

Allergic Emergencies in the Physician's Office

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Introduction

Allergic office emergencies may be fatal, although fatalities are fortunately very rare. Office practices should be reviewed periodically to familiarize personnel with early detection of anaphylactic symptoms, location and use of emergency medications, when to call for emergency assistance, and organization of staff responsibilities and procedures to try to reduce allergen injection errors, errors in preparation of allergy extracts, and inadvertent use of extracts prepared for epicutaneous (prick) skin testing injected during intradermal testing.

Depending on the specialty of the physician, certain causes of anaphylaxis may be more likely. Unrecognized latex hypersensitivity (1) could occur in any setting and is more likely to occur in atopic subjects (2). In an allergist-immunologist's office, some of the causes for anaphylaxis or immediate generalized reactions include allergen immunotherapy, food challenges, medication challenges, latex exposure, skin testing, and iv γ -globulin infusions. Acute severe asthma with respiratory failure may mimic anaphylaxis or be the major manifestation of anaphylaxis when a peanut-allergic patient with asthma develops anaphylaxis. Additional office conditions include Munchausen's anaphylaxis (purposeful true reactions from aspirin or foods in sensitized patients), Munchausen's stridor, and undifferentiated somatoform idiopathic anaphylaxis (3-5). In the latter condition, the patient has little to no meaningful insight into the cause of the anaphylaxis.

The ophthalmologist faces the rare, but serious problem of immediate generalized reactions from fluorescein dye injections (6). Elderly patients or patients with diabetes mellitus who require fluorescein

angiography may be less likely to recover from hypotensive reactions because of underlying cardiovascular disease. Any physician administering antibiotics must be prepared for anaphylactic reactions especially when parenteral injections are administered. Although penicillin is a very safe medication, unexpected anaphylaxis can occur and be fatal even with resuscitation efforts. The radiologist faces allergic emergencies from radiographic contrast media infusions, latex hypersensitivity reactions from an enema tip (7), and carboxymethylcellulose (8) used as a suspending agent in barium sulfate enema suspensions. The anesthesiologist facing the sudden onset of an anaphylactic reaction in an anesthetized patient should consider causes, including muscle relaxants, radiocontrast media, antibiotics, blood (plasma) products, plasma expanders, latex, and opioid analgesics.

Office Equipment for the Allergist-Immunologist

A position statement by the American Academy of Allergy, Asthma, and Immunology published in 1994 advised the following equipment for offices where allergen immunotherapy was being administered: stethoscope, sphygmomanometer, tourniquets, syringes, hypodermic needles, 14-gage needles or smaller for pediatric patients for iv fluid administration, aqueous epinephrine HCl (1:1000 concentration), injectable diphenhydramine, corticosteroids for iv administration, a vasopressor, an oral airway, oxygen and equipment for its administration, and aminophylline for iv infusion (9). Additional equipment, such as a laryngoscope, DC cardioversion equipment, tracheostomy tray, and intracardiac injection needles, and medications were deemed of such rare need that they were not recommended in the setting of allergen immunotherapy injections. These 1994 recommendations were reiterated in a 1998 position paper of the World Health Organization (10). The practice parameter document prepared by the Joint Task Force on Practice Parameters of the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology in 1998 also recommends the same equipment with the addition of bronchodilators for iv or inhaled routes (11).

Office Personnel Responsibilities

The treatment of anaphylaxis requires rapid recognition and implementation of proper therapy. However, prevention of anaphylaxis from allergen immunotherapy should be a priority and designed into office procedures. Office personnel responsibilities and training should include:

1. Identification of early signs or symptoms of anaphylaxis.
2. Alerting the physician in the office for all systemic reactions to immunotherapy.
3. Recognizing gaps in injection schedules and adjusting the dose as indicated.
4. Paying attention to patient names, identification numbers, injection therapy vials, concentrations of extracts, volume to be administered, and charting to minimize "clerical" errors during immunotherapy.
5. Knowing where emergency medications and equipment are located.
6. Knowing emergency phone numbers for emergency medical services or paramedics.
7. Refusing to administer injections to patients who insist on receiving their injection despite audible wheezing from an asthma exacerbation.
8. Identifying patients who do not wait 20 or 30 min after injections so their injection site can be inspected.

There may be other responsibilities as well. Because individual vials are not prepared for patients undergoing hymenoptera venom immunotherapy, perhaps having each concentration of venom (1 $\mu\text{g/mL}$, 10 $\mu\text{g/mL}$, 100 $\mu\text{g/mL}$) recorded on a separate sheet for each patient will help the nurse or physician administering immunotherapy select the correct concentration for each patient. Furthermore, avoiding distractions, such as telephone interruptions, during allergy injections can reduce the incidence of injection errors. Some physicians use color-coded extract vials to identify different dilutions of extracts; alternatively, each person's vials may be located in a rack where all vials of the same dilution are placed consistently in the same row. There may be additional ways to minimize the chance of choosing the incorrect dilution for a given patient.

Physician Responsibilities

The physician must assume overall responsibility for the safe administration of allergen immunotherapy or other office challenges that might result in anaphylaxis. Some of the potential high-risk situations where anaphylaxis may occur during injection therapy are as follows:

1. Unstable asthma.
2. Previous systemic reactions to immunotherapy.
3. Beginning a new vial of extract.
4. Patients with many positive immediate skin tests.
5. Current use of β -adrenergic antagonists or possibly angiotensin-converting enzyme (ACE) inhibitors.

6. Pollen extract administration.
7. Too rapid a rate of increase in allergy extracts used for allergen immunotherapy (11).

Although these seven points have been published, it is of interest that patients having large locals are not necessarily at risk for systemic reactions. Nevertheless, repeatedly large local reactions should not be ignored. The dose of extract should not be increased and may have to be decreased until the patient then can receive increasing dosages without experiencing large local reactions. Otherwise, patients may become discouraged with the prospects of weekly injection-site induration and pain. Pollen extract administration would apply to a high percentage of allergen immunotherapy recipients implying that all patients receiving immunotherapy should be considered patients at risk for anaphylaxis. Similarly, pollen allergic patients can be expected to react to many pollens and may have been sensitized to dust mites, fungi, and animals. Thus, the very patients who require allergen immunotherapy are the ones who would be labeled at risk of the development of systemic reactions based on having a number of positive immediate skin reactions to common allergens. The use of β -adrenergic antagonists, such as for secondary prevention of myocardial infarction, identifies patients with compromised cardiovascular reserve should severe anaphylaxis occur. The possible role of ACE inhibitors contributing to a higher incidence of immunotherapy reactions remains speculative. Interest in this area has evolved from an increased risk of anaphylactoid reactions during hemodialysis in patients receiving these medications (12).

Prevention of anaphylaxis includes attention to purchasing of extracts, and preparation and labeling of extracts in order to avoid mixing or diluting errors. Mailed-out extracts need the proper injection schedule and other instructions for the personnel in the office where injections will be given. Is there a procedure for reducing the dose when a new vial is started even if no local or systemic reactions have been occurring? Do office personnel or physicians answer questions about immunotherapy from the site where injections are given? When out-of-office injections are being given and the patient reports having acute ocular pruritus and sneezing after the last two injections but there is no recording of symptoms on the injection schedule, who informs the patient and physician of the problem and need for improved recognition at the off-site location? The allergist-immunologist, who is prescribing allergen immunotherapy, will be responsible for insisting that injections be given in his/her office when repeated local reactions or systemic reactions are occurring. This determination may apply to other patients in some circumstances where the goal is to prevent systemic reactions from immunotherapy. Once it is clear

that the dose is being tolerated, then a decision can be made to let the patient receive injections at the off-site location with a physician available. The American College of Allergy, Asthma, and Immunology has prepared a 1998 position statement regarding administration of allergy extracts in primary care physician's offices outside of the prescribing allergist-immunologist's office (13). It was stated that it is the responsibility of the "treating allergist to provide detailed instructions to the primary care physician or his or her facility concerning:

1. Adjustment of allergen doses during the buildup phase as well as at maintenance.
2. New vials.
3. Seasonal allergen peaks.
4. Missed injections.
5. Follow-up to local and systemic reactions."

Extract vials should be labeled clearly with expiration dates, patient name, and contents. It was suggested that the treating allergist-immunologist provide a protocol for treatment of local and systemic reactions and that the primary care physician should be informed regarding waiting times. Further, the suggestion that each patient's photograph be attached to individual instruction sheets was made. This author believes that the extract vial should have the patient's name, expiration date, and concentration of allergens without having a list of all the allergens included. That information can be present on the administration work sheet, which also has instructions for treatment of systemic allergic reactions.

Anaphylaxis may result from allergen skin testing, and many physicians place epicutaneous (prick) tests first to be followed by intradermal tests for negative or 2+ or less epicutaneous responses. For academic physicians who may be teaching medical students or residents how to perform skin testing, it is imperative to avoid using the epicutaneous extracts for intradermal injections. In a report of six fatalities from skin testing, five patients had been tested intradermally and one patient by both epicutaneous and intradermal methods (14). Unfortunately, it is unknown what injection volumes or allergen concentrations were used, but epicutaneous testing would identify patients with antiallergen IgE antibodies with less allergen being injected (approx 3/1,000,000 mL of a 1 : 10 or 1 : 20 dilution) than with intradermal tests (0.02 mL of a 1 : 1000 dilution). Five of six patients had onset of anaphylactic symptoms within 3–20 min. In one patient, the time of onset was not described, but this 24-year-old male had experienced a previous respiratory arrest from skin testing from nuts and was reported to be wheezing at the time of intradermal skin testing during the fatal episode (14). Skin testing did not include foods. Two

other of the six patients succumbed following anaphylaxis from intradermal skin testing to either walnut or flaxseed. These reports have led to the practices of not performing intradermal skin tests to foods and of always placing epicutaneous skin tests first to aeroallergens and other allergens before intradermal tests are carried out. In addition, acutely wheezing unstable asthma patients should not undergo skin testing until their respiratory status has improved.

Skin testing with hymenoptera venoms is very safe when carried out by allergist-immunologists. From a group of 3236 patients of whom 89% had reported a previous systemic allergic (anaphylactic) reaction to hymenoptera species, just 45 (1.4%) of patients had evidence for a systemic reaction during immediate skin testing (15). Only 8 (0.025%) were considered severe. In comparison, systemic reactions to epicutaneous testing with aeroallergens were reported as 0.04%. In summary, immediate skin testing by appropriately trained physicians and nurses is a very safe technique, which remains the most useful method to demonstrate antiallergen IgE antibodies.

The physician in charge of the skin testing (or immunotherapy) should have ultimate responsibility for emergency treatment of patients who develop anaphylaxis. Periodic review of emergency medications, equipment, and employee preparedness is necessary. Indeed, such training might lead to avoidance of fatalities, such as occurs when an excessive dose of epinephrine is administered. In a case report of a 7-yr-old child with asthma who experienced anaphylaxis from an immunotherapy injection, 1.0 ml of iv epinephrine 1:1000 concentration (1000 µg dose) resulted in ventricular fibrillation and death (14).

Risks of Conventional Allergen Immunotherapy Injections

Allergen immunotherapy with currently available aqueous extracts is a safe and efficacious procedure (16,17). It remains the only available immunologic biologic modifier with the possible exception of long-term use of intranasal corticosteroids. The systemic reaction rate following immunotherapy with aeroallergens can be expressed per patient per course of injections, which involves shots over several years or per single injection. The literature cites anaphylactic reactions per patient course of immunotherapy from 0.8 to 46.7% and a per-injection rate of 0.02–3.2% (14,18). Therefore, there remains a real risk of anaphylaxis with each injection. Often, certain patients experience several anaphylactic reactions and others have none during a course of allergen immunotherapy. In a study of ragweed immunotherapy for adults with asthma, 7/64 (10.9%) patients who finished the first year of injections experienced anaphylactic reactions from ragweed

injections (19). The 7 patients had 14 occasions of anaphylaxis, of which 5 episodes were so mild that no medications were administered. It was stated that a placebo-group patient received a ragweed injection accidentally and developed bronchospasm and hypotension with rapid recovery with treatment. In a study of immunotherapy in 121 allergic children with asthma, systemic (anaphylactic) reactions occurred in 21/61 (34%) of treated patients (20). Some 114 anaphylactic reactions were recorded in the 21 children for which treatment was administered for 52 reactions. Overall there was a 2.6% systemic reaction rate or 2.6/100 injections (20). These two studies reported systemic reactions in 10.9–34% of patients per course of immunotherapy in patients with asthma (19,20). Such incidences are within the reported range of the literature. In the pediatric asthma study, the systemic reaction rate per injection was higher than the 0.25–0.5% cited in the literature or 1:200 to 1:400 injections (21,22). It has been argued that a systemic reaction rate of 2.6%/injection is so high as to discourage patients from continuing injections, whereas a rate of 0.5% or less favors continuation of immunotherapy. A number of studies have reported lower frequencies of systemic reactions to immunotherapy. For example, over a 10-yr period when 79,593 injections were administered at the Mayo Clinic, 109 (0.13%) systemic reactions occurred in 94 patients (23). No fatalities occurred, and most reactions were treated with antihistamine and sc epinephrine. Two patients developed hypotension. It was reported that systemic reactions were just as likely to occur during the build-up period as during maintenance injections, and local reactions were present at the time of the systemic reaction in just 31% of reactions (23). Some other studies from experiences in private practices of systemic reaction rates have included from 0.02% (1:4700 injections) (18), 0.06% (1:1600 injections) (24), to 0.25% (1:400 injections) (22). Some suggestions for minimizing systemic reactions to conventional immunotherapy are presented in Table 1.

Risks of Rush Injection Therapy

In an effort to reach maintenance allergen doses quickly that then will result in reduction of symptoms, allergen immunotherapy has been administered by rush, semirush, and clustered methods. The rate of systemic reactions must be accepted as being two to six times higher than with conventional, often weekly, immunotherapy (21). Two studies are illustrative. In a pilot study in 11 children, who received rush immunotherapy over 2 d, 6 (54.5%) developed systemic reactions, with 2/6 patients not experiencing local reactions before the systemic reaction had occurred (25). Dedicated nurses are required for this procedure with physicians ready to treat anaphylactic reactions.

Table 1
Suggestions to Minimize the Incidence of Allergen
Immunotherapy Systemic Reactions

Situation	Suggestion
Allergen immunotherapy patient is 1 wk late for injection	Administer scheduled dose
Allergen immunotherapy patient is 2 wk late for injection	Reduce dosage by 0.05 mL
Allergen immunotherapy patient is 3 wk late for injection	Reduce dosage by 0.10 mL
Allergen immunotherapy patient is missing visits once a month while scheduled to receive buildup injections each week	Explore reasons for improving compliance with scheduled phase injections
Allergen immunotherapy injection causes swelling that is 10 cm in diameter by the next day	Reduce dose by 0.05 mL on next injection
The patient reports the previous injection caused nasal and ocular pruritus, but no large local reaction or evidence of urticaria or bronchoconstriction	Repeat dose or reduce by 0.05 mL
Repeated injections at an outside office result in painful injection-site induration lasting 2–3 d	Next injection is given by the allergist-immunologist's nurse to guarantee a sc, not an im injection; the dose is not increased
Acute urticaria and mild dyspnea occur at 0.20 mL of a 10,000 Allergy Unit/mL injection	Subcutaneous epinephrine, H1 antagonist; reduce dose by 33% on the next injection
Successive weekly injections of 0.20 mL of a 10,000 Allergy Unit/mL extract have caused 10-cm areas of induration lasting 48 h	Reduce dose to 0.15 mL; if tolerated, repeat this dose 1–2 times before increasing
A patient beginning yellow jacket immunotherapy received 0.05 mL of an extract containing 100 µg/mL instead of 0.05 mL of an extract containing 1 µg/mL	Have epinephrine 1 : 1000 concentration ready (0.01 mL/kg up to 0.3 mL in adults); take vital signs; examine closely; be prepared to treat anaphylaxis ^a

^aAfter the situation has been resolved, examine circumstances that led to the error.

In another study where patients were hospitalized for the first night of the study, but where the aim was to administer injections over 3 d, 36.2% of patients experienced anaphylactic reactions, including 8/18 (44.4%) in children (26). It was reported that most reactions were "severe." In both studies, investigators attempted to reduce the risk of

anaphylaxis (systemic reactions) with pharmacologic pretreatment. For example, in the first study, pretreatment was with astemizole 15 mg twice daily on d 0 before injections began, 10 mg on d 1, and 5 mg on d 2 along with prednisone 30 mg on each day (25). In the second study, methylprednisolone 0.5 mg/kg, ketotifen 1 mg, and theophylline 5 mg/kg were administered at the time of immunotherapy and continued during the rush protocol (26). Peak flow measurements were utilized. Nevertheless, there was a high incidence of rush immunotherapy-induced anaphylactic (systemic) reactions despite precautions and pretreatment or concurrent treatment. These findings have occurred in another study where in a 1-d rush immunotherapy program, systemic reactions occurred in 5/22 (23%) of patients despite pretreatment (27).

Another approach to allergen immunotherapy is that of daily injections with 5–6 injections/wk (28). Patients could reach maintenance levels and begin to achieve clinical improvement within 1 mo of starting injections. For example, in patients with seasonal allergic rhinitis, 59 adults (ages 20–24) received daily injection therapy and were compared with 12 controls receiving weekly injections. In both groups, it took a median of 31 injections to reach an intended maintenance dose of 0.5 ml of a 1 : 100 w/v of short ragweed or timothy grass extract (28). No pretreatment was administered, and the incidence of systemic reactions was similar between the groups: 1.3%/injection in daily treated patients vs 1.6%/injection in weekly treated controls. Stated another way, with a 1.3%/injection incidence applying to 31 injections to maintenance doses, one can estimate that 40% of patients experienced a systemic reaction in the daily treatment group compared with 48% of control patients. However, some patients will have multiple systemic reactions and others none during the course. Data were not presented regarding the total number of systemic reactions/patient. However, daily immunotherapy is not more dangerous than weekly therapy. Both groups had substantial increases in anti-allergen IgG antibodies. Clearly, in offices where allergen immunotherapy is being administered, trained personnel must be ready to recognize and treat anaphylactic reactions. Pretreatment has not been able to eliminate these reactions, although in a study using 14 (clustered over 7 wk) injections to a maintenance dose of 100,000 standardized units of grass or birch pollen extracts, loratadine 10 mg ingested 2 h before immunotherapy was shown to decrease the incidence of anaphylactic reactions from 79% in placebo-treated patients to 33% in those patients who were pretreated with loratadine (29). The number of systemic reactions during this clustered treatment schedule was 9.5%/injection in the placebo-treated patients compared with 5.8%/injection in the loratadine group. In both groups, this clustered schedule resulted

in a very high per injection reaction rate that presents seemingly unnecessary risks to patients.

In summary, rush immunotherapy schedules have been used for aeroallergen injections and are associated with higher anaphylactic reaction rates than with weekly injection schedules. Pretreatment does not eliminate the higher risks of reactions occurring so that office personnel must be attentive and ready to recognize and treat such patients receiving rush injections. It should be stated that safer (less allergenic) preparations of allergy extracts would be prepared. One such formulation that is not commercially available is polymerized allergens (30). Short courses of injections are required to reach maintenance doses with an extremely low incidence of anaphylactic reactions because the polymerized allergens are less likely to activate mast cells. With the cluster approach is a reduction in reactions and retained immunogenicity as demonstrated by 6- to 10-fold increases in anti-allergen IgG antibodies (30). Safer forms of allergen immunotherapy obviously will reduce the incidence of office anaphylactic reactions.

Anaphylaxis from Provocative Challenges

Protocols for medication or therapeutic agent challenges have been published (31). Patient safety must be a priority. Examples of challenges of incriminated medications include:

1. β -adrenergic antagonists in patients with asthma.
2. Aspirin or a nonsteroidal anti-inflammatory drug in a patient with arthritis or severe pain.
3. Penicillin, cephalosporin, sulfonamide, or other antibiotic.
4. Local anesthetics.
5. Vaccines, and other medications.

A clear indication for the challenges should be present, and the patient must agree to the challenge. Not all challenges should be carried out in an office setting, and the allergist-immunologist should be prepared to reject referring physician requests to perform challenges that are not indicated. Similarly, when a patient insists on being challenged with sulfamethoxazole-trimethoprim despite a history of exfoliative dermatitis or Stevens-Johnson syndrome from that medication, the challenge should not be performed unless it becomes mandatory and is confirmed by an infectious diseases consultant.

It may be useful to perform a provocative challenge to exclude a doubtful case of medication allergy rather than trying to confirm reactions in patients with convincing histories of allergic drug reactions. For example, although extremely rare, a patient who was considered to have experienced new-onset idiopathic anaphylaxis in fact had reacted to acetaminophen (32). At the time of her anaphylactic reaction,

the only medication she had ingested was acetaminophen. She denied aspirin idiosyncrasy. A subsequent cautious office challenge with increasing doses of acetaminophen resulted in development of shock with hospitalization and recovery. The patient had elevated urinary histamine and serum tryptase concentrations. Although this patient could tolerate aspirin safely, she had an unanticipated severe reaction to acetaminophen. Thus, even in circumstances where anaphylaxis may be extremely unlikely, the physician and nurses caring out challenges have to be prepared for anaphylaxis.

Office challenges to confirm food hypersensitivity should be performed only after careful analysis of the benefits vs risks. This author believes that a convincing history of an anaphylactic reaction (including acute urticaria alone) confirmed with a positive immediate epicutaneous test is sufficient to label a patient as allergic. An oral challenge would not be indicated since even 7 mg of peanut can induce anaphylaxis. Alternatively, when a patient complains of food allergies, but has nonreactive epicutaneous reactions to reactive extracts, an oral challenge can be carried out in the office if it is necessary to convince the patient of the absence of current immediate sensitivity to the food. There may be some anxiety symptoms during the challenge, and office staff should be ready to document objective signs of food hypersensitivity since acute hyperventilation may cause dyspnea.

Conclusion

Allergen immunotherapy may result in anaphylaxis without previous warning signs, such as a previous systemic reaction. Large local reactions are not predictive of future systemic reactions based on several published studies. Emergency medications and equipment should be kept current, and emergency preparedness by staff must be a priority. The overall rarity of severe anaphylaxis in a physician's office may create a sense of false security. Staff should know when to call for emergency help, and it is advised that they inform the physician immediately of all immunotherapy systemic reactions. Early administration of sc epinephrine will help control and stop most but not all systemic reactions to injection therapy.

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