



## Allergy: Early, accurate diagnosis is a basis for effective treatment

Allergy is now recognized as a growing public health problem worldwide and is associated with decreased school and work productivity.<sup>1</sup> Early, accurate diagnosis is now the standard of care with the emphasis having moved from treatment prior to diagnosis to the use of in vitro testing that can guide therapy through early allergen identification.

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## What is allergy?

The term allergy is generally used to describe an immunoglobulin E (IgE) mediated immune response to substances that are not generally harmful to the body. Natural allergen sources, such as pollens, dust mites, dog dander, molds, insect venoms, and foods, are identified through the immune system and it is the reaction of the immune system to the allergen that produces the signs and symptoms associated with this disease. IgE is produced on first exposure to the allergen by  $\beta$ -cells on first exposure to the allergen and these IgE molecules then bind to mast cells and basophils. The individual is now sensitized and when subsequent allergen exposures occur, the cell-bound IgE binds the allergen triggering the release of histamine and other mediators that produce allergy signs and symptoms. These include eczema, pruritus, conjunctivitis, allergic rhinitis, asthma, anaphylaxis, and even death. Diagnostic tests play a key role in the management of allergy, but a thorough medical history must be taken, as well as a physical exam carried out when tests are ordered, so that test results can be interpreted and accuracy maximised. Multiple different manifestations of allergic disease, such as eczema and food allergy or allergic rhinitis and asthma, are commonly found in a single patient, and frequently the patient experiences them in a defined sequential pattern known as the allergy march.

## The allergy march

The allergy march is a series of allergic diseases that follow a fairly defined path as the allergic patient ages (Figure 1). Typically, eczema occurs between birth and three months of age; gastrointestinal symptoms related to food allergens are most prevalent during the second year (but can occur earlier); allergic rhinitis and other upper respiratory conditions due to inhalant allergens as well as recurrent otitis media generally manifest between ages three and seven; and asthma is usually diagnosed between ages seven and fifteen.<sup>2</sup> In the young child, elevated food-specific IgE antibody levels are associated with the significantly elevated risk of developing inhalant

allergen sensitivities later in childhood.<sup>3</sup> Early diagnosis and appropriate treatment of allergies is vital to interrupting the disease progression and thus derailing the allergy march.

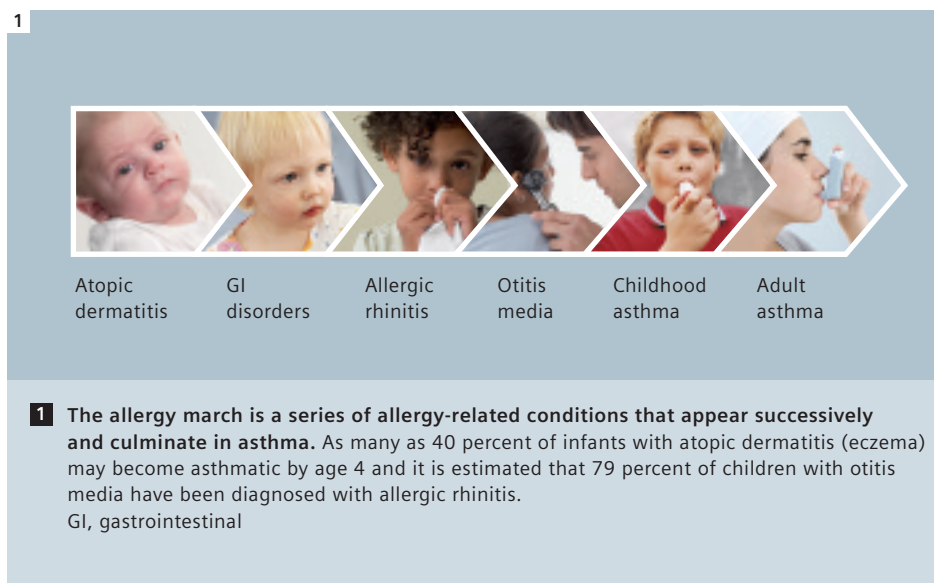
The allergens most often associated with eczema include cow's milk, egg, wheat, soy, and peanut: 30 percent of all skin disorders in toddlers are due to eczema.<sup>4-6</sup> Failure to treat eczema is associated with the development of gastrointestinal symptoms that are frequently related to allergy,<sup>7-9</sup> and evidence suggests that food allergy may be the root cause of symptoms in 10 to 15 percent of colicky infants. In infants diagnosed with gastroesophageal reflux, 16 to 42 percent are found to be allergic to cow's milk, while among infants already diagnosed with allergy, 50 to 60 percent have gastrointestinal related symptoms.<sup>5, 6, 10, 11</sup> Left undiagnosed, allergy related gastrointestinal symptoms may result in growth retardation. In addition, it has been demonstrated that children with early and long-lasting food allergies are three times more likely to develop allergic rhinitis, and five times more likely to develop asthma.<sup>10-12</sup>

Otitis media is yet another step in the allergy march and ten million children with otitis media are treated in the US every year for an approximate cost of five billion dollars per year.<sup>7</sup> The prevalence of recurrent otitis media has grown steadily over the years, especially among infants: evidence suggests that this is linked to allergic disease, particularly allergic rhinitis. Allergic rhinitis can

produce eustachian tube inflammation and dysfunction thus providing an ideal environment for infection.<sup>13-17</sup>

Overall, allergic rhinitis is estimated to affect 20 to 40 million Americans and is very common among children. It is also generally accepted as the step prior to asthma in the allergy march.<sup>18</sup> In rhinitis patients, history and physical alone produce a correct diagnosis of allergic disease only 50 percent of the time, so objective evidence is required. In children, allergic rhinitis often signifies the emergence of respiratory illness and completion of the shift from food to inhalant allergen sensitivities.

More than 20 million people have asthma and for some it is the final step in the allergy march;<sup>19</sup> among asthmatics 60 percent have allergic asthma.<sup>20</sup> In children with asthma, 90 percent also have established allergies.<sup>5</sup> Approximately 40 percent of infants who have atopic dermatitis (eczema) may develop asthma by the age of three to four years.<sup>5</sup> The Canadian Childhood Asthma Primary Prevention Study demonstrated a 56 percent reduction of asthma frequency by age seven in high-risk children through an intervention program for the first year of life that included avoidance of allergen exposure through avoidance of pets, secondhand smoke, and dust mites.<sup>21</sup> The results of this study clearly suggest that early intervention facilitated by early and accurate diagnosis of the specific allergen may be critical for preventing asthma and the culmination of the allergy march.



## The importance of early diagnosis

The importance of early allergen identification is shown by evidence from several long-term multicenter prospective studies. In the study on the prevention of allergy in children in Europe (SPACE), a four-percent reduction in sensitization to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (house dust mites), egg, and milk was observed at one year of age when dust mite-impermeable mattress casings were used for newborns at high risk of atopy (a genetic predisposition to allergy, in this study evidenced by having at least one parent with a diagnosis of inhalant allergies confirmed by diagnostic tests).<sup>22</sup> A similar result was observed in this study's young school-aged cohort (five to seven years).<sup>23</sup>

The landmark Preventative Allergy Treatment (PAT) study results concluded that progression of allergy to asthma could be prevented in grass and/or birch pollen-allergic children suffering from seasonal rhinoconjunctivitis (hay fever) by treatment with subcutaneous specific immunotherapy (SIT).<sup>24</sup> This study enrolled children between the ages of six and fifteen years and followed their progress for over ten years. The prophylactic benefit of SIT persisted long after completion of therapy, resulting in approximately 50 percent reduction in the development of asthma for up to seven years after completion of therapy.<sup>25, 26</sup> This study and others support the strategy of early, accurate diagnosis using diagnostic tests in conjunction with other clinical information to facilitate early, effective treatment that can halt the allergy march.

## The role of sensitive and specific tests in early diagnosis

According to the guidelines of both the American Academy of Allergy Asthma and Immunology (AAAAI)<sup>27</sup> and the European Academy of Asthma, Allergy and Clinical Immunology (EAACI)<sup>28</sup>, therapy should not be initiated without specific identification of the allergen, which can be determined by either in vivo or in vitro (IgE) tests that are sensitive and specific. Accumulating evidence suggests that even levels below the traditionally

accepted 0.35 kU/l cutoff are also indicative of allergic disease.<sup>29-31</sup> (This cutoff was imposed by technical limitations of early automated equipment.<sup>32</sup>) Other studies have shown that low levels of IgE in umbilical cord blood in conjunction with hereditary factors may be the best predictors of inhalant allergen sensitization later in childhood.<sup>33</sup>

## Allergy testing: in vivo methods

In vivo allergy test is an umbrella term that encompasses several different procedures (Figure 2), all of which entail directly exposing the patient to the suspected allergen. The test is positive if the patient has an objective response. These tests can be divided into skin-based tests and food challenges. In the skin-based tests (skin prick test, intradermal test, scratch test, and skin patch test) the allergen is placed on or in the skin along with positive and negative controls for comparison. A positive response is characterized by redness and swelling generally termed the wheal and flare. Typically, the diameter of the wheal is used to determine the amount of reactivity to the allergen; larger wheals represent a greater level of reactivity. In a food challenge, the patient ingests the suspected allergen and signs and symptoms are documented. This test must be performed in a facility that is equipped to handle potentially life-threatening reactions.<sup>34</sup> Ideally, the food challenge test is performed in a double-blind, placebo-controlled manner. With this method, neither the allergist nor the patient knows which sample contains the suspected allergen or the placebo. This type of test is often performed as a last resort and open challenges (where the physician and the patient are aware of

the allergen) are typically done instead. Food challenges are not performed in patients with a history of a severe allergic response as they have a very high risk for anaphylaxis and death.

## Allergy testing: in vitro methods

Unlike in vivo allergy tests, which rely on the release of histamine and other mediators for a positive result, in vitro allergy tests measure the concentration of IgE in the circulation that is specific for a particular allergen and thus have certain advantages over in vivo tests (Figure 3). A distinct advantage of in vitro testing is that it can be used effectively by physicians of all specialties to diagnose a specific allergy and does not require the extensive training that is needed for in vivo testing. In vitro testing also allows labs to be closely involved in the diagnosis of allergic disease by providing objective testing that is sensitive and specific. Moreover, since the patient is not exposed to the allergen, the risk of precipitating an allergic response that is life threatening is extremely low.

Despite the wide-spread use of in vivo allergy tests among allergists, there are certain situations where in vitro tests may be indicated over skin testing (Figure 4).<sup>35</sup> In vitro IgE testing is a valuable diagnostic tool for allergists and primary care physicians because it is comparable to in vivo testing and facilitates accurate diagnosis and appropriate therapeutic intervention. The use of the 3gAllergy<sup>®</sup> kit from Siemens and similar in vitro assays can foster a more effective collaboration among clinical laboratories, allergists, and primary care physicians in the diagnosis and management of allergy for the benefit of millions of patients worldwide.

**2**

- Skin prick test
- Intradermal test
- Scratch test
- Skin patch test
- Food challenge test

**2** In vivo allergy tests

**3**

- Antihistamines, antidepressants, and other interfering drugs do NOT need to be discontinued
- Fully quantitative results
- One blood draw for multiple determinations

**3** Advantages of in vitro tests

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- Negative skin test despite high clinical suspicion of allergy
- Skin conditions such as eczema that preclude skin testing
- Patients taking long-acting antihistamines, tricyclic antidepressants, and other drugs that limit response to allergens in skin tests
- Useful in very young or elderly patients because they generally have reduced histamine reactivity in skin tests
- Patients with a clinical history that indicates an increased risk of anaphylaxis
- Pregnant patients (to avoid any possibility of a systemic reaction)

**4 Situations in which in vitro tests may be preferred over skin tests**

**Conclusions**

In vitro tests are playing an increasingly important role in diagnosis and are well-established tools that are endorsed by European and American professional allergy organizations. Current evidence supports the utility of diagnostic tests (in vivo and in vitro) in facilitating early diagnosis for prompt, effective treatment. It is not acceptable to treat presumptively without allergen identification. Early treatment has been shown to improve quality of life and prevent progression of the allergy march to asthma (a disease that is associated with significant morbidity and mortality) and thus facilitate better patient outcomes.

**References**

- 1 Lack G. Pediatric allergic rhinitis and comorbid disorders. *J Allergy Clin Immunol* 2001; 108:S9-15.
- 2 Yunginger JW, Ahlstedt S, Eggleston PA, et al. Quantitative IgE antibody assays in allergic diseases. *J Allergy Clin Immunol* 2000; 105:1077-84.
- 3 Leung DYM. Atopic dermatitis. In *Pediatric allergy: principles and practice* (Leung DYM, Sampson HA, Heha RS, Szefer SJ, eds), 2003: 561-73. Mosby-Year Book, Inc, St. Louis, MO.
- 4 The Allergy Report: conditions that may have an allergic component, 2000; 3:69-70. American Academy of Allergy, Asthma & Immunology Inc, Milwaukee, WI.
- 5 Høst A, Andrae S, Charkin S, et al. Allergy testing in children: why, who, when and how? *Allergy* 2003; 58:559-69.
- 6 Chamlin SL, Frieden IJ, Williams ML, Chren MM. Effects of atopic dermatitis on young American children and their families. *Pediatrics*. 2004; 114:607-11.

- 7 The Allergy Report: diseases of the atopic diathesis, 2000; 2:111-36. American Academy of Allergy, Asthma & Immunology Inc, Milwaukee, WI.
- 8 Sampson H. Can we diagnose atopy with a laboratory test? *Ann Allergy Asthma Immunol*. 2004; 93:307-8.
- 9 Hamburger HA. Diagnosing allergic diseases in children: practical recommendations for consulting pathologists. *Arch Pathol Lab Med* 2004; 128:1028-31.
- 10 Sicherer SH. Clinical aspects of gastrointestinal food allergy in childhood. *Pediatrics*. 2003; 111:1609-16.
- 11 Kulig M, Bergmann R, Tacke U, Wahn U, Guggenmoos-Holzmann I, MAS Study Group. Long-lasting sensitization to food during the first two years precedes allergic airway disease. *Pediatr Allergy Immunol* 1998; 9:61-7.
- 12 Australasian Society of Clinical Immunology. Allergy adverse reactions to food. Available at: [www.allergy.org.au/aer/infobulletins/adverse\\_reactions.htm](http://www.allergy.org.au/aer/infobulletins/adverse_reactions.htm). [Accessed 25 April, 2005].
- 13 Lanphear BP, Byrd RS, Auinger P, Hall CB. Increasing prevalence of recurrent otitis media among children in the United States. *Pediatrics*. 1997; 99:1-7. Available at: [www.pediatrics.org/cgi/content/full/99/3/e1](http://www.pediatrics.org/cgi/content/full/99/3/e1). [Accessed 9 November, 2008].
- 14 Wickman M. When allergies complicate allergies. *Allergy* 2005; 60(suppl 79):14-8.
- 15 Jones M, Wilson L, Malis D. Otitis media. *Emedicine.com*. Available at: [www.emedicine.com/ped/topic1689.htm](http://www.emedicine.com/ped/topic1689.htm). [Accessed 9 November, 2008].
- 16 Skoner DP. Complications of allergic rhinitis. *J Allergy Clin Immunol* 2000; 105(6 Pt 2):S605-9.
- 17 Fireman P. Otitis media and eustachian tube dysfunction: connection to allergic rhinitis. *J Allergy Clin Immunol* 1997; 99:S787-97.
- 18 Gentile DA, Shapiro FG, Skoner DP. Allergic rhinitis. In *Pediatric allergy: principles and practice* (Leung DYM, Sampson HA, Geha RS, Szefer SJ, eds), 2003:287-97. Mosby-Year Book, Inc, St. Louis, MO.
- 19 Milgrom H. Understanding allergic asthma [AAAAI news release]. American Academy of Allergy, Asthma & Immunology; June 18, 2003. Available at: [www.aaaai.org/media/news\\_releases/2003/06/061803.html](http://www.aaaai.org/media/news_releases/2003/06/061803.html). [Accessed 11 February, 2005].
- 20 National Center for Health Statistics. Asthma prevalence, health care use and mortality, 2002. Available at: [www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm](http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm). [Accessed 9 November, 2008].
- 21 Chan-Yeung M, Ferguson A, Watson W, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. *J Allergy Clin Immunol* 2005; 116:49-55.
- 22 Halmerbauer G, Gartner C, Schierl M, et al. Study on the Prevention of Allergy in Children in Europe (SPACE): Allergic sensitization in children at 1 year of age in a controlled trial of allergen avoidance from birth. *Pediatr Allergy Immunol* 2002; 13(Suppl. 15):47-54.
- 23 Arshad SH, Bojarskas J, Tsitoura S, et al. Prevention of sensitization to house dust mite by allergen avoidance in school age children: a randomized study. *Clin Exp Allergy* 2002; 32:843-9.
- 24 Jacobsen L, Niggemann B, Dreborg S, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; 62:943-8.
- 25 ETACR Study Group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo controlled trial: first results of ETACR. *Pediatr Allergy Immunol* 1998; 9:116-24.
- 26 Ollert MW, Weissenbacher S, Rakoski J, Ring J. Allergen-specific IgE measured by a continuous random-access immunoanalyzer: interassay comparison and agreement with skin testing. *Clin Chem* 2005; 51:1241-9.



- 27 American Academy of Allergy Asthma and Clinical Immunology Practice Guidelines. Available at: [www.aaaai.org/members/resources/practice\\_guidelines/](http://www.aaaai.org/members/resources/practice_guidelines/) [Accessed 9 November, 2008].
- 28 European Academy of Asthma, Allergy and Clinical Immunology (EAACI): [www.eaaci.net](http://www.eaaci.net).
- 29 Grunwald T, Bockisch B, Spillner E, Ring J, Bredehorst R, Ollert M. Molecular cloning and expression in insect cells of honeybee venom allergen acid phosphatase (Api m 3). *J Allergy Clin Immunol* 2006; 117(4):848-54.
- 30 Almeida-Morais M. In: *3gAllergy: International Allergy Conference Proceedings*. (Clouet JC, ed), 2005; 9-11. Diagnostic Products Corporation, Los Angeles, CA.
- 31 Halken D. Early sensitization and development of allergic airway disease – risk factors and predictors. *Paed Resp Rev* 2003; 4:128-34.
- 32 Mirhosseini M, Levy R. Improving allergy testing: the evolution of in vitro assays for allergen-specific IgE. *News & Views*, 2006, Issue 2.
- 33 Ahlstedt S. Mediators in allergy diagnosis. *ACI Int* 1998; 10(2):37-44.
- 34 WebMD. Available at: [www.webmd.com/allergies](http://www.webmd.com/allergies)
- 35 Mirhosseini M, Bal T. Accurate allergy diagnosis – a worldwide problem in vitro allergen-specific IgE testing – a solution. *News & Views*, 2006; Issue 2.