Introduction:

Immunotherapy (IT) has been a therapeutic modality for more than 100 years (1). Numerous studies have demonstrated the efficacy of IT for the treatment of allergic rhinitis (AR) and allergic (extrinsic) asthma. IT prevents or delays the onset of allergic asthma and the acquisition of new allergies in individuals with allergic rhinoconjonctivitis. IT also diminishes the severity of pre-existing asthma in individuals receiving this therapy. Of note, IT is a “steroid-sparing” treatment regimen for asthmatics. Thus, this therapy improves the respiratory status of individuals with allergic asthma and enables the reduction of inhaled steroid use. Recent studies (2,3) further documented significant medical cost savings with IT. In fact, healthcare related expenditures were reduced by 33% to 41% in both an 11 year retrospective pediatric study and in a similar study of adult patients receiving IT.

Despite the significant advantages enumerated above, there are potential risks inherent to IT treatment, albeit affecting a small percentage of patients. These adverse reactions encompass mild pruritis at the injection sites to near fatal or fatal anaphylaxis.

The purpose of this article is to address the recognition and treatment of anaphylaxis, and to discern the contributing factors and preventative measures that would reduce the incidence of severe or fatal IT – induced adverse reactions.

Severe adverse reactions:

Reports from Europe documented that 0.2% of patients undergoing IT experienced severe systemic reactions; while a ten-fold higher 2% manifest mild systemic reactions only (4). Based upon American surveys of board-certified allergists, there is one fatal reaction occurring for every 2.8 million injections administered (5). Between 1990 and 2001, another study (6) documented 41 fatal reactions which were equivalent to 3.4 deaths annually or approximately 3.4 deaths per 8 million injections. In contrast, near fatal reactions (involving shock and/or severe bronchospasm) occurred once per 1 million injections in the US. European studies demonstrated a higher frequency of IT-induced near fatal reactions (7). This difference in part may be due to differences in dosing regimens and in the methods utilized for the commercial production of allergen-extracts.
**Clinical signs and symptoms:**

Hypotension has been reported in above 80% of cases involving a near fatal or fatal reaction to IT. This is followed by acute dermatologic findings such as urticaria, angioedema, and pruritus. Seventy percent of near fatal and 29 percent of fatal reactions manifest cutaneous signs. Fatal reactions often occur without dermatologic findings. This absence of cutaneous signs has been thought to cause delays in the identification of acute anaphylaxis and the initiation of appropriate treatment responses by the involved physicians. This delay has been hypothesized to be an important cause of a fatal outcome in selected cases.

Of note, approximately 50% of both near fatal and fatal reactions were characterized by bronchospasm. However, frank respiratory failure was more frequently seen in patients with fatal reactions. All patients manifesting respiratory failure, who required intubation, were asthmatics. In one study, more than half of the patient’s with a near fatal reaction who required intubation, had a pretreatment FEV1 of less than 70% of predicted (5). The frequency of clinical manifestations of both near fatal and fatal reactions is depicted in table one below.

**Table I: clinical manifestations found in IT-induced fatal and nonfatal reactions** (modified from reference 8).

<table>
<thead>
<tr>
<th></th>
<th>FATAL</th>
<th>NEAR FATAL</th>
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<tbody>
<tr>
<td>Urticaria and angioedema</td>
<td>49%</td>
<td>18%</td>
</tr>
<tr>
<td>All dermatologic signs</td>
<td>70%</td>
<td>29%</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
<td>47%</td>
<td>41%</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>51%</td>
<td>50%</td>
</tr>
<tr>
<td>Hypotension/shock</td>
<td>88%</td>
<td>81%</td>
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</table>

**Severe anaphylaxis:**

Fatal anaphylaxis is most often attributable to uncontrolled asthma. As discussed above, in one study all the patients requiring intubation for respiratory failure, as a consequence of severe anaphylaxis, were asthmatics (5). In addition, approximately 50% of both fatal and non-fatal cases of anaphylaxis are characterized by bronchospasm. The latter pathologic sign is more often triggered in asthmatics due to their highly reactive airway status. This is further exemplified by noting that in a survey reported in 2004, close to 90% of patients with fatal reactions and close to 50% of patients with near fatal reactions were asthmatics (9, 10). In fact, between 43% and 53% of individuals who experienced fatal anaphylaxis, their diagnoses were documented as poor or labile asthma. Furthermore, between 54 to 62% of these individuals had either prior emergency room visits or hospitalizations for asthma exacerbations (5).
These results are supported by similar findings in European studies (11). Analyses of IT-induced fatal anaphylaxis in asthmatics documented that spirometric FEV1 results were less than 70% of predicted in 50% of cases. It has thus been recommended that immunotherapy administration be deferred in asthmatic patients with recent or current asthma exacerbations as exemplified by an FEV1 of less than 70% of predicted.

Clinics that regularly administer IT to their asthmatic patients often assess their patients’ respiratory status prior to therapy. This is done by the use of spirometry or peak flow assessment. Ideally, the assessment should be done prior to IT administration and 20 to 30 minutes post administration. If the pre-administration value is less than 70% of predicted (or if lower than normally documented for a particular patient), the IT should be delayed and the patient should be medically evaluated. If the post-administration assessment demonstrates a significant decrease in pulmonary status, then a medical evaluation is warranted. Most (approximately 80%) of IT-induced adverse reactions occur within 30 minutes of IT administration. Thus, requesting that all (asthmatic and non-asthmatic) patients undergoing IT remain in the clinic under observation for 30 minutes is advised. As a matter of fact, both American and European studies have documented instances of delayed severe fatal reactions that occurred more than 30 minutes postinjection (8,10,17). Because of the possibility of delayed reactions, some European practitioners recommend a 60 minute postinjection observation period (17).

Other disorders and conditions, aside from uncontrolled asthma, are contraindications for the initiation of IT. These disorders and conditions in part include most moderate to severe autoimmune disorders (assessed on a case by case basis), CHF, uncontrolled COPD, uncontrolled hypertension, labile arrhythmias, and the use of beta blockers. Previous reports have documented fatal outcomes in patients who were on beta blocker therapy. This contraindication also applies to the use of beta blocker ophthalmic drops for the treatment of glaucoma. It is thought that the use of these agents (including selective beta antagonists) would decrease the adrenergic response and thereby, the efficacy of epinephrine administration in cases of anaphylaxis. Furthermore, the long-term use of beta blockers can diminish the patient’s FEV1 and thereby increase the severity of the possible adverse reactions induced by IT. Finally, beta blocker use has also been implicated in promoting and prolonging the hypotension experienced in some IT-induced anaphylactic reactions (10).

Patients with labile arrhythmias, uncontrolled hypertension, or a propensity for developing cerebral vascular accidents might not fare well from the hypertension and tachycardia induced by epinephrine administration. Thus, these disorders and the recent or ongoing use of beta blockers are contraindicated. In refractory anaphylaxis (not responsive to epinephrine therapy), the administration of IV glucagon may significantly improve the patient’s health status. In cases manifesting refractory hypotension, usually evident in those patients with beta blocker associated refractory anaphylaxis, glucagon administration is very efficacious (21).

Precaution has also been advised about the initiation of IT for patients prescribed angiotensin-converting enzyme (ACE) inhibitor therapy (21). This precautionary advisement arises from the reports of several patients on ACE inhibitor therapy who experienced IT-induced anaphylaxis. However, the
2010 AAAAI immunotherapy practice guidelines suggest that the major concern about ACE inhibitor therapy pertains to venom immunotherapy (VIT; e.g. bumble bee, wasp, yellow jacket, and hornet). Individuals receiving VIT who are being treated with ACE inhibitors have a greater risk of developing a severe systemic reaction than do their counterparts who are not on ACE inhibitor therapy. In contrast, the utilization of angiotensin receptor blockers is not associated with such a risk (21).

Patients with a medical history of IT-induced systemic reactions have a greater risk of experiencing a subsequent fatal outcome to IT-induced anaphylaxis. Studies have demonstrated that 36% of patients with fatal reactions previously experienced a systemic reaction; whereas, only 9% of those with non-fatal reactions had previous systemic reactions (5,15).

**Other Factors contributing to IT-induced Fatal Anaphylaxis:**

Errors in dosing and IT administration have been implicated in causing 25% of IT-induced non-fatal anaphylactic reactions (5,8). Similar results have been reported in European studies (15). These results support the concept of careful planning and for care when administering IT. Care is also required in the route of administration chosen. This is exemplified by noting that some patients who were accidently administered injections via the intramuscular rather than the subcutaneous route, experienced fatal anaphylactic reactions (15).

The phase of IT administration also influences the risk of a severe adverse reaction. Recent studies have shown that both non-fatal and fatal anaphylaxis is experienced more frequently when maintenance doses of IT are administered in comparison to injections administered during the build-up phase of IT. This risk is further increased if IT is administered during the pollination season. This is thought to be due to the patient’s increased allergen exposure from both the environmental source and that provided in the IT.

Finally, as discussed above, the delay in administering epinephrine and/or the use of an inadequate dose during the treatment of anaphylaxis, increases the risk of a fatal outcome.

**Recognition and Treatment of Anaphylaxis:**

Anaphylaxis is an acute life-threatening reaction which is mediated by IgE dependent pathways if caused by an allergic etiology (e.g. vaccine allergy, drug allergy, food allergy and infrequently as a consequence of allergy injections). The major concerns are the complications of cardiopulmonary compromise that may lead to a fatal outcome. Usually urticaria (hives) and angioedema are early signs; however, in rapidly progressive anaphylaxis these findings may be delayed (as previously discussed with fatal reactions). With respect to allergy injections (immunotherapy; IT), 70 to 80% of local or systemic reactions occur within the first 20 to 30 minutes after IT administration. Delayed reactions do occur, and it is not unusual to find what is called a “late phase reaction” that occurs 8 to 12 plus hours after the first onset of acute anaphylaxis. The late phase reactions tend not to be as severe as the acute IT-induced reactions.
In acute anaphylaxis, the most common findings are cutaneous (urticaria and angioedema followed by flushing) in up to 90% of patients. This is followed by respiratory findings (dyspnea, wheeze, upper airway angioedema) in up to 60% of cases. The next most frequent symptoms and signs are the presence of dizziness, syncope, and hypotension in up to 35% of patients. Also, abdominal symptoms such as nausea, vomiting, diarrhea, and cramping pain are seen in up to 30% of patients with acute anaphylaxis (18).

The initial assessment of a patient with suspected anaphylaxis is critical. This assessment should enable one to differentiate between anaphylaxis and a vasovagal reaction (see table II). Anaphylaxis can present with or progress to states of: hypotension, tachycardia, evident angioedema, decreased consciousness (hypoxia), erythema and/or urticaria, dyspnea/wheezing, nausea/vomiting, and a “sense of impending doom.” In contrast, individuals experiencing a vasovagal reaction manifest: bradycardia, an absence of respiratory distress, no evident erythema or urticaria although the skin is usually cool and pale, and the blood pressure is usually normal or increased.

### Table I. Anaphylaxis vs. Vasovagal Reaction

<table>
<thead>
<tr>
<th>Findings</th>
<th>Anaphylaxis</th>
<th>Vasovagal</th>
</tr>
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<tbody>
<tr>
<td>Heart rate</td>
<td>Tachycardia</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>hypotension</td>
<td>Hypotension, improves or normalizes when placed in a supine position</td>
</tr>
<tr>
<td>Respiratory:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>++</td>
<td>rare</td>
</tr>
<tr>
<td>Wheezing</td>
<td>++</td>
<td>rare</td>
</tr>
<tr>
<td>Skin:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>+++</td>
<td>none</td>
</tr>
<tr>
<td>Urticaria (hives) /angioedema</td>
<td>+++</td>
<td>none</td>
</tr>
<tr>
<td>Cool and pale</td>
<td>None</td>
<td>Common</td>
</tr>
</tbody>
</table>
The differentiation of these 2 states is important since most individuals experiencing a vasovagal reaction will recover quickly with minimal intervention. The treatment in essence is to keep the patient in a supine position until fully recovered. In contrast, anaphylaxis requires immediate medical intervention in order to ensure a good outcome.

The patient evaluation includes an assessment of the ABCs meaning airway, breathing, circulation and the level of consciousness. If evidence of a respiratory or cardiac arrest has occurred, start CPR and call 911.

If the pulse oximetry is low or repetitively fluctuates to values below 90% on room air, then begin oxygen administration and continue to monitor the pulse oximetry readings. If anaphylaxis is evident, epinephrine administration is the treatment of choice; whereas H1 antihistamines (e.g. Benadryl), H2 antihistamines (e.g. Ranitidine) and steroids are second-line medications. In most medical offices, epinephrine should be administered at a 1:1000 dilution I.M. at 0.01mL/kg with a maximum dose of 0.5mL (in adults and 0.3 mL in children). This can be repeated as often as every 5 minutes, but be sure to monitor BP, other vital signs, and your patient’s clinical response. Also note that short-term tachycardia and tremors are common initial responses to epinephrine. Some suggest that the I.M. injections should be placed in the thighs, rather than the arms, due to a theoretic higher rate of epinephrine absorption. Epinephrine administration can be repeated every 5 to 15 minutes until there is significant clinical improvement. However, if palpitations, tremors, and anxiety occur and persist, watch out, these are signs of hyperadrenalism.

Maintain the patient in a supine position with his or her feet elevated until the time of full recovery. This position helps to prevent orthostatic hypotension and promotes the shunting of blood from the periphery to vital areas such as the brain and heart (19). There have been anecdotal reports of fatal outcomes if patients are allowed to, or enabled to sit or stand while being treated for anaphylaxis. Most likely, during these occurrences circulation is not effectively shunted to the heart and brain.

For IT-induced anaphylaxis, decreasing the absorption of the allergens may further diminish the extent and severity of the anaphylaxis. Some have suggested that this may be achieved by injecting 0.15 to 0.3 mL of 1:1,000 aqueous epinephrine (0.1 to 0.2 mL in children) into the site (19).

If the pulse oximetry readings are: low, or the patient is on beta blockers and/or has a pre-existing cardiac condition, or the anaphylaxis is prolonged or the patient is requiring the administration of albuterol nebulizations due to wheezing, then oxygen should be administered. If an airway needs to be established and maintained, then the use of a one-way valve mask with an oxygen port may be utilized. Ambubags of greater than 700 mL are required in adult patients in order to overcome a 200 cc anatomic dead space (18). At times, an oxygen flow rate of 8 to 10 liters/minute may be required. For those with
the appropriate equipment, a few severe cases of anaphylaxis may require intubation to maintain an airway (table III).

If wheezing persists after the administration of epinephrine, then albuterol via nebulization should be administered (2.5 mg% in adults and 1.25 mg% in children under 6 years old). This treatment can be repeated every 15 minutes, or continuously if the appropriate equipment is available. Needless to say, oxygen should be administered simultaneously.

In anaphylaxis, up to 50% of intravascular fluid can transfer to the extravascular space in a matter of minutes. Thus, hypotension ensues and the use of IV saline is recommended. In adults, 1 liter should be infused within 5 minutes at the rate of 5 to 10 mL/kg. In children, up to 30 mL/kg should be infused during the first hour. For those with CHF or renal compromise the infusion amounts and rates may be lowered (19,20). These patients need to be observed for the signs and symptoms of potential fluid overload.

Both H1 (Benadryl) and H2 (Ranitidine) antihistamines may be utilized in the treatment of anaphylaxis. Their onset of action is much longer than epinephrine; hence, these drugs can be used in addition to, but not in place of epinephrine. Studies demonstrated that the administration of both Benadryl and Ranitidine is more effective than Benadryl alone. For parenteral administration 1 to 2 mg/kg of diphenhydramine (Benadryl) with a maximum of 50 mg per dose should be considered. Expect somnolence to occur in response to the diphenhydramine administration. In a similar manner, Ranitidine (Zantac) may be administered I.M. to adults as a dose of 50 mg, while in children the dose is 1 mg/kg with a maximum dose of 50 mg. If administered via an intravenous line (for severe cases), first mix the ranitidine with D5W to a volume of 20 mL. Then infuse the 20 mL over a 5 minute time period. If the anaphylaxis is not severe or no IV access is available, then IM administration is sufficient and does not require dilution in D5W. Alternatively, oral administration of Benadryl (at the same as the parenteral dose) and 150 mg of ranitidine for adults, or 2 mg/kg/dose of liquid ranitidine (15 mg/ml) for children weighing up to 50 kg is acceptable in less severe cases (table III).

There is a role for steroids in the treatment of anaphylaxis. Although the initial benefits may not appear until approximately 6 hours after administration, steroid use can in some cases prevent the late phase reaction and in many cases significantly minimize the symptoms. Steroid administration may also diminish the extent and duration of urticaria and diminish the bronchospasm often seen in anaphylaxis. For mild cases, adult patients should be given 40 to 60 mg of prednisone orally. In children the administration of 1 mg/kg up to a maximum of 40 mg is recommended. In more moderate to severe cases the IV/IM administration of 40 to 125 mg of methylprednisolone (q6h) is recommended. In pediatric cases, use 1 to 2 mg/kg IV/IM q6h (table III).
Table III. Treatment of Anaphylaxis*

1. Distinguish Anaphylaxis from a Vasovagal reaction and assess ABC (see text)
2. Place the patient in a supine position with the legs elevated.
3. Monitor vital signs and pulse oximetry every 2 to 5 minutes
4. If anaphylaxis is evident administer epinephrine—may repeat q 5-15 minutes (see text)
5. Provide oxygen up to 10 Liters/minute if required. If an airway needs to be maintained, use an ambubag of greater than 700 mL for adult patients.
6. If wheezing is evident, despite the use of epinephrine, administer albuterol via nebulization (see text)
7. Administer diphenhydramine and ranitidine PO or IM/IV (see text)
8. Administer steroids PO or IM/IV (see text)
9. Infuse IV normal saline for associated hypotension (see text)
10. If epinephrine has been administered, the patient will need to be observed for 4 to 6 hours or longer; therefore, calling 911 is advised to transport the patient safely to the nearest ER for observation and treatment.

*modified from table 5 (Ref. 19)

The patient with anaphylaxis, even a mild case, warrants observation for 4 to 6 hours with vital sign monitoring and possible ongoing therapy. More severe cases merit hospitalization for a 24 hour observation period. Most primary care offices do not have the facilities and personnel for such extended care. Thus, I recommend that after the first IM epinephrine is administered, a call should be placed to 911 in order to have the patient transferred to the nearest ER. A complete record of vital signs and medications utilized should accompany the patient to the ER. It is also advised to have the patient take oral Benadryl q6h for an additional 24 to 36 hours and oral prednisone daily for an additional 2 to 3 days. A follow up appointment in 24 to 48 hours would also be appropriate. Primary care providers are also advised to periodically carryout mock anaphylaxis codes in order to educate staff.
References: