Anaphylaxis in the allergy practice

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Background: **Otolaryngologists managing patients with allergic rhinitis are faced with the possibility of anaphylactic reactions in the office, especially when providing allergen immunotherapy.**

Methods: **Literature review was performed and recent published articles on anaphylaxis were examined. Details on pathophysiology, incidence, signs/symptoms, and treatment of anaphylaxis are included in this review article.**

Results: **Although anaphylaxis is a rare event with allergy testing and immunotherapy, it can result in fatal consequences. Clinical manifestations of anaphylaxis are rapid, and the upper and lower airways, skin, conjunctiva, and gastrointestinal and cardiovascular systems are often affected, individually or in combination. Treatment of anaphylaxis in the office begins with proper preparation in advance. The most important drug in the treatment of anaphylaxis is epinephrine, which should be administered early during an anaphylactic reaction. Recognition of the risks factors for anaphylaxis, such as uncontrolled asthma, may be helpful in order to prevent anaphylaxis.**

Conclusion: **Fortunately, Anaphylaxis is a rare occurrence in the allergy office if strict attention is paid to proper testing and treatment principles. Maintaining a high level of vigilance and preparedness is important to increase the chances of a favorable outcome should an anaphylactic episode occur.** © 2014 ARS-AAOA, LLC.

Key Words:
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Otolaryngologists managing patients with allergic rhinitis are faced with the possibility of anaphylactic reactions in the office, especially when providing allergen immunotherapy. Anaphylaxis is a severe, immediate hypersensitivity reaction that results in rapid onset of symptoms which can quickly progress into life-threatening airway obstruction and vascular collapse. It is important for physicians, and especially allergists, to recognize the early clinical signs of anaphylaxis and institute rapid, deliberate treatment when it occurs. An understanding of the etiology, epidemiology, and pathophysiology of an anaphylactic reaction may enhance a physician's ability to prevent, recognize, and effectively manage this condition. Although anaphylaxis has many etiologies, this review focuses on anaphylaxis related to allergy testing and immunotherapy. This review also focuses on "routine" office management of anaphylaxis. More intensive interventions and medications are available for severe or protracted anaphylactic reactions in the hospital setting, but they are beyond the scope of this publication.

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Incidence

Probably the greatest concern of the clinical allergist, with regard to anaphylaxis, is the occurrence of anaphylactic responses to antigen immunotherapy. Information about the incidence of fatal reactions to immunotherapy injections is relatively sparse. The largest study concerned with the safety of allergy immunotherapy was conducted by a group of physicians in the American Academy of Otolaryngic Allergy.[1] The study evaluated the overall safety of immunotherapy given in the office environment and at home. This study included 1,144,000 injections given in the prescribing physician's office, at home, or in other physician's offices. The overall minor reaction rate was 0.009%, whereas the rate of major reactions was 0.005%. There were no hospitalizations and no deaths. Due to proper selection of patients eligible for home injections, the rate of reactions was less in the home injection group compared to the office injection group. The study also identified risk

TABLE 1. Major risk factors for immunotherapy-related anaphylaxis: percentage of major reactions associated with these risk factors

Risk factor	%
Buildup immunotherapy	90
Active asthma	46
New vial, first injection	10
Prior systemic reaction	7
Vial prepared in another office	6
β Blocker treatment	4
Error (wrong patient's vial)	3

factors for major reactions during immunotherapy. Table 1 lists the percentages of patients experiencing a major reaction who exhibited each risk factor in this study.

Immunology and pathophysiology

Systemic anaphylaxis results from the release of mast cell and basophil mediators in sufficient quantity to evoke a systemic response involving multiple end organs. The signs and symptoms elicited by mast cell mediator release depend on the organ system in which those mast cells reside: skin, gastrointestinal (GI) tract, respiratory tract, and cardiovascular system. Other cell types, including basophils, monocytes, eosinophils, antigen-presenting cells, and epithelial cells, may participate in this process and affect the duration and intensity of the reaction with their interactions and secreted products.

One of the most important mediators is histamine, which causes vasodilation, increased vascular permeability, mucus hypersecretion, smooth muscle spasm, and eosinophil chemotaxis and activation. Tryptase, chymase, heparin, and other chemokines and chemotactic factors are also involved. These mediators activate other inflammatory systems, but may also have an attenuating role in the chain-reaction of inflammatory events in an anaphylactic episode.[2]

Mast cell degranulation products can activate other important biochemical pathways that contribute to an anaphylactic episode, such as the kininogen-kallikrein system, coagulation cascade, and the complement cascade through the actions of tryptase.[2] In addition to preformed mediator release from mast cells, newly generated lipid mediators, including leukotrienes (LT) B4, C4, D4, E4, platelet-activating factor, prostaglandin D2, and others, are involved. Recurrent or biphasic anaphylaxis may be secondary to inflammatory cell activation and recruitment (like eosinophils) and may occur up to 12 hours after the initial attack.[3]

Physiologic changes in anaphylaxis

The main cardiovascular clinical feature of anaphylaxis is hypotension. Anaphylactic hypotension is due to fluid extravasation and vasodilation, resulting in a mixed distributive-hypovolemic shock. There may be vasodilation, reversible cardiac depression, and paradoxically, bradycardia.[4]

Anaphylactic shock is a severe and prolonged hypotension caused by mediators such as histamine and prostaglandins released by tissue mast cells and circulating basophils.

In anaphylactic deaths, pathologic findings include laryngeal edema, mucus plugging and hyperinflated lungs, and myocardial damage. Also, a dilated right ventricle, eosinophilia in the pulmonary vessels and GI tract, and congestion of abdominal viscera are noted. These findings indicate that death from anaphylaxis is usually a result of cardiovascular collapse or upper/lower airway obstruction.[5]

Knowledge of the physiologic changes occurring during anaphylaxis can help the clinician more quickly recognize the signs and symptoms of anaphylaxis in the clinical setting.

Signs and symptoms of anaphylaxis

The clinical manifestations of anaphylaxis occur as a result of the systemic release of mediators from basophils and mast cells, and therefore involve some predictable signs and symptoms in organs with high concentrations of these cells.[6] The upper and lower airways, skin, conjunctiva, GI system, and cardiovascular system are often affected individually or in combination. The most common signs and symptoms have been described in several publications. Kemp et al.[7] published the largest series detailing the clinical manifestations of anaphylactic reactions in 266 patients. The findings of this study are listed in Table 2. The onset of symptoms of anaphylaxis is usually fairly rapid. When an antigen is introduced by injection, symptoms typically begin within 5 to 20 minutes,[8] but more delayed initial reactions can certainly occur. It is rare for anaphylaxis to occur beyond 60 minutes after antigen injection.[8,9]

Anaphylaxis may occur in biphasic or protracted patterns. After recovering from an initial episode of anaphylaxis, recurrent symptoms may develop. This process is known as biphasic anaphylaxis. This is thought to be a consequence of the classic late-phase allergic reaction. The recurrent symptoms begin from 1 to 28 hours after resolution of the initial episode. The secondary reaction usually involves the same organ symptoms as the original reaction.[10] The true incidence of biphasic anaphylaxis is not known. The reported frequency varies from 4% to 23% of anaphylaxis cases.

Other conditions can mimic anaphylaxis. Table 3 lists conditions that should be considered in the differential diagnosis.

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TABLE 2. Common signs and symptoms of anaphylaxis

	Patients affected (from Kemp et al.[7]) (n = 266) (%)
Urticaria, angioedema	90
Shortness of breath, wheezing	60
Dizziness, syncope	29
Flushed skin	28
Abdominal cramps, diarrhea	26
Laryngeal or tongue edema, choking, dysphagia	24
Nausea, emesis	20
Hypotension	20
Rhinitis symptoms	16
Conjunctivitis symptoms, periorbital edema	12
Substernal or esophageal discomfort	6
Headache	5
Generalized pruritis (no rash)	4
Vision change	2
Seizure	2

TABLE 3. Differential diagnosis of anaphylaxis

Anaphylactoid reactions
Scombroidosis
MSG
Sulfites
Medications
Vancomycin
Morphine
Anesthetic agents
Aspirin and NSAIDs
Hyperosmolar solutions
Radiologic contrast agents
Shock of other causes
Hemorrhagic
Cardiogenic
Endotoxic
Systemic mastocytosis
Hyperimmunoglobulin E syndrome
Hereditary angioedema
Carcinoid syndrome
Pheochromocytoma
Urticarial vasculitis
Panic attacks
Vasovagal reaction
Globus hystericus
Münchausen syndrome

MSG = monosodium glutamate; NSAID = nonsteroidal anti-inflammatory drug.

Prevention of anaphylaxis

Several measures can be taken to decrease the risk of anaphylaxis related to allergy testing and immunotherapy. Physicians should begin by recognizing the factors that increase the risk of anaphylaxis (Table 1). The presence of risk factors should prompt extra caution in allergy testing and immunotherapy. Patients who have brittle medical conditions should be tested and treated with more caution.[11] Allergic asthma is a common indication for immunotherapy. Uncontrolled asthma is a significant risk factor for anaphylaxis and extra watchfulness is necessary.[12,13] Additional caution should be used with skin testing or giving immunotherapy whenever there is high environmental exposure to an allergen, such as during peak allergen season. It is prudent to observe a patient in the office for 20 to 30 minutes after an immunotherapy injection because most anaphylactic reactions occur within that time period.

Treatment of anaphylaxis

Treatment of anaphylaxis in the office begins with proper preparation in advance. As with most office procedures, it is helpful to have a plan already in place for treating allergy emergencies.

If an anaphylactic reaction occurs, the primary goal of the physician should be to quickly recognize the problem and initiate the proper emergency care to stabilize the patient until the patient can be transferred to a hospital with emergency care specialists and comprehensive resuscitation equipment.

It is useful to have a written basic anaphylaxis treatment algorithm stored with the equipment for quick reference if necessary (Table 4). Table 5 lists the dosages of the basic drugs commonly used in the treatment of anaphylaxis. As in any medical emergency, treatment should start with basic life support measures. Once the diagnosis of anaphylaxis is established, an ambulance should be immediately called for transport to a hospital setting. Next, the person's airway and breathing should be assessed, and supported as necessary. Pulse and blood pressure measurements are used to assess circulation. The patient should be placed in a supine position with the feet elevated to increase venous return. If anaphylaxis has been caused by allergen injection, a tourniquet should be applied proximal to the injection site to reduce the rate of allergen absorption.[14] Every

TABLE 4. Anaphylaxis treatment protocol

1. Supine position, elevate legs, and loosen clothing
2. Check airway and vital signs
3. Assess further to confirm anaphylaxis diagnosis
4. Quick review of medical history and current medicines
5. Administer epinephrine
6. Call ambulance for hospital transport
7. Apply tourniquet proximal to injection site
8. Consider injecting epinephrine solution around allergen injection site
9. Consider ice pack at injection site
10. Reassess respiratory status
11. Give oxygen if available, start with low flow
12. Monitor vital signs frequently (blood pressure, pulse, respirations)
13. If bronchospasm, give albuterol inhaler. Repeat if not effective.
14. If continued bronchospasm, ipratropium inhaler
15. Loosen tourniquet every 5 minutes
16. Repeat epinephrine if needed (every 5–10 minutes adults/15–20 minutes pediatrics)
17. Start peripheral IV line
18. If hypotension, give IV fluid bolus
19. If severe hypotension, consider IV epinephrine
20. Support blood pressure if needed with vasopressors (ie, dopamine)
21. Give H_1 antihistamine
22. Give H_2 antihistamine
23. Administer corticosteroid
24. For persistent symptoms or special circumstances (beta blockade) try alternate medications
a. Glucagon
b. Heparin
c. Atropine for bradycardia
d. Magnesium for bronchospasm
25. In dire respiratory status or rapid progression of laryngeal edema, perform tracheal intubation for respiratory support
26. ACLS or PALS protocols whenever appropriate
27. Transport to hospital

ACLS = advanced cardiovascular life support; IV = intravenous; PALS = pediatric advanced life support.

TABLE 5. Basic medications and dosing for office management of anaphylaxis

Epinephrine
Adult dosing
0.3–0.5 mg IM (0.3–0.5 mL of a 1:1000 solution)
May repeat every 5–10 minutes
Pediatric dosing
0.01–0.03 mg/kg IM (0.1–0.3 mL/kg of 1:1000 solution)
May repeat at 15-minute intervals
Albuterol
Adult: metered dose inhaler: 2–4 puffs
Pediatric: (nebulizer) 0.25–0.5 mL in 1.5–2 mL saline
Diphenhydramine
Adult: 100 mg IV push
Pediatric: 1 mg/kg IV push
Ranitidine
Adult: 50 mg slow IV push
Pediatric: 2 mg/kg (up to 50 mg) slow IV push
Dexamethasone
Adult: 20 mg IV or PO
Children: 0.5–1 mg/kg up to 20 mg IV
Methylprednisolone
Adult: 40 mg IV
Pediatric: 0.5 mg/kg IV

IM = intramuscular; IV = intravenous; PO = by mouth (per os).

5 minutes the tourniquet should be loosened for several minutes. A dilute solution of epinephrine can also be injected around the allergen administration site to further decrease absorption. A local anesthetic premixed with epinephrine is commonly available and sufficient for this task. The injection of epinephrine around the allergen administration site should not delay or take the place of administering a therapeutic dose of epinephrine.

The most important drug in the treatment of anaphylaxis is epinephrine.[15] It is important to administer epinephrine early during an anaphylactic reaction. Several publications cite the increased risk of fatal outcomes when epinephrine is not given early during the course of anaphylaxis.[16,17] It has been postulated that the delayed administration of epinephrine stems from a fear of the potential harmful effects of epinephrine. The benefits of epinephrine use have been documented to far outweigh the potential harmful side effects when used during anaphylaxis treatment.[18]

Several studies have addressed the route of administration of epinephrine.[19–21] The preferred route of administration is intramuscular (IM). Injection in the vastus lateralis muscle of the lateral thigh is preferred due to its rich vascularity. The typical dose for IM injection in adults is 0.3 to 0.5 mL of a 1:1000 solution. For children, the IM dose is 0.01 to 0.03 mg/kg, which corresponds to 0.1 to 0.3 mL of a 1:1000 solution. These IM doses can be obtained from single-use or multiuse 1:1000 epinephrine vials. Some physicians stock commercially available pediatric and

adult epinephrine autoinjectors in their emergency kit for quick use.

Bronchial obstruction was found in 50% of cases. It is therefore important to aggressively treat airway and ventilation compromise during anaphylaxis. Epinephrine is effective in treating bronchospasm. Beta agonist inhalers, such as albuterol, can be effective in overcoming bronchospasm, though multiple administrations may be required.[15,22] If bronchospasm does not adequately reverse with albuterol, inhaled ipratropium may be a useful adjunctive treatment, especially in patients on beta blockers.

Although not nearly as important as epinephrine, antihistamines can be useful adjunctive medications.[23–25] Studies have shown superior results when H_1 and H_2 antihistamine agents are used concomitantly.[23,24] Intravenous antihistamines should be administered slowly to reduce potential adverse cardiovascular effects. H_2 antihistamines administered alone may be detrimental during anaphylaxis, so they should not be administered alone, and H_1 agents should be administered first.

Hypotension can be severe, protracted, and resistant to therapy during anaphylaxis. Hypotension can result from a combination of decreased cardiac function, loss of vascular tone, and shift of intravascular volume to extravascular spaces. Replacement of intravascular volume is the most important first step in treating hypotension. The rate should be adjusted based on overall medical conditions and blood pressure response.[14] Children may require up to 30 mL/kg in the first hour, once again titrated to blood pressure effects.

The use of corticosteroids in the treatment of anaphylaxis has been recommended in the past, mostly in an attempt to decrease the incidence of biphasic reactions. Steroids are not considered to be helpful in the acute phase of anaphylaxis. For patients experiencing a severe anaphylactic reaction, intravenous dosing is appropriate. Commonly used steroids include dexamethasone, hydrocortisone, and methylprednisolone. Due to the relatively low rate of significant adverse events with steroid use, they should probably be given to all patients with anaphylaxis and even for severe generalized reactions.

As mentioned earlier, several medications can make anaphylaxis treatment more difficult. Patients on beta-blockers present a particular challenge. Although many physicians do not knowingly start immunotherapy on patients taking beta-blockers, patients are often started on new medications after immunotherapy is in progress. Beta blockers prevent the salutary effects of epinephrine, when given in an anaphylactic emergency. Unopposed alpha adrenergic stimulation from epinephrine may cause coronary constriction or exaggerate the systemic pressor effects of epinephrine. Finally, beta-blocker treatment may increase the risk of anaphylaxis up to 3-fold in patients receiving immunotherapy.[26]

Glucagon is another medication that has been recommended as an adjunctive treatment for patients on beta-blockers, as well as those with protracted anaphylaxis.[27–30] The usual recommended dose is 1 to 5 mg intravenous push, followed by an infusion of 5 to 15 μg per minute.[27]

Other medications have the potential to complicate anaphylaxis treatment. Tricyclic antidepressants block catecholamine reuptake at nerve junctions, which can increase the chances of hypertension or arrhythmias with vasopressor use. Monoamine oxidase inhibitors block the degradation of catecholamines, increasing the risk of complications with vasopressor use. The doses of epinephrine and dopamine should be reduced by 90% to reduce the chances of severe adverse effects.[14]

In addition to the measures outlined in this article, basic principles of advanced cardiac life support should be adhered to as needed, depending on the patient's condition. The goal of office treatment of anaphylaxis is to stabilize the patient until transport to a hospital for continued care. After treatment of anaphylaxis in the office, it is wise to review the circumstances around the event to look for contributing factors. This may produce findings that will help decrease the likelihood of future anaphylactic episodes. The treatment process should be examined to see if changes need to be made to the office's anaphylaxis protocol. Supplies should also be replenished.

Conclusion

Fortunately, if strict attention is paid to proper testing and treatment principles, anaphylaxis is a rare occurrence in the allergy office. Understanding the factors that increase the risk of anaphylaxis and the mechanisms involved in anaphylactic reactions can help guide the clinician in preventing and treating these severe allergic reactions. Maintaining a high level of vigilance and preparedness is important to increase the chances of a favorable outcome should an anaphylactic episode occur.

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