Clinical Care Statements

AMERICAN ACADEMY OF OTOLARYNGIC ALLERGY

In response to member requests, your AAOA Board of Directors recently adopted the following Clinical Care Statements. These statements are being distributed in the **AAOA Today**, our membership newsletter, and posted on our website **www.aaoaf.org** for easy reference for our members.

Our intention is to assist otolaryngologists by sharing evidence-based summaries on recommended therapies and practices from the current medical literature. They do not attempt to define a quality of care for legal malpractice proceedings. They should not be taken as recommending for or against a particular company's products. The Clinical Care Statements are not meant for patients to use in treating themselves or making decisions about their care. Advances constantly occur in medicine, and some advances will doubtless occur faster than these Clinical Care Statements can be updated.

Otolaryngologists will want to keep abreast of the most recent medical literature in deciding the best course for treating their patients.

This compendium of work was only achievable through the tireless efforts of our Clinical Care Statement Workgroup

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Compendium of Clinical Care Statements

Note: American Academy of Otolaryngic Allergy's (AAOA) Clinical Care Statements attempt to assist otolaryngic allergists by sharing summaries of recommended therapies and practices from current medical literature. They do not attempt to define a quality of care for legal malpractice proceedings. They should not be taken as recommending for or against a particular company's products. The Statements are not meant for patients to use in treating themselves or making decisions about their care. Advances constantly occur in medicine, and some advances will doubtless occur faster than these Statements can be updated. Otolaryngic allergists will want to keep abreast of the most recent medical literature in deciding the best course for treating their patients.

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Anaphylaxis

Definition

Anaphylaxis is defined as:[1, 2, 3]

1) The acute onset of a reaction (minutes to hours) with involvement of the skin, mucosal tissue or both and at least one of the following: a) respiratory compromise or b) reduced systemic blood pressure or signs/symptoms of end-organ dysfunction.
2) Two or more of the following that occur rapidly after exposure to a particular allergen for that patient: involvement of the skin/mucosal tissue, respiratory compromise, reduced blood pressure or associated symptoms, and/or persistent gastrointestinal symptoms.
3) Reduced blood pressure after exposure to a known allergen.

Clinical Presentation

Anaphylaxis has many different signs and symptoms and can present differently among patients. The most common manifestation of anaphylaxis is cutaneous, including urticarial and angioedema, and can occur up to 90% of the time. However, the absence of cutaneous signs does not rule out anaphylaxis.[4] The respiratory system is the second most common system affected, including dyspnea, bronchospasm, and wheezing. The gastrointestinal and cardiovascular systems can be affected as well, including nausea, vomiting, diarrhea, abdominal pain, and hypotension.[5] Other less common manifestations can occur such as headache.

Signs and symptoms of anaphylaxis can appear within minutes of exposure to an allergen. Be aware that some reactions can appear greater than 30 minutes after exposure. Anaphylaxis can be biphasic, meaning that symptoms can recur hours after resolution of the initial phase. When this occurs, most of the time it is within 10 hours. Patients should be monitored for at least a few hours after initial resolution of symptoms with consideration of overnight observation after more severe episodes (the optimal duration of the observation period has not been established in the literature).[7]

When discharged, patients must be counseled of these facts and strong consideration should be made to provide auto-injectable epinephrine along with instructions for use.[2, 3]

Management of Anaphylaxis–Immediate Intervention[3]

Clinicians must be aware that initial mild symptoms may progress rapidly into a life-threatening situation unless identified and treated promptly. Epinephrine is the only first-line treatment, and delay in administration can lead to serious consequences. Treatment recommendations and decisions to transfer patients to a different care setting are made on an individual basis by the physician. Please note that the following recommendations do not have to be followed in the stepwise order presented and many of these interventions should happen simultaneously.

1. Assess airway, breathing, and circulation. Monitor vital signs.
2. Administer epinephrine:
   Aqueous epinephrine 1:1000 dilution (1 mg/ml): 0.2-0.5 ml IM in lateral thigh or subcutaneously every 5 min as necessary to control symptoms. In children, 0.01 mg/kg, MAXIMUM SINGLE DOSE is 0.3mg.
3. Call 911.
4. Place patient in supine position with lower extremities elevated.
5. Administer oxygen.
6. Obtain IV access and administer rapid IV fluid replacement.
7. Place tourniquet above injection site.
8. Consider diphenhydramine 1-2 mg/kg or 25-50 mg/dose parenterally. NOTE: H1 antihistamines are second-line and should not be administered instead of epinephrine in the treatment of anaphylaxis.
9. Consider ranitidine for children and adults and cimetidine for adults only. For ranitidine, use 50mg in adults and 12.5-50mg (1 mg/kg) in children. For cimetidine, use 4 mg/kg IV in adults. There is no pediatric dose for cimetidine.

   NOTE: H2 blockers are considered second-line and should not be administered instead of epinephrine.

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10. Consider inhaled beta-agonist (MDI or nebulized) for bronchospasm.
11. Consider IV steroids. NOTE: steroids do not work acutely and should not be used in place of epinephrine.
12. Consider advanced cardiac life support measures for cardiopulmonary arrest during anaphylaxis.
13. Endotracheal intubation or a surgical airway may be needed if respiratory distress persists or worsens after initial treatment.
14. Consider glucagon in patients taking beta-blockers with refractory symptoms. The recommended dose is 1-5 mg administered IV over 5 minutes followed by a 5 to 15 mcg/min infusion; titrate infusion rate to achieve an adequate clinical response.

    In children, the dose is 20–30 mcg/kg (maximum: 1 mg), followed by an infusion of 5 to 15 mcg/minute; titrate the infusion rate to achieve an adequate clinical response.

Please note that epinephrine is the only medication that is required to be available in the office where allergy skin testing and immunotherapy are performed. Keeping some of the above medications on hand can be considered by individual physicians and practices based on their location and proximity to pharmacy services.

Prevention

Clinicians should recognize that there are certain factors that could potentially put patients at increased risk of anaphylaxis. These include active asthma, immuno–therapy escalation, vial prepared in another office, errors in dosing, injection of wrong patient serum, immuno–therapy injections during peak allergy season, first injection from a new vial, and history of anaphylaxis.[6]

It remains controversial if preceding large local reactions predict systemic reactions.[7] Underlying medical conditions must be taken into consideration if treatment of anaphylaxis may pose a significant health risk (e.g., administration of epinephrine in patient with cardiovascular disease).

Medications prescribed for common medical conditions can also place patients at increased risk. Beta-blocker therapy may render a patient more refractory to management with epinephrine. ACE inhibitors have been shown to increase risk of anaphylaxis in those undergoing venom immunotherapy.[8]

Patient Education

Patients undergoing immunotherapy and those with a history of anaphylaxis should be instructed on how to recognize signs and symptoms of anaphylaxis. They should also be instructed on how to properly administer auto-injectable epinephrine. Family members of children should be educated on recognition and initial treatment of anaphylaxis with epinephrine.

Preparation

Offices and facilities administering immunotherapy should be prepared to treat anaphylaxis. Physicians and office staff should have an established protocol in place, which can be reinforced with rehearsal drills.[6] Anaphylaxis treatment medications, in particular epinephrine, should be immediately available and replaced if used or expired. Health providers administering injections should be trained in the recognition and management of anaphylaxis. It is recommended to continually review medications patients take prior to administration of immunotherapy to avoid placing patients at higher risk of a systemic reaction.

1 Sampson HA, Munoz-Furlong A, et al. *Second symposium on the definition and management of anaphylaxis: Summary report–second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis network symposium* J Allergy Clin Immunol 2006; 117:391-7.

2 Tang A. *A Practical Guide to Anaphylaxis.* Am Fam Physician 2003; 68:1325-32.

3 Lieberman P, Nicklas R, et al. *The diagnosis and management of anaphylaxis practice parameter: 2010 Update.* J Allergy Clin Immunol 2010; 126:477-80.

4 Lieberman P. *The risk and management of anaphylaxis in the setting of immunotherapy.* Am J Rhinol Allergy 26, 469-474, 2012.

5 Hurst DS, Gordon BR, et al. *Safety of Home Based and Office Allergy Immunotherapy: a multicenter prospective study.* Otolaryngol Head and Neck Surg 1999; 121:553-561.

6 Simons FE, Ardusso LR, et al. *World Allergy Organization Anaphylaxis Guidelines: 2013 Update on the Evidence Base.* Int Arch Allergy Immunol. 2013;162(3):193-204.

7 Lieberman P. *Recognition and First-line Treatment of Anaphylaxis.* Am J Med. 2014 Jan;127(1 Suppl):S6-11.

8 Simons FE, Ardusso LR, et al. *World Allergy Organization Anaphylaxis Guidelines: 2013 Update on the Evidence Base.* Int Arch Allergy Immunol. 2013; 162(3):193-204.

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Compounding of In Office Vials

Physicians with training and expertise in allergen immunotherapy are qualified to safely compound allergy immunotherapy vials in their own office if specific criteria are met. The revised USP 797 guidelines **http://www.usp797.org/** must be followed. In addition, the AAOA/JCAAI Joint Task Forces Immunotherapy Guideline: **http://www.jcaai.org** recommendations should be taken into consideration. Ultimately, a formal mixing standard should be adopted and implemented for each office. This standard should focus on guidelines for aseptic technique and sterility, adequate training of compounding personnel, and appropriate physician supervision.

The compounding bill, passed by Congress in November 2013, enforces regulation of compounding pharmacies. Note that the preparation of allergenic extract vials is considered compounding. The statute contains two provisions that do impact allergy immunotherapy:

1. All compound sterile preparations have a prescription.
2. Physicians must comply with all of the USP 797 sterile compounding rules.[1]

[1] Lin, SY et al. *Impact of newly revised sterile medication compounding guidelines USP <797> on allergy vial prep.* Otolaryngology–Head and Neck Surgery (2008): 139, 5-6.

Duration of Immunotherapy

The purpose of this AAOA clinical care statement is to guide physicians in determining the appropriate duration of specific immunotherapy (SIT). To date, there are no specific tests to help physicians predict which patients will relapse after discontinuation of SIT.

Evidence:
In two studies examining mite SIT for duration of 1 year or less, efficacy was lost after 1 year.[1, 2]

Des Roches et al. conducted a controlled, prospective study to assess the duration of efficacy of specific immunotherapy after discontinuation. The rate of relapse after discontinuation of SIT was significantly higher in the group who received SIT for under 35 months. A longer duration of SIT was associated with increased efficacy.[3]

Durham et al. conducted a randomized double-blind, placebo-controlled cessation study of grass pollen immunotherapy. They showed that, after three to four years of grass pollen SIT, efficacy remained comparable in patients who discontinued SIT and in those who continued injections. Clinical benefit was observed for at least three years after discontinuation.[4]

The duration of immunotherapy efficacy has also been studied in Hymenoptera hypersensitivity with no clear consensus. Some studies showed that a 3–year duration of SIT was protective, whereas others showed better outcomes in those treated with at least a 4–year duration. Relapse rate and severe reactions are greater in those patients whose duration of SIT was less than 5 years. Multiple studies suggest that a 5–year duration of immunotherapy for Hymenoptera hypersensitivity is sufficient in most patients.[5]

Recommendation:
In summary, the rate of relapse decreases in relationship to the duration of treatment, but data is lacking to accurately determine the ideal duration of SIT.

The decision to discontinue specific immunotherapy is made between the physician and patient and must be individualized. The best available evidence supports a 3–5 year duration of SIT.

1 Price JF, Warner JO, et al. *A controlled trial of hyposensitization with adsorbed tyrosine Dermatophagoides pteronyssinus antigen in childhood asthma: in vivo aspects.* Clin Allergy 1984; 14:209-219.

2 Smith A. *Hyposensitization with Dermatophagoides pteronyssinus antigen: trial in asthma induced by house dust.* BMJ 1971; 4:204-6.

3 Des Roches A, Paradis L, et al. *Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. V. Duration of the efficacy of immunotherapy after its cessation.* Allergy. 1996 Jun; 51(6): 430-3.

4 Durham SR, Walker SM, et al. *Long-term clinical efficacy of grass-pollen immunotherapy.* N Engl J Med. 1999 Aug 12; 341(7): 468-75.

5 Cox L, Nelson H, et al. *Allergen immunotherapy: a practice parameter third update.* J Allergy Clin Immunol. 2011 Mar; 127(3): 840.

Home Subcutaneous Immunotherapy

The American Academy of Otolaryngic Allergy (AAOA) encourages the preferential practice of administering immunotherapy in a medical office setting with professionals trained in the recognition and management of anaphylactic reactions. The AAOA also recognizes the need for patients to make decisions affecting their personal healthcare choices, including the choice of home–administered immunotherapy, after receiving risk and benefit information from qualified healthcare providers through an informed consent process. The physician should assess the risks and benefits of in-office versus home–administered immunotherapy for each individual patient, taking into account the severity of allergic disease, coexisting medical conditions and medications, and other relevant individual patient characteristics. The risk and benefits should be discussed with each individual patient.

- The AAOA recognizes that subcutaneous immuno–therapy is a valuable treatment option for patients suffering from allergic diseases, such as allergic rhinitis and conjunctivitis.
- The AAOA also recognizes the safest place for administration of injection immunotherapy is in the office of a medical professional trained in the administration of immunotherapy and the recognition and treatment of potential immuno–therapy complications, including anaphylaxis. The relative safety of home-administered immuno–therapy when patients are properly selected based on physician risk assessment has been documented.[1]
- Some patients, due to life factors that limit their ability to follow a regime of immunotherapy injections restricted to a medical office environment, may have access issues to allergy care. Limited access to immunotherapy could increase a patient's risk of developing a more morbid allergic disease such as allergic asthma.
- Medical professionals regularly assess the risks and benefits of a particular medical intervention, explain these risks and benefits to a patient, and allow the patient to make decisions on which medical treatments to accept (in an informed consent process). The informed consent process is commonly practiced without formal documentation (such as with common medications), but sometimes is formalized in a signed document, particularly with interventions considered to carry more significant risk of adverse effects (such as surgical interventions and some medications with more significant risks of adverse effects).
- Patients are routinely given medical treatment options with recognized risks to accomplish desired potential benefits. The AAOA affirms the right of patients to make decisions about personal medical therapy options when they are properly informed of the potential risks and benefits by a qualified medical professional.
- If a medical professional determines a particular patient has an acceptable risk/benefit ratio to allow the option of home immunotherapy, and the patient decides to proceed with the option of home immunotherapy, the physician should provide clear directions and training on the proper technique for handling and administering the immunotherapy products. The patient should also be trained in the recognition and treatment of potential adverse events, including the availability and use of epinephrine auto-injectors. All injections at home should be given in the presence of another responsible adult provided with instructions in the recognition of potential anaphylaxis and basic initial treatment of anaphylaxis, including epinephrine auto-injector administration and contacting emergency services.

1 Hurst DS, Gordon BR, Fornadley JA, et al. *Safety of home-based and office allergy immunotherapy: A multicenter prospective study.* Otolaryngology–Head & Neck Surgery 1999; 121:553-61.

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Immunotherapy Vaccine Preparation—Practical Issues

After undergoing allergy testing, either in vivo or in vitro, a patient may elect to pursue subcutaneous allergy immunotherapy. Once prescribed, the immunotherapy vaccine vials may be formulated in physician's office, under sterile conditions.

Diagnostic services including allergy testing codes are generally assigned a level of physician supervision to be covered by Medicare when the service is not personally performed by a physician. There are 3 levels of supervision–personal, direct, and general defined as follows:

General Supervision–means the procedure is furnished under the physician's overall direction and control, but the physician's presence is not required during the performance of the procedure. Under general supervision, the training of the nonphysician personnel who actually perform the diagnostic procedure and the maintenance of the necessary equipment and supplies are the continuing responsibility of the physician.

Direct Supervision–in the office setting means the physician must be present in the office suite and immediately available to furnish assistance and direction throughout the performance of the procedure. It does not mean the physician must be present in the room when the procedure is performed.

Personal Supervision–means a physician must be in attendance in the room during the performance of the procedure.

Codes 95004, 95024 and 95027 are all assigned a direct supervision status indicator.

Most therapeutic services including immunotherapy injections such as Codes 95115 and 95117 and preparation of a vial (95144 and 95165) are as "incident to" service and not as diagnostic tests. Incident to services require direct supervision meaning the physician is in the office suite when the service is performed.

Allergy vaccines prepared for the delivery of immuno–therapy must include additives for bacteriostasis and potency preservation. There are three available diluents and additives presently used in the preparation of immunotherapy vaccines used for either subcutaneous or sublingual routes. It is recommended that agent or agents that are bacteriostatic and act as antigen stabilizers be utilized. These options include glycerin (10 or 50%), which can act as both a bacteriostatic agent and antigen stabilizer in higher concentrations; phenol, which is bacteriostatic; and human serum albumin (HSA), which acts as a stabilizer and decreases antigen adherence to the glass vial; or combinations of these agents.[1, 2, 3, 4, 5]

A marked decrease in antigen potency was noted when phenolated saline was used alone.[2, 5, 6] Phenolated saline can be used with HSA, and also has an additive effect on preservation when used with 10% glycerin.[4] When preparing immunotherapy vials for sublingual therapy one should consider using 50% glycerin as the diluent, to incorporate the bacteriostatic and stabilizing properties and improve palatability.

In addition, it is recommended that allergy practitioners maintain consistency with antigen lots and antigen suppliers as much as possible to reduce variation of potency and dose.[5] However, the Academy recognizes the need to switch antigen suppliers under certain circumstances. Caution should be used when changing

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lots of individual antigens, and especially when changing antigen suppliers, as potency can vary significantly, even in well-characterized or standardized extracts.
The clinical implication of changing lots of antigen supplier should also be determined by the clinician as the patient's risk factors and history with immuno–therapy should be incorporated into the decision.

If an antigen supplier switch is necessary, options include:

1. Re-testing the affected patient with the antigens from the new antigen supplier to establish new endpoints for immunotherapy thereby establishing a new safe initial dose.
2. Implementing the recommendations of the antigen supplier for conversion.

In all circumstances, a new vial test is highly recommended whenever new lots of antigen or new antigen suppliers are used.

Also, several clinical scenarios have been identified in which a single treatment vial for immunotherapy may not be adequate. It is recommended to consider separation into more than one vial antigens with known high proteolytic activity from antigens that are sensitive to proteases or antigens with low proteolytic activity to preserve their potency over the course of immuno-therapy treatment.[6, 7] In addition, at least temporary separation of antigens into more than one vial may be considered when there are antigens to which a patient is highly
sensitized and antigens to which the patient is less sensitized, in order to minimize the risk of reaction as well as avoid hindering advancement of less sensitive antigens during escalation.[6, 7, 8] Also, separation may be necessary if the number of antigens included in the patient's vaccine exceeds what is allowable based on the total volume of the treatment vial.[6, 7]

1 Cox L, et al. *Allergen Immunotherapy: A practice parameter third update.* J Allergy Clin Immunol. 27(1): S1-S55. 2010.

2 Nelson HS. *Effect of preservatives and conditions of storage on the potency of allergy extracts.* J Allergy Clin Immunol. 67(1): 64–69, Jan 1981.

3 Nelson HS, et al. *Studies of allergen extract stability: The effects of dilution and mixing.* J Allergy Clin Immunol. 98(2): 382-388, Aug 1996.

4 Gilbert KC, et al. *Antibacterial properties of additives used in injection immunotherapy.* International Forum Allergy Rhinology, 2(2): 135-8, Mar-Apr 2012.

5 Bosquet J, Lockey R, Malling H-J. *Allergen immunotherapy: Therapeutic vaccines for allergic diseases–A WHO position paper.* J Allergy Clinical Immunology. 102(4):558-62. Oct 1998. Benefit Policy Manual, sections 60 to 60.4 **http://cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf**

6 King HC, et al. *Allergy in ENT Practice, second edition.* Theme Medical Publishers, Inc. New York, NY, 2005: 226-229, 273-79

7 Haydon RC III, Gordon BR. *Aeroallergen immunotherapy.* In: Krause HF, et al., ed. Allergy and immunology: an otolaryngic approach. Philadelphia: Lippincott Williams & Wilkins, 2002; 170-1.

8 Ward WA Jr. *Skin endpoint immunotherapy.* In: Krause HF, ed. Otolaryngic allergy and immunology. Philadelphia: WB Saunders, 1989; 155-62.

In Vitro

The American Academy of Otolaryngic Allergy (AAOA) supports the use of in vitro testing as a diagnostic option.

Similar to skin testing techniques, in vitro testing aims to confirm the suspicion of IgE–mediated disease by confirming the presence of allergen–specific IgE in the allergic patient. Serologic evaluations for allergic disease include RAST, mRAST, CAP, and more recently molecular allergy/component testing. In Vitro testing is especially helpful in patients who are not candidates for skin prick testing (SPT).[1]

In vitro testing can be considered an alternate to skin prick testing. Compared to skin prick testing, in vitro testing correlation varies with individual antigens and ranges from less than 50% to greater than 90%. Negative in vitro test results; however, need to be correlated clinically as negative results may not exclude clinical disease.[1] In some situations, skin prick testing is not as accurate as in vitro testing.[2]

The American Academy of Otolaryngic Allergy recommends the use of in vitro testing in the following subsets of patients.

- Severe or poorly controlled asthmatics
- Reactions, severe to anaphylactic, to food or venom
- Widespread dermatologic conditions
- Uncooperative patient
- Use of (or unable to discontinue) medications that may mask the cutaneous response or may make anaphylaxis more difficult to treat.

Molecular allergy/component-resolved testing includes single molecular allergen/component testing, allergen specific panels covering a single allergen, or micro-array semi-quantitative testing panels.

Molecular allergy technology still requires more extensive FDA review before it can become integrated to current allergy practice standards. Its ability to distinguish true sensitization from cross–reactive sensitization in poly–sensitized patients, to better determine the risk of systemic reaction in food allergy, and to improve the indications for immunotherapy in specific clinical contexts will position its use relative to conventional serologic specific IgE testing.[3]

The American Academy of Otolaryngic Allergy recommends further consideration of molecular allergy as an additional diagnostic means in allergy diagnosis.[3]

1 Bernstein, L. et al. *Allergy Diagnostic Testing: An updated practice parameter.* Annals of Allergy, Asthma, and Immunology March 2008; 100:S44.

2 Gabriele De Bos, MD, et al. *Discordance Between Aero Allergen Specific Serum IgE and Skin Testing in Children Younger Than Four years.* Ann Allergy, Asthma, Immunol 110 (2013) 438-435.

3 Canonica, WG, A WAO–ARIA–*GA²LEN consensus document on molecular–based allergy diagnostics,* World Allergy Organization Journal 2013, 6:17–**http://www.waojournal.org/content/6/1/17**

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Medicines to Avoid Before Allergy Skin Testing

The American Academy of Otolaryngic Allergy (AAOA) has developed this clinical care statement to assist healthcare providers in determining which medicines patients should avoid prior to skin testing. These medicines are known to decrease or eliminate skin reactivity, causing a negative histamine control. Providers should have a thorough understanding of the classes of medicines that could interfere with allergy testing. With proper patient counseling, the goal is to yield interpretable skin results without unnecessary medicine discontinuation.

Antihistamines suppress the histamine response for a variable period of time. In general, first-generation antihistamines can be stopped for 72 hours, however, several types including Cyproheptadine (Periactin) can have active histamine suppression for up to 11 days. Second-generation antihistamines also suppress testing for a variable length of time, up to 7 days. Astelin (Azelastine) nasal spray has been shown to suppress testing for up to 48 hours.[1, 2, 3, 4, 5, 6, 7]

Short-term oral corticosteroids (30 mg daily for a week) do not suppress skin testing.[8] There is a difference of opinion about the effects of long-term or relatively high-dose steroids, i.e. greater than 20 mg of prednisone per day, on the suppression of immediate skin tests.[9, 10]

Topical glucocorticosteroids can block the histamine response.[11, 12, 13] Application of potent topical steroids have been shown to stop the histamine response for up to three weeks.[14]

Tricyclic antidepressants can suppress the antihistamine response from 7 to 14 days depending upon the type.[15, 16]

Benzodiazepines should be discontinued for 7 days before the testing and include clonazepam, diazepam, lorazepam, and midazolam.[15] Alprazolam has also been shown to inhibit skin testing.[17]

H2 blockers have the potential to suppress histamine skin reactions for up to two days and include cimetidine, ranitidine, and famotidine.[18, 19]

Beta blockers are a risk factor for more serious and treatment resistant anaphylaxis, making the use of beta blockers a relative contraindication to inhalant skin testing.

Treatment with omalizumab (anti-IgE antibody) can suppress skin reactivity for up to six months.[20, 21]

Topical calcineurin inhibitors have a variable affect. Pimecrolimus[22] did not affect histamine testing but tacrolimus[12] did.

Herbal products have the potential to affect skin prick testing. In the most comprehensive study,[23] using a single–dose crossover study, it was felt that common herbal products did not significantly affect the histamine skin response. However, complementary and other alternative medicines do sometimes have a significant histamine response[24] and included butterbur, stinging nettle, citrus unshiu powder, lycopus lucidus, spirulina, cellulose powder, traditional Chinese medicine, Indian ayurvedic medicine.

Leukotriene receptor antagonist did not affect skin testing.[25, 26, 27]

Selective serotonin reuptake inhibitors (SSRIs) do not affect skin testing.[15, 28]

Selective norepinephrine reuptake inhibitors (SNRIs) and protein pump inhibitors (PPIs) are felt not to need to be discontinued.[15]

Cyclosporin did not affect skin histamine response.[29]

ACE inhibitors did not affect histamine skin response.[30]

Healthcare providers should take into consideration that many of these studies are done when the patient is taking one pharmaceutical agent for a short time. It is unclear, if a patient is taking multiple pharmaceutical/herbal agents that alone have a minor effect, whether the combination of these drugs could suppress the histamine response. Therefore, it is imperative that the provider have a positive skin histamine response before proceeding with diagnostic skin testing.

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Medicines to Avoid Before Allergy Skin Testing

1 Bernstein, L. et al *Allergy Diagnostic Testing: an updated practice parameter.* Annals of Allergy and Asthma Immunology 2008; 100:S18.

2 Long, WF., Taylor, RJ., Wagner, CJ., Leavengood, DC., Nelson, HS. *Skin test suppression by antihistamines and the development of subsensitivity.* Journal of Allergy and Clinical Immunology 1985; 76:113-7 (111).

3 Cook, TJ., MacQueen, DM., Wittig, HJ., Thornby, JI., Lantos, RL, Virtue, CM. *Degree and duration of skin test suppression and side effects with antihistamines: a double blind controlled study with five antihistamines.* Journal of Allergy and Clinical Immunology 1973; 51:7107. (111).

4 Phillips, MJ., Meyrick Thomas, RH., Moodley, I., Davies, RJ. *A comparison of the in vivo effects of ketotifen, clemastine, chlorpheniramine and sodium cromoglycate on histamine and allergen induced weals in human skin.* Br J Clin Pharmacol. 1983; 15:277-86. (11a).

5 Almind, M., Dirksen, A., Nielsen, NH., Svendsen, UG. *Duration of the inhibitory activity on histamine-induced skin weals of sedative and non-sedative antihistamines.* Allergy. 1988; 43:593-6 (111).

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Medicines to Avoid Before Allergy Skin Testing

Suppressant Effects of Drugs on Immediate Skin Tests*

MEDICATIONS	MEAN DAYS SUPPRESSED	MAX DAYS SUPPRESSED
First Generation Antihistamines[1]	2	5
Second Generation Antihistamaines	2	7
Antihistamine Nasal Sprays	0	1
Antihistamine Eye Drops	0	1
Tricyclic Antidepressants and Tranquilizers		14
Histamine2 Antihistamines (H2 Blocker)	0	2
Topical Corticosteroids		Up to 21

Medications that DO NOT Need to be Stopped Prior to Allergy Skin Prick Testing*

Angiotensin-Converting Enzyme (ACE) Inhibitors	Benazepril Captopril Enalapril Lisinopril Perindopril Quinapril Ramipril
Immunosuppressant	Cyclosporin
Nasal Steroid Sprays	Beclomethasone Dipropionate Nasal Budesonide Nasal Ciclesonide Nasal Fluticasone Propionate Fluticasone Furoate Nasal Mometasone Furoate Nasal Oxymetazoline Triamcinolone Acetonide
Norepinephrine Reuptake Inhibitors (SNRIs)	Duloxetine Venlafaxine
Protein Pump Inhibitors (PPIs)	Esomeprazole Lansoprazole Omeprazole Pantoprazole Rabeprazole
Serotonin Reuptake Inhibitors (SNRIs)	Citalopram Escitalopram Fluoxetine Paroxetine Sertraline

*See prior references[1] Some exceptions see prior references

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Nurse Practitioners and Physician Assistants in the Practice of Allergy in the Otolaryngology Office

The American Academy of Otolaryngic Allergy (AAOA) recognizes the training and expertise available from within the Nurse Practitioner (NP) and Physician Assistant (PA) communities. An increasing number of otolaryngology practices are finding these practitioners to be a valuable asset for extending the reach of the practice in the community.

The AAOA, through its stated mission of supporting otolaryngologists who practice allergy, is prepared to assist in the training and continuing education of NP/PAs associated with an allergy practice. It is understood that any training or support of NP/PA training is considered an extension of, and in conjunction with, the training and support of the otolaryngologist who is practicing allergy.

NP/PAs may interact with otolaryngic allergy in several different ways, depending on the preference of the otolaryngic allergy physician, the applicable state laws, and the training of the practitioners themselves. *A recurring theme of this statement is that applicable state laws vary greatly from state to state, and from NP to PA within states.* Practice situations described in this document that may sound reasonable and be perfectly reasonable in one state may be illegal across a the state border. It is vital to consult federal and state regulations when considering the addition of a NP/PA to the practice.

Physician extenders in otolaryngology with minimal contact with allergy care.
The first and most straightforward relationship of NP/PAs to the allergy operation is to have no specific training or role in allergy operations. This would be analogous to a physician partner in the practice who has no training or specialty interest in allergy, such as a head and neck specialist. The physician extenders would give no shots and would refer patients suspected of allergic disease to the otolaryngic allergy practitioner or 'team' in the office as needed.

The critical consideration with this arrangement is whether the physician extender be the only practitioner in the office when a medical assistant or nurse is giving shots? For this to be a safe practice, the NP/PA must have at least BLS and an understanding of the emergency practices involved in treating anaphylaxis. Additionally, the state regulatory board must permit the NP/PA to be the provider 'authorizing' and responsible for the therapy.

This means that even a NP/PA who is not primarily involved with allergy testing or treatment must have a basic knowledge of emergency procedures and be authorized by the state and the supervisor's guidelines to be the practitioner in the office while immunotherapy is being administered.

Physician extenders who provide allergy testing and treatment.
While it may not be economically viable to have a trained physician extender acting purely in the role of administering allergy shots or testing, a small practice may find this an expedient role for a portion of the physician extender's time. In this situation, training from both the otolaryngic allergy physician and supplemental education from the AAOA is considered necessary and prudent, much as a nurse or medical assistant (MA) would be trained prior to assuming testing and treatment duties. Essentially all states would permit physician extenders to fill the role of MA or allergy nurses; the question is to what extent they may practice with autonomy.

It is the position of the AAOA that, while a well-trained physician extender may provide allergy diagnosis and testing, all functions of test interpretation, dose calculation, and vial preparation should be carried out in conjunction with, and under the direct supervision of, the physician practicing otolaryngic allergy.

Optimal Dosing

Efficacy of immunotherapy depends on reaching and maintaining an optimal dose of immunotherapy in a safe and efficacious manner. The goal of optimal therapy is to affect and maintain an immunologic response to reduce allergy reactivity. The starting dose, as determined by quantitative testing, should be used to begin immuno–therapy, but the optimal dose for maintenance therapy would be 5-20 mcg per dose, which is about 1000-2000 BAU per injection and 1000-4000 in more recent practice guidelines.[1] However clinically, the patient may note improvement of symptoms at a "symptom-relieving dose" which may be much lower than the effective dose necessary to achieve a long-term clinical benefit. Patients should still be advanced to the maximal tolerated dose or effective dose to obtain clinical immunologic response and overall symptom reduction.

Clinically, all patients may not tolerate dosages at that range and should still be escalated to the highest–tolerated dose. Dosages at this level are more likely to provide immunologic response without significant adverse reaction to obtain appropriate clinical results.

The efficacy of immunotherapy depends on achieving an optimal therapeutic dose of each of the constituents in the allergen immunotherapy extract.

The maintenance dose of allergen immunotherapy must be adequate. Low maintenance doses are generally not effective (eg, dilutions of 1:1,000,000, 1:100,000, and 1:10,000 vol/vol). A consideration when mixing extract is the need to deliver an optimal therapeutically effective dose of each of the constituents in the allergen immunotherapy extract. Failures to do so will reduce the efficacy of immunotherapy. This might occur because of a dilution effect; that is, as one mixes multiple extracts, the concentration of each in the final mixture will be decreased.

The maintenance concentrate should be formulated to deliver a dose considered to be therapeutically effective for each of its constituent components. The maintenance concentrate vial is the highest–concentration allergy immunotherapy vial (eg, 1:1 vol/vol vial). The projected effective dose is called the maintenance goal. Some subjects unable to tolerate the projected effective dose will experience clinical benefits at a lower dose. The maintenance dose is the dose that provides therapeutic efficacy without significant adverse local or systemic reactions and might not always reach the initially calculated projected effective dose. This reinforces that allergy immunotherapy must be individualized.

1 Cox L, *Allergen Immunotherapy: A practice parameter third update*. AAAAI task force report; J Allergy Clin Immunology, Vol 127, number 1: S1-S55

Risk Factors for Testing or Immunotherapy

The American Academy of Otolaryngic Allergy (AAOA) recognizes the importance of allergy skin testing and immunotherapy in the clinical practice of allergy. Although felt to be a safe practice in most patients, certain populations need to be given special consideration as they have been identified as being at a higher risk for complications during skin testing and treatment of allergies with immunotherapy. This is not intended to be an all-inclusive list.

Pregnancy

Allergy immunotherapy can be continued during pregnancy. Escalation and skin testing should be avoided.

The most recent update on allergen immunotherapy states that allergen immunotherapy can be continued but is usually not initiated in the pregnant patient. Allergen immunotherapy is usually not initiated during pregnancy because of concerns about the potential for systemic reactions and the resultant adverse effects on the mother and fetus. For this reason, if the patient becomes pregnant during escalation and the dose is unlikely to be therapeutic, discontinuation of immuno–therapy should be considered.

Asthma

Asthma patients should be under good asthma control prior to undergoing skin testing or before the initiation or continuation of immunotherapy. In asthma patients, consider evaluating lung function prior to admin–istration of immunotherapy.

Immunotherapy is effective in the management of allergic asthma; however, uncontrolled asthma has been repeatedly identified as a high-risk factor for systemic reactions during skin testing and allergen immunotherapy.

The most recent update on allergen immunotherapy states that allergen immunotherapy in asthmatic patients should not be initiated unless the patient's asthma is stable with pharmacotherapy. It is also rec-ommended that allergy injections should be withheld if the patient presents with an acute asthma exacerbation. Before the administration of an allergy injection, the asthmatic patient should be evaluated for the presence of asthma symptoms. One might consider an objective measure of airway function (peak flow).[1, 2]

Beta Blockers

The AAOA recognizes that exposure to a beta-adrener-gic blocking agents is a risk factor for more serious and treatment resistant anaphylaxis. Therefore it is prefer-able to not perform inhalant skin testing and immuno-therapy on patients taking beta blockers.

The balance of possible risks and benefits is not the same for patients with the potential for life-threatening stinging insect reactions who are also taking a beta–blocker. In these patients, the benefits of venom immunotherapy may outweigh any risk associated with concomitant beta-adrenergic blocker administration. The individualized risk/benefits of immunotherapy should be carefully considered in these patients.

Beta blockade can enhance mediator release in the setting of IgE-mediated anaphylactic reactions. There–fore, concomitant treatment with beta-adrenergic blockers may result in more protracted and difficult to treat ana-phylaxis. Studies looking at patients taking ophthalmic and cardio-selective beta-blockers have found unusually severe anaphylactic reactions and for this reason, the absence of increased risk in this population cannot be assumed.[3, 4, 5, 6, 7]

Other Risk Factors

Other predictors of future allergic reactions include, prior allergic reactions, immunotherapy escalation, first treatment vial and technical (dosing/wrong vial) error.[8, 9]

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Skin Testing Techniques for Immediate Hypersensitivity Reaction

There are multiple techniques for allergy testing, including in vivo and in vitro modalities, available to confirm or identify aeroallergen allergic disease as well as the level of sensitivity. It is important to have a technique that is standardized with the use of appropriate controls to be reproducible, sensitive, and specific.

Skin testing techniques for immediate and delayed sensitivity are of vital importance and the mainstay of testing to identify and confirm allergic disease.

1. **Scratch Testing** is a technique that is less sensitive, more painful, not reproducible, and not recommended for diagnostic testing.[1]
2. **Prick Testing** Prick and intradermal testing are the preferred techniques for IgE–mediated hypersensitivity with the use of a relatively non-traumatic introducer device. Reproducible results need to be obtained based on the location of testing on the body, potency of allergen extracts, and the proficiency of the skin tester.[2]
3. **Intradermal Testing** both single intradermal and intradermal dilutional testing is a specific and likely more sensitive means to detect sensitivity, compared to prick testing.[1]
4. **Modified Quantitative Testing** is an accurate and more cost–effective method of testing than intradermal dilutional testing while still obtaining quantitative results.[3, 4] The use of quantitative testing aids in improving patient care by facilitating the accurate diagnosis of aero–allergen disease.

Prick tests are used to confirm clinical sensitivity induced by aeroallergens, foods, some drugs, venoms and a few chemicals. Prick tests are widely used for confirmation of clinical immediate hypersensitivity induced by a wide variety of naturally occurring allergens such as inhalants and foods.[2]

1 Trevino, RJ. *The importance of quantifying skin reactivity in treating allergic rhinitis with immunotherapy.* ENT Journal, May 2000; 79(5): 364.

2 Bernstein, L. et al. *Allergy Diagnostic Testing: an updated practice parameter. Annals of Allergy, Asthma, and Immunology 2008,* Volume 100, Number 3, Supplement 3. S15-S29.

3 Krouse, JH. *Skin Testing for inhalant allergy 2003: current strategies.* Oto-HNS Journal, October 2003; 129 (4 Suppl): 33-49.

4 *Council on Scientific Affairs. In vivo diagnostic testing and immunotherapy for allergy. Report I, Part I, of allergy panel.* JAMA 1987; 258(10): 1363-7.

State Regulations

Otolaryngic allergists need to be aware of their individual state regulatory laws regarding the practice of allergy in their location. This applies to scope of practice, licensure, and dispensing laws.

- When midlevel providers are involved in delivering allergy care, state laws regarding location of practice, level of independence, and type of training should be followed.
- Regulatory requirements for ancillary staff regarding level of training required for allergy testing and administration of injections vary by state.
- Some states have medication dispensing laws that may apply to immunotherapy (e.g., sublingual or subcutaneous).
- Some states have requirements for basic and advanced life–support training of allergy providers and staff.

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Subcutaneous Immunotherapy (SCIT) for Aeroallergen Immunotherapy

Allergic disease is a prevalent problem that affects approximately 20-25% of the population.[1, 2] Diagnosis of this disease process is based on clinical evaluation and quantitative in vitro or in vivo testing necessary before initiating immuno–therapy.[3] In addition to allergen avoidance and pharma–cotherapy, additional treatment options include sub–cutaneous immunotherapy. This option has been shown to be effective in multiple randomized controlled trials in patients with allergic disease.[2, 4] Clinically relevant allergen identification and documentation of IgE-mediated disease is necessary prior to starting subcutaneous immunotherapy. Consideration for immunotherapy is based on the severity and duration of disease and response to or tolerance to medical therapy.[2]

The decision to begin allergy immunotherapy might depend on number of factors, including but not limited to: patient preference, adherence, medication require-ments, response to avoidance measures, adverse effects of medications, coexisting allergic rhinitis and asthma, and possible prevention of asthma in patients with allergic rhinitis. Additionally, the level of sensitivity will determine the starting dose for safe and effective therapy. [5]

Individual results may vary; however. On average, duration of therapy is usually 3-5 years for adequate immunologic response.[6, 7, 8, 9] A physician or provider must evaluate patients periodically during therapy, to determine safety and efficacy, monitor adverse reactions, and make appropriate adjustment to therapy, especially during the escalation phase. Though extremely rare, the risks for serious potentially life–threatening responses exist.[10] Patients need to be counseled on the potential risks and benefits of immunotherapy with informed consent.[11]

1 *Airborne Allergens: Something in the Air.* NIH Publication No. 03-7045; National Institute of Allergy and Infectious Disease. US Dept of Health and Human Services; 2003.

2 Schiller, JS., Lucas, JW., Peregoy, JA. *Summary of Health Statistics for US Adults; National Health Interview Survey 2011.* National Center for Health Statistics US Dept of Health and Human Services for Disease Control and Prevention. Vital Health Stat 2012; (252); 12 207.

3 Krouse JH, Mabry RL. *Skin Testing for Inhalant Allergy 2003; Current Strategies.* Oto HNS:129(4)supplement:S33- 49.

4 The Journal of allergy and clinical immunology, vol 102, issue 4, pp 558-62.

5 Gordon, BR. *Immunotherapy: rationale and mechanisms.* Otolaryngology Head Neck Surgery 1992; 107:861-865.

6 Oto-HNS 1995; 113:597-602.

7 Allergy 1996;51:430-433.

8 King HC, Mabry RL, et al. *Allergy in ENT Practice: The Basic Guide.* 2nd ed. New York, Thieme; 2005.

9 Cox L, Cohn JR. Ann Allergy Asthma Immunol 2007;98:416-426.

10 Cox L et al. J Allergy Clin Immunol. 2011 Jan;127 (1Suppl):S1-55. Epub 2010 Dec 3.

11 Hurst DS, Gordon BR et al. *Safety of Home Based and Office Allergy Immunotherapy: a Multicenter prospective Study.* OtoHNS 1999; 121:553-561.

Sublingual Immunotherapy

Sublingual immunotherapy (SLIT) is a validated, safe, and effective form of immunotherapy in adults and children.[1, 2, 3, 5] It is widely incorporated as a therapeutic option both internationally and domestically, and it is an acceptable option for delivering antigen–specific immunotherapy.

Subcutaneous injection is the main route of immuno–therapy delivery in the United States; however, in the last 20 years, SLIT administration has become widely adopted.[2] Several advantages of SLIT include safety, increased tolerance, including in children, and improved access.[4]

Efficacy for SLIT may vary dependent on antigen selection. Single agent immunotherapies, i.e., grass pollen tablets, are shown to be effective.[6] In multi–sensitized patients, additional antigens may be required for treatment optimization. Dosing algorithms are in use, and optimal dosing continues to be evaluated.

1 Radulovic S, Calderon MA, Wilson D, Durham S. *Sublingual immunotherapy for allergic rhinitis.* Cochrane Database of Systematic Reviews 2010, Issue 12. Art. No.: CD002893. DOI: 10.1002/14651858.CD002893.pub2.

2 Lin, SY et al. *Sublingual Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and Asthma: A Systematic Review.* JAMA 2013: Vol 309, No. 12 pp 1278-1288.

3 Kim, J, et al. *Allergen-Specific Immunotherapy for Pediatric Asthma and Rhino conjunctivitis: A Systematic Review.* Pediatrics. Vol. 131. No. 6 June 1, 2013. pp 1155-1167

4 Leatherman, BD et al. *Sublingual Immunotherapy: Past, Present, Paradigm for the Future. A review of the literature.* Oto-HNS. Volume 136: 3, Supplement, March 2007.

5 Cox, L, et al. *Allergen immunotherapy: A practice parameter third update.* 2011

6 Senna, GE, Calderon, M. and Milani, M. *Allergy immunotherapytablet: Grazax for the treatment of grass pollen allergy.* Expert Rev Clin Immunol. 2011 Jan; 7 (1): 21-7.

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Vial Testing

The American Academy of Otolaryngic Allergy (AAOA) supports the use of vial testing on patients prior to the initiation of subcutaneous allergy immunotherapy.

The vial test may improve the safety and comfort of subcutaneous allergy immunotherapy. Vial testing serves as a biologic indicator of tolerance to the mixed antigen vial.[1] A large skin wheal after an intradermal vial test may indicate the antigen concentration is too high for the patient. This may result in pain and discomfort that, if continued, may result in patient noncompliance to therapy. In addition, although there is a paucity of data on this topic, a large local skin reaction may identify those that may be at a higher risk for developing a systemic reaction.

Vial testing is the process of applying a much smaller dose (typically 5-fold less) of the treatment vial intradermally to assess for a skin wheal. Typically, a 4-mm wheal is applied as an intradermal injection. If after 10 minutes, the wheal size is 13 mm or less, then the first subcutaneous injection may be given during this visit. If the size is 13 mm in size, then the injection should be given on the next visit. If the size is greater than 13 mm, then the treatment vial needs to be diluted 5 fold and another vial test performed in a week.[1, 2]

Persistently large wheals may indicate an error in the mixing of the treatment vial or a higher prevalence of the offending antigen in the environment. If large wheals persist after dilution, further dilution or selective retesting may be performed.

1 Krouse, JH, Chadwick, SJ, Gordon, BR, Derebery, MJ. *Allergy and Immunology–An Otolaryngic Approach.* Lippincott 2002.

2 King HC, Mabry RL, Mabry CS, Gordon BR, Marple BF. *Allergy in ENT Practice: The Basic Guide.* Thieme, 2004.