The treatment group significantly decreased the dose of inhaled

FIGURE 2. Asthma Symptom Threshold Before and After Exposure Reduction[4]

BEFORE TRIGGER EXPOSURE REDUCTION



Allergic sensitization is cumulative, with clinical symptoms appearing after the allergen load exceeds a patient's threshold of tolerance. In this case, birch pollen and viral infections, added to underlying cigarette smoke, mold, and dust mite sensitization, caused asthma symptoms.

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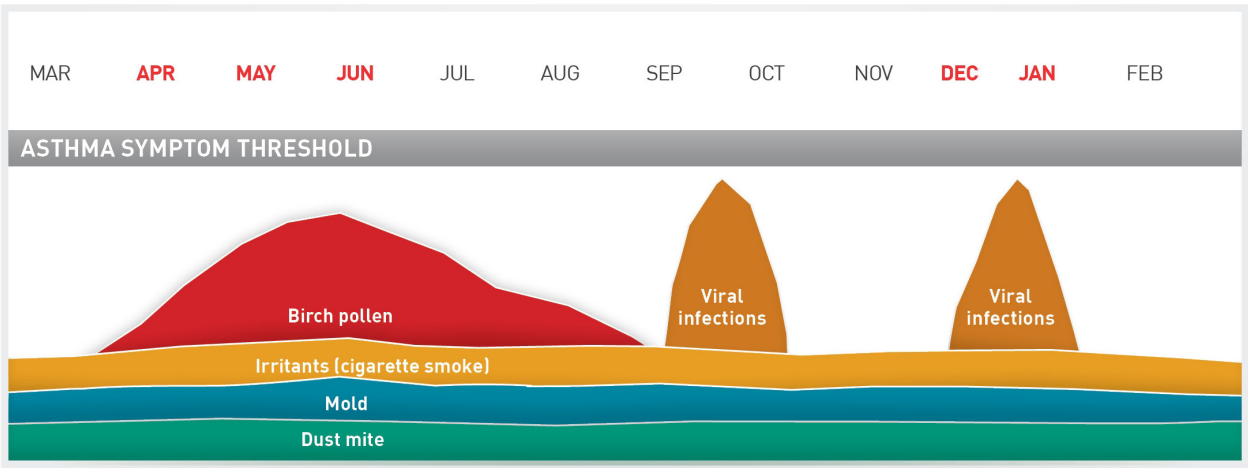
AFTER TRIGGER EXPOSURE REDUCTION



Targeted reduction of exposure to dust mite and mold allowed this patient to remain below the symptomatic threshold, despite exposure to perennial birch pollen and seasonal viral infections

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steroids (from a mean 408 to 227 μg/d; $P < .001$), and after one year, the dose was decreased by at least 50% in significantly more children in the treatment group than in the placebo group (73% vs 24%, respectively; $P < .01$).

Morgan et al[17] compared environmental intervention tailored to allergic sensitization and allergen-avoidance (intervention group) with home visits and no allergen-avoidance (control group) in a group of inner city children with allergic asthma. Patients in the intervention group experienced 21.3 fewer days per year with asthma symptoms than the control group, 32 fewer days of wheezing over 2 years, a 13.6% reduction in unscheduled office visits, and fewer emergency

department visits and hospitalizations. The overall effect of intervention was similar to therapy with inhaled corticosteroids.

Janson et al[18] studied a group of adults with moderately severe asthma who were given an individualized action plan for environmental control based on allergy testing. Treatment reduced nighttime awakenings and resulted in more symptom-free days, less use of beta agonist rescue therapy, consistently better inhaled corticosteroid adherence, and improved asthma control.

These results support the benefits of reducing exposure to allergens as pictured in **FIGURE 2**. In this example, environmental control of dust mite and mold allows the patient to remain below the symptomatic threshold despite exposure to perennial birch pollen and seasonal viral infections. It should be noted, however, that targeted reduction only works if the targets are identified and the patient understands how to reduce exposure.

REDUCING THE COST OF ALLERGIC DISEASE

Targeted exposure reduction may help reduce asthma symptoms and, therefore, the need for costly medication.[39,42] Better asthma control may also mean fewer lost days of work or school, fewer symptomatic days (which can cost as much as $126.71/day), and savings due to fewer unplanned doctor/emergency department visits, fewer medications, and greater productivity.[17,32,43] Specific IgE blood testing has been criticized as being more costly than SPT. One health maintenance organization found that a single blood test was more expensive than a single skin test, but overall costs were comparable because more allergens were used for SPT than for blood testing.[44] Given the prevalence of asthma and other allergic diseases in the primary care setting and the availability of reliable s-IgE blood testing, family physicians are ideally positioned to positively affect the cost and the outcomes of atopic disease. Covered by most managed care plans, improved asthma patient care, which may include s-IgE testing, is consistent with quality-of-care initiatives introduced by the Patient Protection Affordable Care Act (PPACA) of 2010, accountable care organizations (ACOs), and the Center for Medicare and Medicaid Services (CMS) participation in the Physician Quality Reporting System (PQRS), which added a new asthma measures group in 2011.[45] Importantly, an accurate diagnosis may help lower the overall cost of managing allergic disease.

Zethraeus et al[46] compared the cost of s-IgE testing to not testing in a prospective, nonrandomized clinical trial of 721 children with respiratory or skin problems seen in a primary care setting. Costs for physician visits were similar in the tested and untested groups, but per-patient costs decreased by 30% in the s-IgE tested group over a 2-year period. The savings were almost entirely due to decreased need for medications (eg, antihistamines, bronchodilators, and corticosteroids). In the tested group, the percentage of patients correctly diagnosed with allergies rose from 54% to 87%.

The economic advantages of accessible asthma management have been documented in community-based programs that included allergy testing and an emphasis on preventable morbidity.[43,47,48] In Orange County's Breathmobile program, the percentage of enrolled children who were hospitalized for asthma fell significantly from 18.5% to 3%, and emergency department visits fell from 38% to 16% in 1 year, representing substantial savings.[47] In Baltimore's Breathmobile program, each symptom-free day saved $79.43, with greater savings for children aged 5 to 11 years ($116.84) and those with intermittent asthma ($126.71). The San Francisco General Hospital's Pediatric Asthma Clinic implemented guideline-based asthma care and documented savings of $426 in reduced emergency department visits, $1072 in fewer hospital admissions, and $1199 in total cost of treatment for each child.[48]

RECENT ADVANCES IN ALLERGY TESTING

A single allergen source, such as peanuts, eggs, or milk, contains many potentially allergenic protein molecules. New molecular allergy blood testing now makes it possible to identify and quantify sensitivity to specific antigenic components. This information is useful in assessing allergic risk and counseling patients about avoidance of specific allergen triggers. For example, patients who are sensitive to peanuts, eggs, or milk may be at risk for an anaphylactic reaction or exhibit only mild symptoms after exposure, depending on the specific antigenic components to which they react. Component testing can distinguish between clinical allergy and cross-reactivity, and establish the risk of reaction to heat-stable vs heat-labile food proteins. A patient sensitized to peanut components Ara h 1, 2, and 3 has a high risk of a severe allergic reaction to peanut, whereas mild/moderate sensitization to peanut components Ara h 8 and 9 indicates a much lower risk of an allergic reaction. In some cases, heating denatures antigenic proteins.

That may explain why a study showed that 70% of children with egg sensitization can tolerate cooked eggs, which greatly expands their dietary choices.[49]

CONCLUSIONS

The risks associated with early sensitization and progression of clinical symptoms make early diagnosis and management of IgE-mediated disease desirable. Strong evidence exists that identifying and reducing exposure to allergic triggers helps relieve symptoms and improves control in rhinitis, asthma, and other allergic diseases, such as eczema. Specific IgE blood testing identifies and quantifies sensitivities, and can be useful in assessing allergic risk and counseling patients about avoidance of specific allergic triggers. Numerous studies have documented the benefits of targeted reduction in improving the quality of life for patients and reducing health care utilization and costs. ●

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