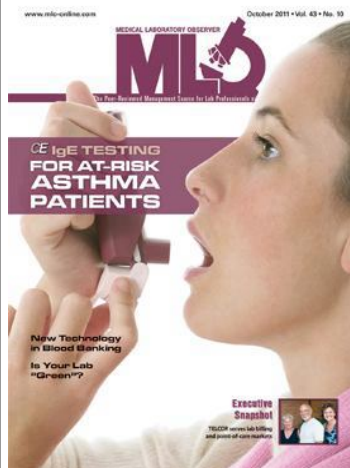


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LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. Discuss the synergistic effects between viral infections and allergies.
2. Discuss risk factors for developing asthma to include allergen profiles and

Blunting the synergistic effect of viral infections and allergies—IgE testing for at-risk asthma patients

By Robert Reinhardt, MD, DABFM

As inevitably as the start of school each fall, emergency department visits for asthma exacerbations spike in September (Figure 1).¹ Blame the combined effect of seasonal outdoor allergens, circulation of cold and flu viruses, and ideal conditions for spreading upper respiratory infections (URIs) as students return to school. For patients with asthma, the risk of hospitalization increases nearly 20-fold if they have been exposed to allergens and have a viral infection.² In one study, weekly monitoring of children with asthma during the cold season indicated that nearly all were infected with viruses.³ With less than a third of human rhinoviruses (HRV) carrying over from the previous year, new viral insults arrive each fall to perpetuate asthma morbidity.

Given the predictable nature of this epidemic, what can be done to protect patients with asthma? An effective strategy calls for concentrating on the risks of asthma exacerbation that can be modified, among them targeted allergen reduction. That, in turn, depends on accurately determining specific allergen sensitivities.

This article reviews current knowledge about the synergy between allergen sensitization and viral infections, and considers our role in providing reliable specific-IgE blood testing (s-IgE) to the physicians who manage patients with asthma.

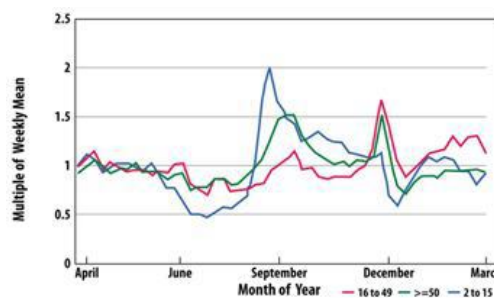


Figure 1. Weekly mean number of emergency department visits for asthma exacerbations¹ (Represents the annual cycle of asthma exacerbations in children aged 2 to 15 years and adults aged 16 to 49 years and older than 50 years. Graph modified from Johnson NW.) Emergency department visits for asthma exacerbations peak in September, when the combination of allergen exposure and seasonal viral infections dramatically increase the risk for hospitalization.

between allergens and viruses.

The synergy of allergen sensitization and viral infections

Several studies have examined the interplay of asthma, allergen sensitization, and viral infections. Murray and colleagues compared 80 children ages 3 to 17 years who were admitted to the hospital for acute asthma exacerbations with matched groups of stable asthmatics and children admitted for non-respiratory illnesses.² The combination of allergen sensitization and exposure, plus virus detection, significantly increased the risk of hospital admission ($P < 0.001$). A significantly higher proportion of asthmatics suffering acute attacks were virus infected (44%), sensitized, and highly exposed (76%) compared to stable asthmatics (18% and 48%, respectively; $P < 0.001$). Neither allergen sensitization and exposure nor virus infection alone could be independently linked to an increased risk of hospital admission. These data suggest a synergistic interaction

determination of specific allergen sensitivities.

3. Describe various aspects of s-IgE testing for allergies to include interpretation and use of s-IgE test results.
4. Explain guideline-based care for s-IgE testing.

In another study, Olenec and colleagues monitored 58 asthmatic children ages 6 to 8 years for infections and illness weekly during cold season (April and September).³ They identified 52 different strains of HRV, 7 enteroviruses, 6 adenoviruses, 5 coronaviruses, 5 influenza viruses, 5 metapneumoviruses, 6 bocaviruses, and 3 parainfluenza viruses. The majority of viruses detected—72% to 100%—were new each season, and no single strain was detected in more than two collection periods. Viral infection was nearly universal among the children in April and September. Virus-positive illnesses lasted more than twice as long and resulted in significantly more severe cold ($P<0.0001$) and asthma symptoms ($P=0.0002$) and significantly more frequent loss of asthma control (47% vs. 22%; $P=0.008$) than virus-negative illnesses. Among the virus-positive children, 53% had overlapping cold and asthma symptoms. Although viruses were detected as often in the sensitized as unsensitized children, the sensitized children experienced 47% more symptomatic viral illnesses per season than the unsensitized children ($P=0.03$). Cold and asthma symptoms were also significantly more severe in

sensitized vs. unsensitized children (Figure 2). The authors concluded that aeroallergen sensitization might be a critical factor for severe viral illnesses.

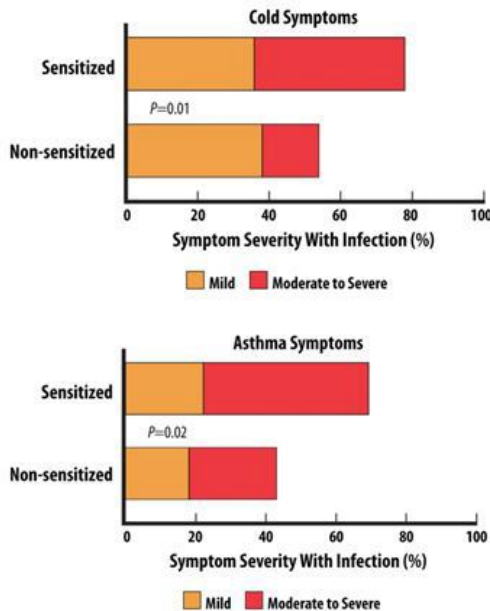


Figure 2. Effect of allergen sensitization on the severity of cold and asthma symptoms³ (Graphs modified from Olenec JP, et al.). Allergic patients were nearly three times more likely to experience moderate-to-severe cold symptoms and two times more likely to experience moderate-to-severe asthma symptoms than non-allergic patients.

Nonmodifiable vs. modifiable risk factors

Among the risk factors for developing childhood asthma are a family history of allergies and/or asthma, low birth weight, secondhand smoke before and/or after birth, allergic sensitization and exposure, frequent respiratory infections, and growing up in a low income, urban environment.⁴ Obviously, nothing can be done to modify some of these risks. But other risk factors, such as secondhand smoke and allergen exposure, are amenable to proactive intervention. Specifically, the National Institutes of Health asthma guidelines counsel, "It is essential to identify and reduce exposure to relevant allergens."⁵

The goal of targeted, reduced exposure to trigger allergens, identified by s-IgE testing, is to decrease the allergic burden below an individual's symptomatic threshold (Figure 3). Allergic sensitization is a cumulative process, and a patient will manifest clinical symptoms only if the allergen burden exceeds that person's level of tolerance. The concept of a personal "allergic threshold" was suggested by studies of asthmatic children who had allergies and moved back and forth from a low-altitude, allergen-rich environment to a high-altitude, allergen-sparse environment in the Italian Alps.⁶ A number of randomized controlled trials have subsequently confirmed the benefits of reducing exposure to allergens. Halken et al. randomly assigned 60 children aged 6 to 15 years to active (mattress and pillow casings) or control (placebo mattress and pillow casings) groups and followed them for a year.⁷ The active treatment group significantly decreased their use of inhaled steroids to control asthma (mean, 408 to 227 $\mu\text{g}/\text{d}$; $P<0.001$). In addition, significantly more children in the active group (73%) than in the control group (24%) reduced their dose of inhaled steroids by at least 50% ($P<0.01$).

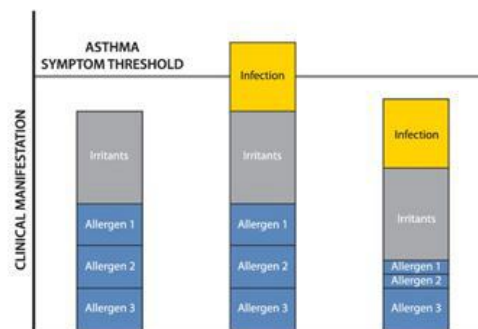


Figure 3. The cumulative effect of allergen exposure and viral infections. A person can be sensitized to several allergens but at levels lower than the symptomatic threshold. However, the synergistic effect of seasonal viral infections plus allergic sensitization can manifest in clinical symptoms. Targeted allergen reduction works to reduce the allergen load even if the patient succumbs to viral infection.

Morgan et al. randomly assigned 937 inner-city children ages 5 to 11 years with allergic sensitization and asthma to targeted allergen reduction or no intervention.⁸ Children whose families received instruction about specific allergen reduction experienced 21.3 fewer days per year with asthma symptoms, a statistically significant reduction of 19.5% over children in the control group ($P<0.001$). Over a two-year period, targeted allergen reduction resulted in 34 fewer days of wheezing, an effect similar to treatment with intranasal corticosteroids. Patients in the intervention group

also had 13.6% fewer unscheduled office visits and fewer emergency department visits than patients in the control group.

The concept of a "safe sleep zone" grew from the success of environmental controls in reducing asthma morbidity. In the bedroom, remediation efforts can be directed at reducing exposure to dust mites, cockroaches, pets and mold, as well as to passive tobacco smoke. Reducing exposure to allergic triggers begins with accurately identifying them. Allergy testing is fundamental to the effective management of asthma as recommended by the National Institutes of Health (NIH) guidelines for all patients with persistent asthma.⁵

The risk of exacerbating asthma by catching the flu is also modifiable. Thus, the Centers for Disease Control (CDC) influenza guidelines recommend

administering seasonal flu vaccine to people who have asthma.⁹

Specific-IgE testing for allergic sensitization

Approximately 80% of patients with allergy-like symptoms are treated in primary-care settings,¹⁰ and the CDC estimates that 76% of patients with asthma are managed by primary-care providers (PCPs).¹¹ By offering a reliable and accessible *in vitro* assay for measuring s-IgE, laboratories support the clinical diagnosis of allergy and help PCPs implement guideline-based care for people with asthma. The NIH guidelines list a number of advantages associated with *in vitro* s-IgE testing (Table 1). The guidelines also note that sensitization alone does not establish clinical allergy, but that sensitization must be interpreted in the context of the patient's clinical history and physical examination. Laboratory managers can help PCPs order s-IgE assays, aid in interpreting results, and provide reference information, such as the role of genetic predisposition or allergen cross-reactivity in allergic diseases.¹²

Does not require knowledge of skin testing technique
Does not require availability of "potent" allergen extracts
Can be performed on patients who are taking medications that suppress the immediate skin prick test (antihistamines, antidepressants)
No risk of systemic reactions
Can be done for patients who have extensive eczema
Easier for most pediatric patients than skin testing
Overcomes poor skin reactivity in very young or old patients

A variety of commercial s-IgE tests have become available since blood tests for allergen sensitization were first introduced more than 25 years ago. Early RAST-based tests yielded a high number of false-negative results and were considered unreliable by both allergists and PCPs.¹³ Current assays employ entirely different technologies that evolved in the late 1980s and early 1990s.¹⁴ Liquid-phase enzyme¹⁵ and solid-phase methods rely on monoclonal antibodies to bind s-IgE, which can then be measured. High-binding capacity is a prerequisite for generating serum dilution curves that parallel the calibration curve. One solid-phase technique, by substituting a sponge for the original paper disks, greatly increased the surface area available for binding s-IgE.¹⁶ This solid-phase technology improved assay sensitivity and provided results in mass units of concentration. Thus, solid-phase technology quickly became the industry standard based on numerous studies worldwide.^{17,18} Fully automated instrumentation has enhanced both the speed and efficiency of s-IgE assays.¹⁹

Table 1. Advantages of *in vitro* s-IgE testing*.

*Adapted from Guidelines for the Diagnosis and Management of Asthma.⁵

The s-IgE assays differ in format, chemistries, reagents, and analytic performance.¹⁸ The American Academy of Allergy, Asthma & Immunology (AAAAI) recommends that quantitative results be reported in units proportional to antibody content.²⁰ Assays should also conform to the World Health Organization 75/502 human IgE reference standard using a multipoint calibration curve for quantification. Testing should comply with the Clinical

Laboratory Improvement Act of 1988 (CLIA-88) and guidelines established by the Clinical and Laboratory Standards Institute (CLSI; the former National Committee for Clinical Laboratory Standards).²¹ In 2004 NCCLS established a protocol for defining the limit of detection (LOD) and limit of quantitation (LOQ) of s-IgE assays.²² One solid-state assay meets NCCLS requirements and reports results from 0.1 kU_A/L to 100 kU_A/L for unmatched sensitivity.^{23,24}

One way of assessing results from various assays is to consider their coefficients of variation (CVs). The CV derives from linear dilutions obtained from a sample diluted through the assay's measuring range.¹³ High interassay CVs suggest less reliable results, while low CVs provide a quantitative, clinically useful measure of the probability of allergen sensitivity. The NCCLS recommends a minimum performance target of 15% CV for s-IgE assays.²⁵ The Diagnostic Allergy Proficiency survey administered by the American College of Pathologists can also be useful in establishing laboratory proficiency.

Clinicians often assume that s-IgE test results are standardized from assay to assay, although results from different systems are not necessarily comparable even if reported in the same units.²⁶ The NIH asthma management guidelines make the same point by noting that predictive values associated with clinical evidence of allergy are test-specific and cannot be applied universally to all assays.⁵ The truth of this fact was demonstrated in a study of blinded samples of known IgE concentrations distributed to six laboratories using five testing protocols for 17 aeroallergens.^{18,27,28} Analysis of 12,708 test results revealed that two of the laboratories using the same equipment came closest to the results expected from an ideal assay. Laboratory managers and personnel will want to work closely with manufacturers and clinicians to be certain that the laboratory data can be effectively communicated and applied clinically.

Current s-IgE testing has been described as well standardized, easily used, and effective in confirming the diagnosis of clinical allergy.²⁹ Most importantly, the sensitivity, specificity, and positive and negative predictive values of *in vitro* blood testing and skin-prick testing are comparable.³⁰ Thus, the s-IgE assay is a practical tool that allows PCPs to approximate specialists in diagnostic precision and to make timely and appropriate referrals.³¹

Allergen profiles

The availability of preselected allergen profiles greatly simplifies the task of selecting allergens for testing. The first profiles were developed by an immunologist who had 25 years of experience in assisting allergy specialists with testing.³² Today's respiratory profiles encompass targeted categories, including allergens typical of the geographic region or classic allergic diseases, such as allergic rhinitis (seasonal outdoor allergens, selected indoor allergens) and asthma (molds, cockroach, dust mites). The profile selections are based on the ability to detect allergic sensitization >95% of the time.^{33,34} The selected inhalant allergens possess high cross-reactivity, so sensitivity to one allergen within a botanical class carries a high likelihood of clinical reactions to other members of the same class.^{35,36} A study in children found that including one highly prevalent inhalant allergen in a profile can identify up to 98% of patients with clinical allergy.³⁷

A profile for a typical patient of 20 inhalant allergens might include two grasses, two or three molds, four trees, two dust mites, cat and dog dander, and cockroach. This selection represents both outdoor and indoor allergens, including two species of dust mites because of their close association with asthma exacerbation. Including key regional allergens maximizes test efficiency without compromising the utility of s-IgE test results. Well-established cross-reactivities help extend the test result for one allergen to others within the same botanical class.³⁵ The median number of *in vitro* allergens ordered for Medicare patients is 24³⁸, compared with 50 per patient for skin-prick testing.³⁹ Per-patient costs for blood and skin testing tend to be comparable³⁸; a single allergen skin test costs less than a single allergen blood test, but typically more allergens are used in skin testing. Specific IgE profiles that use 25 to 30 preselected allergens have demonstrated clinical utility in reliably detecting sensitization and allergic disease.⁴⁰

In some cases, ordering a food profile may be warranted for a child with asthma. That is because approximately 40% of children with atopic dermatitis will develop asthma by school age,⁴¹ and approximately one-third of children with moderate to severe atopic dermatitis have food allergies or sensitivities.⁴² The most recent NIH guidelines for food allergy advise targeted avoidance of specific allergens for individuals with documented food allergy and asthma.⁴³

Interpreting s-IgE test results

Quantitative results of s-IgE testing are expressed in kilounits of antibody per liter (kU_A/L). Reference ranges for the most widely used assay do not necessarily apply to other assays. However, for each assay the probability of symptomatic allergy rises with increasing s-IgE concentrations.⁴⁴ High concentrations of a single allergen (monosensitization) may correlate to clinical disease, but according to one study the probability of having clinically significant disease rose to 75% if there were four or more positive s-IgE tests from a profile of 14 allergens, or a total of s-IgE >34 kU_A/L to the same allergens.⁴⁵ Virtually all profiles report total IgE values. This information is seldom of clinical value as a number of nonatopic conditions can elevate total IgE, including parasitic infections, immunodeficiencies (HIV, for example), myeloma, drug-induced interstitial nephritis, graft-vs.-host disease, and hyper-IgE syndrome.³⁴

Positive s-IgE results can help identify sensitized individuals, determine their allergic triggers, and guide their treatment. In a study of asthmatic adults, 59% of PCPs stated that s-IgE results provided new information that could be applied to their patients' clinical management.⁴⁶ Positive results can be used to enlist patients' cooperation in appropriate treatment with environmental controls, medication or immunotherapy. The indications for omalizumab (Xolair®) include a positive s-IgE test to a perennial aeroallergen. Primary-care providers can also use s-IgE test results as the basis for referring patients to specialists for immunotherapy.

Because the negative predictive value of *in vitro* testing is high,³⁰ negative results point to nonallergic causes for a patient's symptoms.⁴⁷ Negative results also allow patients to avoid the expense of ineffective medication trials, and the inconvenience of cumbersome avoidance measures.⁴⁸

Comprehensive guideline-based care

As healthcare reimbursement moves to fee-for-outcomes, comprehensive guideline-based asthma care will gain in importance. Accountable care organizations (ACOs) will reward cooperation between PCPs, laboratories and hospitals with the common goal of focusing on primary care, wellness and accountability for patients' health. A recent study illustrates how s-IgE testing can improve healthcare utilization. It examined the costs of s-IgE testing vs. no testing in a prospective, non-randomized trial of 721 children with respiratory or skin problems.⁴⁹ Specific IgE testing increased the percentage of patients correctly diagnosed with allergy from 54% to 87% and decreased per patient costs by 43% over a two-year period.

Summary

Results from s-IgE testing can help PCPs implement guideline-based asthma management and reduce the morbidity associated with the synergistic effects of allergen sensitization/exposure and seasonal viral exposure.

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