**COMMON PEDIATRIC DISEASES**

The incidence of asthma and allergic disease is rising. However, pediatrician and primary care physicians have dealt with allergic conditions far more often than they may expect even before the recent increase in allergic conditions. Some examples of immunological disease that the primary care physician sees include asthma, allergic rhinitis, and atopic dermatitis.

Atopy, the genetic predisposition to the development of antigen-specific immunoglobulin E (IgE) antibody formation, involves complex genetic and environmental influences that are not fully understood. In other words, simple Mendelian inheritance patterns do not predict which individuals will develop allergies. Nevertheless, there appears to be a higher incidence of allergies among children of allergic parents.

One becomes “allergic” to a substance through a two-step process. The first step begins with sensitization and is outlined in Fig. 1. During the initial stage of sensitization, one develops significant amounts of IgE antibodies against an inhaled, ingested, or injected substance. Memory B-cells are capable of immediately producing more specific IgE antibody when stimulated.

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Figure 1

The process of sensitization and degranulation in mast cells is analogous to the construction and detonation of a bomb. Initial binding of specific IgE to the naive mast cell surface “primes” the cell for activity, in effect building the bomb. Subsequent binding of allergen to the mast cell is akin to lighting the fuse of the bomb. Intracellular biochemical events lead to the ultimate “explosion”—a cellular degranulation leading to mediator release.

All antigens initially elicit the production of IgM antibodies against an injected or inhaled allergen. With repeated exposure, the antigen may stimulate an event known as class switching, whereby the constant portion of the antibody will “switch” to another class (i.e., IgG, IgA, or IgE). The new antibody will still have the same antigen-recognition region, but it will now be sitting on another constant region (e.g., IgG or IgA). IgE production by B-cells as a result of class switching is regulated by T-cells and macrophages, predominantly, and the cytokines they produce. Cytokines are small molecular- weight molecules that affect cell function at the local level. Two primary cytokines that favor IgE class switching are interleukin (IL)-4 and IL-13. IL-4 and IL-13 are produced by a subset of CD4+ T-cells, also known as T-helper 2 (TH2) cells.

**THE MAST CELL**

Despite gross morphological homogeneity, it is now apparent that mast cells are a heterogeneous cell population. Most pulmonary mast cells contain primarily one neutral protease, tryptase. Skin mast cells, on the other hand, contain large amounts of both tryptase and another protease, chymase. Mast cells in humans are divided and named on the basis of this biochemical difference and are termed MCT (for mast cells containing tryptase) or MCTC(for mast cells containing chymase).

**MEDIATORS OF THE ALLERGIC RESPONSE**

The mediators released by mast cells and basophils can be grouped into two categories: (1) preformed substances contained within granules and (2) newly generated chemicals synthesized following a cellular activation. These mediators comprise the effector function of the mast cell. Together they are able to increase vascular permeability, dilate vessels, cause bronchospasm, contract smooth muscle, and summon inflammatory cells, as summarized in Fig. 2. Few cells in the body produce compounds with such a large and varied spectrum of activity.



Fig. 2. Mast cell mediators and their effects. (Adapted from Lichtenstein L. Allergy and the immune system. Sci Am 1993;369:117–124)

**APPROACH TO THE ALLERGIC PATIENT**

Allergic disease is variable its manifestations, affecting single or multiple organ systems. It may also mimic other conditions. The clinician must be prepared to take an in-depth history, make a comprehensive physical examination, and seek appropriate objective measures in order to adequately consider the differential diagnosis and arrive at a proper diagnosis.

The history is the most important element in the evaluation of allergy. Key features of the history are:

• Worsening of symptoms on exposure to aeroallergens

 • Seasonal variation in symptoms related to pollination of trees, grasses, and weeds

 • A family history of atopic disease

• An environmental history assessing exposure at workplace and home

• The presence of associated allergic conditions

**PHYSICAL EXAMINATION**

An allergic patient’s history may direct the clinician’s examination to a particular area or organ system. A specific allergic symptom, however, should not divert the examiner’s attention from the patient as a whole. Each patient should be approached in a systematic way. Often physical examination may be normal; lack of findings does not rule out allergy.

Clues to allergic propensity are often seen in the patient’s face. Discoloration of the infra-orbital skin or “allergic shiners” may imply nasal congestion and subsequent lymph stasis. Extension of the mid-face or adenoid facies in children with adenoid hypertrophy, an infra-orbital crease or Dennie’s line, and a transverse crease along the lower half of the nose are frequent but not absolute indicators of underlying allergy.

The skin is commonly affected by allergy, although skin findings are often falsely attributed to allergic disorders. Xerosis is unrelated to allergy per se; however, individuals with atopic dermatitis have, in general, exceedingly dry skin. In addition, in subacute atopic dermatitis the skin may contain erythematous, scaling papules. In patients with chronic atopic dermatitis, the skin is thickened with increased markings, known as lichenification.

The most important ancillary test to confirm the diagnosis of allergy is the skin test, which is the gold standard in this regard. The skin test results must be interpreted in light of the history to determine the importance of a positive test.

Eosinophils are often associated with allergy but are rarely increased in allergic rhinitis. More commonly, eosinophils are a peripheral marker of inflammation and are elevated in nonallergic as well as allergic asthma. Eosinophils count is considered abnormal if it is greater than 7% of the total white blood count or greater than 350/mm3.

Nasal smears may be helpful in distinguishing an infectious process in the nose from an eosinophilic process. Predominance of segmented neutrophils implies underlying bacterial infection; more than10 eosinophils/high-power field as assessed by Wright’s stain are frequent in allergic rhinitis.

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**MEASUREMENT OF ALLERGEN-SPECIFIC IGE**

Basic Methods Essentially all available assays for allergen-specific IgE antibodies utilize the principle of immunoabsorption. The allergen of interest is first bound to a solid-phase support such as a paper disk, plastic microtiter well, or cellulose sponge. The patient’s serum is then incubated with the allergen-coupled solid phase. If the patient has antibodies specific for the allergen, the antibodies will become bound to the allergen, and the remaining serum proteins, including unbound antibodies, can be washed away from the solid phase (this is immunoabsorption and separation). After washing, a labeled antihuman IgE antibody is incubated with the solid phase to allow binding of the anti-IgE to any IgE bound to the solid phase. After unbound anti-IgE is washed away, the quantity of anti-IgE bound to the solid phase is measured by quantitating the amount of label present and converting either to units of specific IgE by comparison to a standard curve or to a class score. The initial test for IgE antibodies used radiolabeled anti-IgE antibodies and was called the radioallergosorbent test (RAST). Because of its initial market dominance, RAST is often used as a generic term to mean any test for allergen-specific IgE antibodies, but in reality RAST is a brand name. In recent years other methods have largely supplanted RAST to avoid the problems associated with handling and storing radioactive materials. The major modification in newer assays is the use of enzyme labels in place of radiolabels. Thus, newer assays are specific applications of enzyme-linked immunosorbert assays. Despite the common use of enzyme labels, the term RAST is still commonly used to denote any test used to detect allergen-specific IgE antibodies. Both radiolabeled and enzyme-labeled assays are capable of detecting specific IgE at a concentration of less than 1 ng per mL of serum.

**TOTAL SERUM IGE**

Serum concentrations of IgE vary widely in normal individuals. IgE levels are very low at birth and gradually increase, peaking in the second decade of life, followed by a slow decline into old age.

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**URTICURIA AND ANGIODEMA**

One in five individuals will suffer from (urticaria) hives at some point during his or her lifetime. In children prevalence ranges between 12-15 %. As such, patients presenting with hives will be a common occurrence in the primary care settings. Urticaria is associated with allergic sensitization to food, drug, and inhalant allergies.

**Acute Urticaria and Angioderma**

* Less than 6 week in duration
* Short-lived and self-limiting
* More common in children
* Associated with isolated exposure to allergens (foods, drugs, bee sting, latex)
* Associated with exposure to agents resulting in nonspecific reactions (radiocontrast dye, NSAIDs, codeine)

Physical and Physiological Stimuli that can Result in Urticaria and Angiodema (Physical Urticaria)

|  |  |
| --- | --- |
| Thermal Stimuli | Cold: idiopathic cold urticarialHeat: cholinergic urticarial, local heat urticarial |
| Mechanical stimuli | DermatographismDelayed pressure urticarial/angioedemaVibratory urticarial/angioedema |
| Light-induced urticaria | Solar urticarial, type I-VI |
| Exercise stimuli | Cholinergic urticarialExercise-induced anaphylaxis (with urticaria) |

**Evaluation and Workshop of Urticaria and Angiodema**

*Acute Urticaria/Angiodema*

* History and physical examination
* Consider skin testing or double-blind, placebo-controlled food challenge for possible food allergy.
* Skin biopsy not recommended (will show only dermal edema)

***Chronic Urticaria/Angiodema***

* History and physical examination
* Laboratory studies to be considered (CBC, UA, ESRM thyroid function tests, ANAm serum chemistries, antiperoxidase antibody, antithyroglobulin antibody)
* Skin biopsy if lesion is atypical or if there is suspicion of underlying systemic disease.

**Cytokines Reported to Activate or Prime Basophils for Histamine Release**

Interleukin – 1

Interleukin – 3

Granulocyte-macrophage colony-stimulating factor

Connective tissue-activating protein III

Neutrophil activating peptide-2

Macrophage inflammatory protein -1α and -1β (MIP-1a, MIP-1β)

Monocyte chemotactic and activating factor/monocyte chemoattractant protein-1 (MCAF or MCP-1)

Regulated upon activation, normally T-cell expressed and secreted (RANTES)

Monocyte chemotactic and activating factors-3 and -4 (MCP-3, MCP-4)

**Treatment of Acute Urticaria and Angioedema**

* Avoidance of food, drug, or other allergen
* Symptomatic relief (H1 antihistamines, oatmeal baths)
* Short course (no more than several days) of corticosteroid for severeor protracted episodes and to prevent late-phase response
* Epinephrine to be considered only for acute intervention of severe attacks.

##### Chronic Urticaria/Angioedema

* H1 antihistamines (e.g., nonsedating—cetirizine, fexofenadine, loratadine,desloratidine, or sedating diphenhydramine, hydroxyzine)
* H2 antihistamines (e.g., cimetidine, ranitidine, famotidine)
* Short course of systemic corticosteroid (no longer than 1–2 wk)
* Consideration of alternate-day, low-dose steroid and other immunomodulators in severe, refractory disease.

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**Atopic Dermatitis**

Atopic dermatitis is a complex, multifactorial disorder that first develops in most patients before the age of five. The diagnosis relies on information compiled from all aspects of clinical history, physical examination, and laboratory data. Strong correlations exist between atopic dermatitis and other atopic conditions such as asthma and allergic rhinitis. Underlying IgE-mediated sensitivitiy to both aeroallergens and foods have been shown to be strong triggering factors in atopic dermatitis. In addition, *Staphylococcus aureus* can exacerbate atopic dermatitis both by causing secondary infection of compromised skin and by secreting exotoxins that function as “superantigens” directly stimulating T-cell proliferation. Successful treatment of atopic dermatitis involves a multifaceted approach that addresses avoidance of underlying triggering factors, proper care of dry skin, and pharmacologic management, including oral antipruritic agents, topical corticosteroids, and oral antibiotics when necessary.

**Key Features of the Pathogenesis of Atopic Dermatitis**

* Immediate hypersensitivity may be key to pathogenesis in the majority of patients.
* Exacerbations clearly related to contact with aeroallergens or the ingestion of foods to which a patient is allergic.
* Many patients have IgE-mediated allergic responses to microorganismsgrowing on the skin.
* Nonimmunological factors, such as climate and nonspecificirritants, may play a role.

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## **Food Allergy and Intolerance**

Adverse reactions to foods can be divided into those that are allergic and those resulting from food intolerance. Allergic food reactions are IgE-mediated and are usually limited to individuals with other atopic diseases such as allergic rhinitis, atopic dermatitis, and allergic asthma. The serious form of IgE-mediated reactions to food is anaphylaxis. The most common foods to cause this are peanuts, shellfish, sesame and tree nuts. Acute urticaria from foods is also most commonly caused by these three agents. Atopic dermatitis can be related to food allergy as well.

Food allergy also appears in infancy, and in many instances the problem will subside as the child matures. In general, the more severe the original reaction, the longer this takes. Reactions to peanuts, tree nuts, fish, and shellfish are more likely to be chronic or remain lifelong.

Sensitivity to foods can be determined by allergy testing. Both skin and in vitro tests can be useful in this regard, but the gold standard for the diagnosis of food allergy is the double-blind, placebocontrolled food challenge.

##### Definitions and Classifications

Food allergy, which depicts an immunological, usually involving IgE, reaction to a food; and food intolerance, which involves all other adverse reactions, some of which are the result of unknown mechanisms, but none of which involves immune reactions (Table). Recently, revision of these commonly accepted definitions has been suggested in Europe, as follows: adverse reactions to food would be termed food hypersensitivities, food intolerances would be called nonallergic food hypersensitivities, and either food hypersensitivities or food allergy would be simply known as food allergy.



##### Natural History of Clinical Reactions to Food Allergy

Among children in whom allergic and allergic-like reactions have been documented by DBPCFC during infancy, 80–87% were able to tolerate that food upon rechallenge by 3 yr of age. The usual foods to which these children originally were clinically sensitive were cow’s milk, eggs, soy, or wheat proteins.

**Proven Food Allergy in Infants**

The most likely foods involved in allergic reactions in children below the age of 2 in the United States are

* Cow’s milk
* Eggs
* Peanuts
* Wheat
* Soy
* Sesame