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Office IgE-mediated environmental allergy evaluation and treatment

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Environmental allergens that induce a type I immune hypersensitivity present a widespread and significant reduction in the quality of life for our patients while imposing a stifling cost upon health care and the economy. A prompt, accurate clinical diagnosis with an appropriate management protocol can spare recurrent upper respiratory tract infections and unpleasant sequelae of epithelial inflammation, airway mucous clogging, and mucosal obstruction. In the event where environmental control measures and conservative medical therapy fail, many patients stand to benefit from immunotherapy testing and treatment. In the absence of significant risk factors for therapy, the potential for partial or total resolution of IgE-mediated symptoms makes this an excellent option. With adequate clinical design and anaphylaxis precautions, most outpatient clinic settings can provide safe and accurate environmental allergen evaluation and therapy.

Although environmental allergies do not commonly represent a life-threatening condition, the typical venous engorgement, mucosal edema, increased secretions, itching, sneezing, and potentially more hazardous lower respiratory tract symptoms result in a significant reduction in the quality of life. The most common sources vary by region and exist cyclically in the outdoor environment or perennially indoors (Figure 1). A 2011 analysis revealed that allergic rhinitis cases contributed to 3 additional office visits, 9 more filled prescriptions, and $1500 incremental health care costs annually compared with patients without allergic rhinitis.[1] A recent estimation of indirect and direct costs related to allergic rhinitis was found to be $5.3 billion/y.[2] Asthma is a lower airway hypersensitivity commonly triggered by allergens or irritants. It affects approximately 24 million people in the United States (of which an estimated 7 million are children) and is a common cause of hospitalizations and bacterial suprainfections.

Diagnosis of upper airway allergic disorders is generally made on physical findings of vascular engorgement, hypersecretion, and lymphatic reactivity, but adjuncts can be used to assist in the identification of underlying pathology and its severity. Spirometry aids in the determination of lower respiratory tract involvement and can be used as a semi-quantitative indicator of whether or not systemic allergic manifestations have occurred and to what extent. This is also an essential measurement to ensure against the threat of airway compromise or if there is an expected allergy testing and treatment protocol. Practical ranges may vary, but a common industry standard is to have obstructive pulmonary defects medically managed to a forced vital capacity (FVC) and forced expiratory volume in one second $>80\%$ and forced expiratory flow (FEF) at 25%-75% of the FVC flow curve (FEF 25-75) $>50\%$ for maximal function and prior to the inoculation of any potential allergen to a patient. Sinus computed tomography (CT) evaluation is an extremely useful tool to ensure that proper underlying, structural disease is adequately assessed. As appropriate, rhinosinus pathology could be treated prior to the

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Tree Pollens	Weed Pollens
Cockroach	Cat Hair +/- Pelt
Grass Pollens	Dog Hair
Indoor/Outdoor Mold Spores	Dust Mite

Figure 1 Common Airborne Allergens.

determination of whether allergy testing should even be an element of evaluation for a given patient. Frequently, chronic sinus disease notable on CT may be found to accompany significant chronic allergic pathology of upper respiratory tract tissues and is a useful adjunct in the evaluation of recalcitrant cases of rhinosinus complaints. In some cases, when response to therapy is suboptimal or where the pathophysiology remains elusive, the use of blood or nasal eosinophil evaluation can help to discern allergic from infectious etiologies. Furthermore, in vitro radioallergen-sorbent testing (RAST) for IgE antibody levels can sometimes be helpful in determining the sensitivity a patient may have for a substance that cannot be skin tested—usually food—but can be difficult to interpret between sensitivity and frank allergy. It should be noted that both RAST and skin prick testing have an evidence rating of C (Figure 8) for food allergy detection, and these tests are highly nonspecific.[3] Delayed-type hypersensitivity (type IV) or atopic reactions (type I) may be assessed using skin patch testing to evaluate for dermatitis but are not very useful for IgE-mediated allergy. It is clear that, in certain difficult circumstances, these diagnostics may be beneficial to ascertain food avoidance. For environmental allergens, if immunotherapy is ultimately desired however, it remains necessary to undergo skin testing to the given suspect antigen.

Conservative environmental allergy management

Treatment for allergic symptoms should begin with avoidance and environmental decontamination in adjunct to conservative medical therapy.[6–11] Although proven useful in select cases, air filtration systems and mite-proof mattress and pillow covers fail to show consistent evidence of efficacy.[12] Frequently, avoidance or environmental isolation is unobtainable, especially with insect and food allergies; therefore, a standard course of appropriate medications should be attempted.[13–15] Additionally, if a patient has experienced anaphylaxis or is otherwise at high risk, an intramuscular epinephrine autoinjector should be carried at all times.[16,17]

The use of 0.9%-3% saline solution irrigation into the nares can safely be used with benefit in patients with chronic rhinosinusitis—evidence rating B[12]—and is an accepted method for select patients, such as those with rhinitis of pregnancy and acute rhinosinusitis.[18] The evidence is "less conclusive regarding use for symptoms related to mild to moderate allergic rhinitis and acute respiratory tract infections."[18]

With a long record of more than 50 years of efficacy, first-generation antihistamines are the mainstay of allergy therapy. Treatment failure, however, is common due to sedative and other anticholinergic side effects leading to intolerance and noncompliance. Second-generation antihistamines enjoy the luxury of easier dosing and less frequency of adverse effects and are considered essentially equal based on inconsistent differences found on study.[19,20]

The addition of oral pseudoephedrine, an alpha-adrenergic agonist, to antihistamines significantly improves nasal airflow.[21] One study showed the combination with oral antihistamines resulted in significantly improved nasal symptoms vs either agent used alone.[22] Another study showed that the combination of these 2 classes results in equal improvement to nasal beclomethasone with even better reduction of ocular symptoms.[23] The use of pseudoephedrine does unfortunately come with some limitations, such as questions regarding safety in pediatrics, misuse in illicit crystal-methamphetamine production, and potential for dangerous adverse effects in patients with hypertension, diabetes, coronary artery disease, hyperthyroidism, and monoamine oxidase inhibitor use.[24]

Nasal corticosteroids are highly effective in reducing IgE-mediated submucosal swelling and excessive secretions in the nasopharyx if used correctly and is considered first line for moderate to severe allergic rhinitis.[6] Certain limitations, however, may cause failure of this approach. Although nasal corticosteroids have relatively few adverse reactions,[25–28] already fragile mucous membranes may easily tear or bleed and there is an increased incidence of upper respiratory tract infections due to the connective tissue deposition and immune cell impairment of corticosteroids. Epistaxis occurs in 10% of patients using nasal corticosteroids[28] but generally does not require cessation of therapy. In pediatrics, it is best to choose non-beclomethasone due to possible delayed height attainment,[28] and some evidence points to the potential for subcapsular cataracts and increased intraocular pressure in adults using high doses.[26,28] Some cost prohibitions or self-administration variations may also lead to failure.

Leukotriene receptor antagonists are an effective agent for nasal symptoms, particularly in combination with other agents.[9] The agent montelukast is best utilized for the patient with an incomplete response to other agents, such as intranasal corticosteroids or over-the-counter decongestants in spite of lacking data to support any additional benefit.[29]

Allergic conjunctivitis significantly responds to mast cell stabilizers, especially in combination with topical ophthalmic ketorolac, but either agent could be used alone.[29,30]

In one study, the intranasal anticholinergic, ipratropium, worked as well or better than oral antihistamines[6–8,31] and provided relief from allergic rhinitis rhinorrhea similar to nasal corticosteroids in another study.[20]

Additional approaches show promise to the treatment of allergic pathology. The use of anti-IgE antibody (omalizumab) with which the clinical benefits appear to be at least

additive to conventional strategies.[32] Additionally, stimulation of Toll-like receptors, TLR9, or immunization with peptides or allergens is under evaluation for efficacy and safety as well as feasibility of large panel testing.[33,34]

Many osteopathic manipulative techniques can be employed to improve both the mechanical function and the physiological secretory drainage traits necessary for optimal upper and lower respiratory tract drainage and homeostasis. Cranial and facial methods can help assure that the bones of the cranium move rhythmically, thus reducing auditory tube obstruction and subsequent ear infections commonly related to a temporal bone restriction. Soft-tissue treatment of the neck and upper back also helps lymphatic drainage and encourages proper function of the ears, nose, and throat. Common methods to mobilize the cranial architecture include fronto-zygomatic lift and percussion with effleurage over the frontal, nasal, maxillae, and mastoids. To improve autonomic function to the mucosa and related cavities, venous sinus drainage, supraorbital and infraorbital nerve stimulation, and sphenopalatine ganglion release may greatly reduce upper respiratory tract obstructive and secretory symptoms. Lower respiratory tract allergy, most commonly in the form of bronchospasm, can be minimized by addressing the motion of the ribs, diaphragm, and the adjacent soft-tissue structures. Osteopathic techniques are highly useful in assisting lymph node drainage and can be effective when a child has taken a hard fall. An influence to the tailbone is known to trigger an asthma attack in a child, widely believed to be due to the relationship of the sacrum with the "primary response mechanism" (Frymann et al., personal communication, 2009). Making sure the sacrum is moving properly is very important to successful asthma treatment. Huard[35] identified that the "venous sinus technique" helps to restore optimal intracranial blood flow—measured by ultrasound—in the area of the cranial base and is a commonly applied procedure in the treatment of congestive headaches and sinus congestion. Another method is to massage the sinus ostea directly with surgical cotton swabs of diluted botanical essential oils, which appear to act locally as a decongestant with an induction of sympathetic tone to the sphenopalatine ganglion.[36–38]

Rational for immunologic testing

An IgE-mediated (type 1) immune hypersensitivity occurs by the stimulation and subsequent degranulation of inflammatory mediators by mast cells and eosinophils via antigen recognition of sensitized IgE-presenting B cells (Figure 2).

Skin prick or scratch testing can be used easily and safely to detect vectors of IgE-mediated allergic symptoms in a typical outpatient office setting when proper safety precautions are taken. Biochemical changes in the mucosa and nasal secretions occur following immunotherapy for allergic rhinitis. Compared with placebo, immunotherapy was associated with decreased concentrations of histamine, tosyl-L-arginine methyl esterase (bradykinin activator), and prostaglandin G_2. This immunotherapy effect suggests a reduction in mast cell mediator release and thus downregulates the early immune phases of allergic rhinitis.[4] Similarly, inflammatory cells, such as eosinophils, a primary component of late-phase allergy, may be inhibited by immunotherapy. Selected allergens for testing can be chosen among the predominant regional environmental culprits, typically airborne allergens plus foods, insect venom, and penicillin.[3] These are based on the cyclical plant life as well as the many perennial sources, which may be found indoors such as in moist, moldy basements, household pets, and buried potentially for generations in thick blankets of household dust within carpet or rugs (Figure 3). Although unclear in the literature, intuitively one could deduce that the more potential respiratory tract irritants in one's environment, the greater likelihood of clinically significant allergic symptoms. Although there are many food and hymenoptera antigen extracts available, the most time-proven and safe agents to use in a standard-equipped office derive from the common cyclical and perennial environmental respiratory tract allergen sources. Because the management of food allergy rests with avoidance and epinephrine rescue therapy, testing for food allergies can become quite complex and lacks good treatment options. Drug allergies are approached similarly with only drug desensitization as a therapeutic option; insect stings, although amenable to immunotherapy, are dangerously allergenic. Thus, it should be carefully considered whether patients suspect of drug, food, or insect sting allergies may need more complex evaluations that may be best served in the setting of a board-certified allergist. Most typical environmental allergens, however, can easily be evaluated in a primary care office.

Environmental allergen extracts are manufactured by the purification and concentration of materials, such as dust mite feces, furred animal epidermis and saliva, keratin of cockroaches, fungal spores, and a litany of possible plant pollens. When measured against negative (glycerin or saline) and positive (histamine in glycerin or saline) controls, 15 minutes is generally considered adequate time to induce a skin reaction consistent with the patient's immune sensitivity to the given allergen.

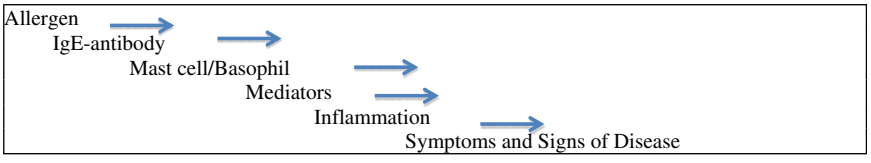

Figure 2 Type 1 hypersensitivity cascade.

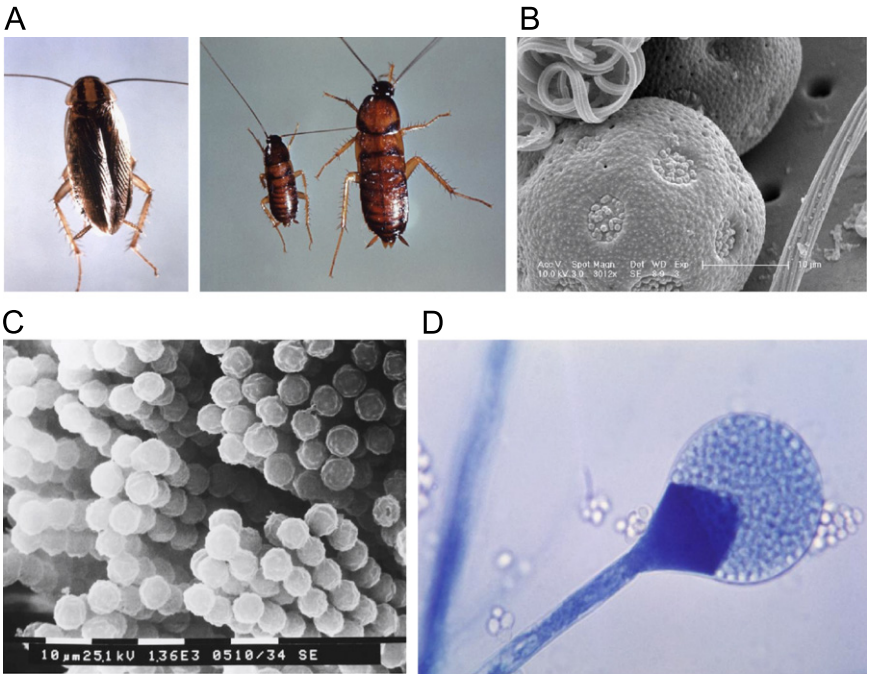

Figure 3 Samples of perennial environmental allergens: (A) cockroach, (B) pollen, (C) *Aspergillus conidiospores*, and (D) *Mucor sporangium*.[5]

Subcutaneous immunotherapy

Every allergy clinic generally develops its own patient selection criteria for the performance of prick or scratch allergy skin testing. In general, the decision to undergo allergy testing should be based on the likelihood of avoidance of an allergen or the clinical failure of conservative medical therapy. Failure can be determined by insufficient response to oral and intranasal therapies, excessive cost of conservative therapy compared with immunotherapy, exhaustion of reasonable environmental allergen control with cleaning, air filters, or dust covers, and a willingness to accept the risks, duration, and expense of immunotherapy. Once the proper candidate is identified and allergen testing interrogates allergen culprits, a prolonged course of immunotherapy can be highly effective at long-term or permanent partial to complete resolution of allergic symptoms.

The risk of systemic reactions, however, is considerable and should be weighed carefully by the patients' IgE-mediated immune system stability and other risk factors for treatment failure. Approximately 5%-10% of patients receiving immunotherapy have some form of systemic reaction. These reactions are classified as moderately severe in 1%-3% of cases, and rare cases of death from fulminant anaphylaxis have been reported in the literature.[6,39–41] In any circumstance where a patient has any symptoms following immunotherapy or is prompted to utilize their epinephrine autoinjector, the patient must agree to call 911 or report to the nearest hospital for appropriate treatment or monitoring.[16,17]

Although those treated with immunotherapy have a significantly decreased incidence of asthma development (25% vs 45% after 3 years of immunotherapy[42]), uncontrolled asthmatic pulmonary obstruction should be considered an absolute contraindication to immunotherapy or testing. In addition, it is widely considered to be unsafe to use concentrated allergens with patients using beta-blocker therapy due to the potential blockade of life-saving epinephrine should anaphylaxis occur. Otherwise, the literature presents inconsistent positions regarding further contraindications and must be weighed carefully by the patient and physician based on reported high-risk factors (Figure 4). There is an increased risk of death from anaphylaxis in patients with unstable coronary artery disease and, therefore, commonly felt to be contraindicated for immunotherapy.[43] There is also some question as to the safety and efficacy of this therapy in pregnant or very young patients due to immune system variability. For patients who become pregnant, their current dose without advancement was continued until gestational completion. A serious risk or benefit decision should also be made with any patient having experienced prior anaphylactic reactions as well as the theoretical immunologic effects of therapy in patients of autoimmune disease. Although studies have not found conclusive evidence of an association between immunotherapy and autoimmune disease, most authorities recommend against use in patients with a history due to the observed increase in IgG levels. There is a theoretical expectation that this change could lead to elevated immune complex deposition disease.[44] Any discussion to initiate skin scratch testing should involve detailed disclosure of the rare but significant risk of these issues to include anaphylactic shock or death. A common deterrent to medical compliance, the prolonged course, and frequent office visits necessary to result in a reliable, persistent benefit should also be clarified prior to beginning the immunotherapy phase.

Once the aforementioned areas have been completely approached or disclosed, we begin our immunotherapy

Pregnancy
Autoimmune Disease
Unstable Coronary Artery Disease
Beta Blocker Therapy
Unstable Asthma or FEV1<70% Predicted
Age Under 5 Years

Figure 4 Relative and absolute contraindications to immunotherapy.

screening by performing a pulmonary function test to ensure an FVC and forced expiratory volume in 1 second >79% and FEF 25-75 >49% prior to delivery of any potential allergen to a patient. Then, following a thorough discussion of environmental modifiers and medical options, it is time to obtain an exhaustive allergy history and examination. Following this, it is time to perform skin scratch testing on the correctly selected cases.

The skin of the back is cleaned with alcohol and marked for the sequence of antigens; then, the 40 preselected antigens for our region are gently applied in groups of 10 via applicator devices (Figure 5). After 15-minute observation, reaction degrees are then recorded focusing on the wheal formation as more reliable than erythema (Figure 6).

In the ideal setting, every immunotherapy patient should have a chart containing the following:

1. Detailed allergy history and examination.
2. Any prior anaphylactic or concerning allergic reactions.
3. Itemized list of skin scratch (+/− RAST) results.
4. Annual visit record to review risks or benefits of immunotherapy.
5. Annual review of any changes in medications or health condition.
6. Sign-off list for each shot visit to ensure no respiratory tract problems.
7. Injection record sheet with correct concentration sequence of viable extract dilutions used.
8. A standard approach in therapy modification to mild-moderate reactions.
9. Detailed patient consent to therapy with reiteration recorded with each visit.

After the discussed concerns have been addressed and the results of skin testing have been explained, the interpretation of skin reaction must be translated into a therapeutic plan. The skin surrounding the allergen inoculation would commonly respond with erythema, but it is the wheal development that provides the best indication of IgE sensitization. Different authorities recommend measurement of erythema or wheal or both. In our clinical experience, we have established a protocol of wheal measurement in millimeters to justify immunotherapy. When the wheal surrounding inoculation is at least 3 millimeters in diameter—regardless of erythema—the sensitivity is deemed adequate to justify therapy directed to this antigen. From a panel of 40 total purified extracts (available from multiple immunologic companies) including positive and negative controls, a comprehensive prescription can be developed. This mixture of positive-reacting allergens can be mixed by the immunologic extract companies or by the practitioner according to meticulous laboratory technique.

Each allergy clinic has established a protocol of mixed allergen prescription dilutions into 4 or 5 ascending concentrations. It is typical to begin the build-up phase with the dilution of 1:10,000 or 1:1000 that of the stock or maintenance concentration vial. The low-concentration vial chosen is used to initiate an ever-increasing volume of mixture delivery leading into stepping up to the subsequent concentration vial at low volume to escalate in the same manner. After reaching an optimal maintenance dose following injections every 2-3 days of increasing concentration or volume of allergen extract solution, injections may be delivered every 3-6 weeks for a total of 3-5 years to achieve statistically consistent symptomatic reduction.

In one study of adults with allergic rhinitis receiving immunotherapy, symptom and medication scores were reduced by two-thirds and endured for 3 years following

Figure 5 Comfortten skin prick devices.[45]

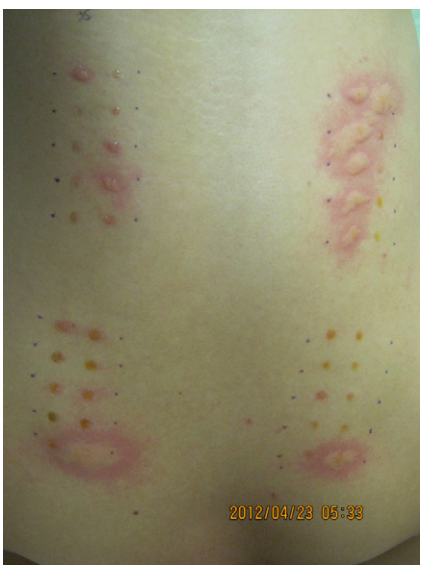

Figure 6 Skin prick marking, application, and wheal-positive reactions (Straley, D. unpublished clinical case).

cessation of therapy.[20] This is also the only known therapy that alters the natural course of the disease.[29] During the early stages of immunotherapy, the serum IgE level actually modestly increases, followed by a sharp increase in allergen-specific IgG. This is suggestive that the early treatment period may be that of greatest risk for anaphylaxis and other adverse effects.[46] Following this phase, the IgG level peaks and plateaus simultaneous to a gradual but consistent decline in IgE levels over a few years time. This continues throughout immunotherapy and likely for years following a full treatment program.[47]

Anaphylaxis emergency preparedness

Adverse reactions to immunotherapy are relatively common but, fortunately, are typically mild. The literature reports an incidence of adverse reactions between 1 and 17 per 1000 injections. The vast majority of these events occurred in patients with very strongly positive skin tests and unstable asthma during therapy. In all patients with asthma, it is important to give injections with great caution. A peak flow level of above 79% of the predicted value needs to be confirmed prior to every administration. In many practices, annual pulmonary function tests are also performed to ensure adequate bronchospastic control. Some authors also suggest that children under the age of 5 present too great risk for immunotherapy due to smaller airways and an increased risk of fatal bronchospasm.[47]

In addition, it is essential that if anytime immunotherapy is administered, a physician should be present for the 30-minute minimum observation period. In preparation for adverse reaction treatment, a typical allergy cart should be maintained in adjunct to the common code cart to contain the following:

1. Epinephrine (1:1000) for intramuscular injection
2. Intravenous access supplies with isotonic fluids
3. Stethoscope
4. Injectable diphenhydramine
5. Injectable methylprednisolone
6. Oxygen and masks with aerosol capabilities
7. Albuterol nebulizers
8. Endotracheal intubation kit
9. Oral suspension of cetirizine or diphenhydramine or both (optional).

In the event of suspected anaphylaxis, an injection of intramuscular epinephrine at 1:1000 dilution maximally dosed at 0.3 mg for children and 0.5 mg for adults in conjunction with airway and hemodynamic management is the first and most critical step in the treatment of anaphylaxis.[48] Essential components of this management should include non-rebreather 100% oxygen and intravenous bolus fluids where hypotension is inadequately responsive to epinephrine.[13,14,16,17,49–51] The early manifestations of concern for anaphylaxis, physiological changes remote from the site of allergen contact, present primarily via vasodilation with extravasation of fluid and increased sensitivity of respiratory tract smooth muscle (Figure 7).[48,49,51] Clinically, this typically is seen as angioedema, urticaria, hypotension, cough, voice changes, stridor, and a cascade of compensatory systemic responses and behavioral decompensation. Skin involvement occurs in 90% of episodes, signs of upper airway obstruction manifest in 70% of episodes, and severe hypotension occurs in 45% of anaphylaxis.[13,14,49,50] The patient may also experience gastrointestinal tract distress and neurobehavioral changes in 45% and 15% of cases, respectively.[13,14,49,50] Any patient not rapidly resolving to these emergency treatments or where significant cardiopulmonary changes (eg, hypoxia, respiratory tract distress, and hypotension) have occurred should be immediately transferred by emergency medical service to the nearest emergency department.[48] It should also be heeded that a rare but potentially lethal second phase of immune reaction can also occur within 8 hours of the initial reaction and thus, regardless of the patient disposition, a 10-24-hour period of close observation is mandate.[16,48,52] Additionally, the use of intravenous corticosteroids may be beneficial in preventing this second phase of a biphasic reaction but is not routinely utilized.[53–55]

In the event of an adverse reaction to immunotherapy, it must be carefully determined with the patient whether or how to proceed with immunotherapy. Common practice is to cut the dose volume of the subsequent injection in half, repeat 3 times, then proceed along the dosing advancement plan. If scheduled injections are missed, it is important to adopt a "sliding scale" plan for a graded decrease in subsequent doses and advancement. The severity of reaction can help guide a more cautious maximum maintenance extract dose.

Dermatologic/Mucosal
- Eyes: periorbital edema & erythema, conjunctival injection, tearing
- Oral: tongue and lip angioedema
- Skin: urticaria, pruritis, flush, morbilliform rash, piloerection, angioedema

Respiratory
- Lower: bronchospasm, wheeze, cough, tightness, tachypnea, reduced peak expiratory flow, cyanosis, respiratory arrest
- Upper: throat sensation, cough, dyspnea, dysphagia, dysphonia, stridor, cyanosis, respiratory arrest

Cardiovascular
- Early: tachycardia, diaphoresis, delayed capillary refill, hypotension
- Late: bradycardia, shock, T-wave inversion or ST depressions, cyanosis,cardiac arrest

Gastrointestinal
- Nausea, vomiting, diarrhea, abdominal cramps

Neurologic
- Headache, dizziness, confusion, tunnel vision, unconsciousness

General
- Anxiety, impending doom, metallic taste, limb paresthesia, malaise, weakness

Children: sudden behavior or irritability changes, cessation of play

Figure 7 Anaphylaxis manifestations.[48,49,51]

Strength of Recommendation	Definition
A	Recommendation based on consistent and good-quality patient-oriented evidence*
B	Recommendation based on inconsistent or limited quality patient-oriented evidence*
C	Recommendation based on consensus, usual practice, opinion, disease-oriented evidence,** and case series for studies of diagnosis, treatment, prevention, or screening.

** Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, quality of life.•** Disease-oriented evidence measures intermediate, physiologic, or surrogate endpoints that may or may not reflect improvements in patient outcomes (i.e., blood pressure, blood chemistry, physiological function, and pathological findings).*

Figure 8 Strength of recommendation.[56]

Discussion

Allergic disease presents in many forms and sometimes can be a diagnostic challenge. The significance of symptom severity upon daily function and comfort with the expanding list of effective therapies obligates a good understanding of allergic disease and the many treatment options. Every patient should first attempt conservative, appropriately selected, standard allergy medications along with environmental allergen control and avoidance with adjuncts, such as air filters or dust covers. When these methods fail or are financially burdensome, it is accepted practice to consider immunotherapy via skin testing and extract dilution injections directed toward IgE-mediated hypersensitivity. Although it may not be suitable for every primary care office, the establishment of a skin sensitization evaluation and immunotherapy program is relatively inexpensive and safe. The long-term benefits can be a significant reduction or even complete elimination of hindering and sometimes dangerous IgE-mediated disease with the associated high health care costs.

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