Published in final edited form as:

J Allergy Clin Immunol Pract. 2017 ; 5(2): 325–329. doi:10.1016/j.jaip.2016.08.008.

Anaphylaxis conundrum: A Trojan Horse Phenomena

Ann Esquivel, MD^a and William Busse, MD^a

^aDepartment of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

Abstract

Anaphylaxis is a serious and potentially life-threatening allergic reaction that may follow the ingestion of foods. Although these reactions usually follow a common clinical pattern and often demonstrate IgE sensitization to the antigen in question, both the clinical presentation and causative allergen may be atypical, surprising, and difficult to identify. Failure to identify the actual cause of the reaction can compromise treatment and complicate long-term care. Here, we present a patient who had symptoms of anaphylaxis after eating salmon, but confirmation of the causative allergen was not readily apparent. This particular case serves as an insightful lesson for patients undergoing evaluation for anaphylaxis and also provides a framework for navigating through a case involving identification of an underlying allergen.

Keywords

Anaphylaxis; Anisakis allergy

Introduction

Anaphylaxis is an acute “allergic” reaction that follows activation and release of mediators from mast cells and basophilic leukocytes.¹ Recognition and diagnosis of anaphylaxis is aided by characteristic features of this allergic reaction: rapid onset of symptoms following antigen exposure, typical target organ responses often including cutaneous manifestations, and previous knowledge of sensitization. However, the clinical picture of anaphylaxis is not always typical, and variabilities in its presentation add complexity to what appears as a readily apparent diagnosis and causative factor. In addition, although anaphylaxis often follows activation of mast cell-bound allergen-specific IgE molecules to release mediators, non-IgE-dependent immunologic reactions, non-immunological responses and idiopathic conditions can also be responsible for these acute reactions. An important step in the care of patients with anaphylaxis involves a recognition and characterization of these reactions, i.e. immunologic vs. non-immunologic. Furthermore, to prevent future episodes of anaphylaxis,

Corresponding author: William Busse, MD, Professor of Medicine, University of Wisconsin Hospitals and Clinics, 600 Highland Avenue, Madison, WI, Telephone: 608.263.6183, Fax number: 608-261-1191, Wwb@medicine.wisc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

it is important to identify and avoid the causative allergen, if possible. As illustrated by the following case, the identification of a specific antigen for anaphylaxis may require careful “detective” work.

Case Presentation

A 58-year-old physician experienced three apparent allergic reactions each after eating salmon. The initial episode occurred following a late night dinner consisting of wild-caught, Alaskan King Salmon, guacamole, and a salad. Apparently, she had eaten this particular type and brand of salmon, as well as the other foods, on many occasions with no adverse reaction. However, approximately two hours after eating dinner with salmon, she developed severe gastrointestinal symptoms consisting of nausea, vomiting, diarrhea, and abdominal cramping. Along with these gastrointestinal symptoms, she had a brief, but definite, syncopal episode. It was not clear, however, if the syncope was related to dehydration from vomiting and diarrhea or anaphylaxis. There were no cutaneous components during this reaction, and no treatment was sought. Within 4 hours, she had recovered completely.

Approach to the diagnosis of anaphylaxis

The first step in the diagnostic approach to our patient was to determine if the reaction was anaphylaxis. Based on her history and the proximity of the reaction to eating, it was highly likely that she had an allergic reaction to a food from her evening meal, even though the onset of her symptoms was somewhat delayed. Although her symptoms consisted primarily of gastrointestinal manifestations, we presumed that her syncope was related to hypotension from anaphylaxis. Her clinical features match two of the five common target organ reactions found in anaphylaxis (Table 1).

Patients with anaphylaxis typically experience the onset of symptoms within 30 minutes of exposure to the causative agent, with initial symptoms frequently including cutaneous flushing and warmth, that is often accompanied by hives or angioedema and other systemic manifestations such as wheezing, vomiting, or syncope. However, as with our patient, not all episodes of anaphylaxis are obvious. In 10–20% of cases of anaphylaxis, skin and mucosal involvement are absent or unrecognized.¹ In addition, the onset of an anaphylactic reaction may be delayed, as seen with red meat exposure in patients with the alpha-gal syndrome and in our patient.²

Criteria for the diagnosis of anaphylaxis are established, and anaphylaxis is considered highly likely if any one of the three criteria noted in Table 2 occurs. Our patient had gastrointestinal symptoms and, presumably, a significant reduction in her blood pressure as the cause of her syncope.

Laboratory tests can also be helpful to confirm an occurrence of anaphylaxis. Trypsin is released primarily from mast cells and basophils and can be useful to diagnose all forms of anaphylaxis or mast cell activation syndromes.^{3, 4} To use measures of trypsin in testing for anaphylaxis, it is recommended that serum be obtained within 1–3 hours after the reaction.³ The minimal elevation considered clinically significant is $1.2 \times$ baseline trypsin levels $+2$ (ng/mL),⁵ with baseline measurements done at least 48 hours after complete resolution of

symptoms. Patients with mastocytosis can have persistently elevated tryptase levels, and, for this reason, it may be useful to repeat a tryptase level 4–6 weeks following the anaphylactic event.^{4, 6} Our patient's tryptase level was normal, but not obtained close to her reaction.

The alpha-gal syndrome is also an important cause of delayed anaphylaxis and arises from sensitization from a previous tick bite, which leads to an eventual development of allergic reactions with red meat ingestion. The reason for the delayed reaction to alpha-gal is thought to be due to the digestive process which leads to a delay in appearance of the antigen in the circulation.² Finally, because our patient's reaction was delayed following the ingestion of food and consisted primarily of significant gastrointestinal manifestations, consideration was given to other diseases such as eosinophilic gastroenteritis.

Anaphylaxis can be classified into three broad categories based on the mechanism of the reaction involved: immunologic, non-immunologic, or idiopathic (Table 3).⁷ In determining the type of our patient's anaphylaxis, despite the high probability of food as the causative factor, other immunologic and non-immunologic factors needed to be considered.

Immunologic anaphylactic reactions that are mediated by IgE antibodies acting through the FcεRI to activate mast cells and basophilic leukocyte release of their mediators. Examples include foods, medications (such as beta-lactam antibiotics), insect venom, and latex. While anaphylaxis seen in the alpha-gal syndrome is delayed in onset, the mechanism is also considered immunologic, with IgE binding to galactose-alpha-1,3-galactose.² Non-IgE immunologic anaphylaxis does not involve allergen activation of specific IgE antibodies or FcεRI but occurs with direct activation of mast cells and basophils and subsequent mediator release.⁷ Examples of non-immunologic anaphylactic reactions include those caused by radiographic contrast agents, opioids, and non-steroidal anti-inflammatory medications. Historically, these have been deemed 'anaphylactoid,' or 'pseudo-allergic' reactions but are now classified as anaphylaxis.⁸ Even though the mechanisms by which mast cell activation occurs are different from IgE responses, the clinical presentation of anaphylaxis in each of these different reaction classifications is similar. Mast cell activation syndrome is also thought to overlap with non-immunologic anaphylaxis.⁵ None of the non-immunologic factors causing mast cell degranulation appeared relevant to our patient. The etiology of idiopathic anaphylaxis is not established.⁹

Approach to identifying the cause of anaphylaxis

Our presumptive diagnosis was anaphylaxis caused by an immunologic reaction to ingested salmon with the next step being an identification of the causative antigen. From her history, the anaphylactic reaction was likely food-related. In considering other possibilities, she denied recent ingestion of ethanol, aspirin, or NSAIDs and had not exercised that day. Furthermore, she had not had contact with either stinging insects or latex products, all major factors associated with anaphylaxis. Having excluded these possibilities, we focused our search for a food-related anaphylactic reaction.

The patient reported three separate reactions to salmon. Two weeks after the first reaction, our patient had again eaten salmon, obtained from the same food distributor as the earlier

fish product, and, within one hour, developed nausea, vomiting, and diarrhea. No syncope occurred this time, however she reported rhinorrhea. The initial event followed a meal with salmon as well as guacamole and a salad. Both of the latter two foods could cause anaphylaxis, but importantly, these foods were absent from the second reaction provoking meal.

A third reaction occurred a few weeks later while she was out-of-town. She again consumed Alaskan King Salmon, which was from the same distributor that supplied her hometown fish dealer. Approximately one hour after eating salmon, she noted gastrointestinal symptoms similar to those experienced with the two prior reactions. In addition to rhinorrhea, she had a pruritic erythematous rash on both of her hands; however, there was no angioedema or light-headedness. Of note, between these episodes of anaphylaxis, she had eaten salmon, on at least three occasions, but from a different fish source, and had no ill effects. Seasoning was also considered as a possible allergic trigger, but the salmon she tolerated was seasoned in the same way as the fish to which she had reacted.

Food poisoning is a possible consideration for our patient as well. Scombroid food poisoning from spoiled fish is caused by histamine, which leads to an acute allergic-like reaction, particularly if large quantities of the histamine-containing fish are consumed.¹⁰ Ciguatera is a foodborne illness caused by eating reef fish contaminated by a toxin made by dinoflagellates living in corals located in tropical waters.¹¹ Importantly, on all occasions when the patient had become ill, her husband had eaten the same salmon, and in the same amounts, but had no adverse reaction. The fact that her husband tolerated the same fish that caused her reactions made food poisoning, such as scombroid or ciguatera, much less likely. In summary, our patient suffered three similar reactions to salmon that affected the patient but not her husband, and she had consumed salmon uneventfully between episodes. This history suggests that her reactions to the salmon were likely caused by some allergen found in the fish and present only occasionally.

Our patient's evaluation had been initiated within 7 days of her third reaction. Because of the strong component of gastrointestinal symptoms, a CBC with differential was obtained because an inflammatory gastroenteritis was considered. Her peripheral blood evaluation revealed a normal white cell count but with 26% eosinophilia and an absolute eosinophil count of 1820 cells/ μ L. One week later, her peripheral blood eosinophilia had fallen to 17%, with an absolute count of 990 cells/ μ L. At that point, an explanation for the initially high eosinophil count was not apparent. An allergic reaction was now our primary consideration, as no other evidence existed for eosinophilic diseases and abdominal symptoms were limited to the acute episodes. Her sedimentation rate, C-reactive protein, liver function tests, creatinine, and tryptase values were within normal limits. Therefore, a systemic disease appeared to be an unlikely explanation for her reactions. Skin tests to a commercial salmon extract were negative as were specific IgE titers. Despite the absence of significant IgE titers to salmon, she was told to avoid the particular brand of salmon associated with her reactions and return for skin prick testing to fresh food products including salmon.

Skin prick testing was then performed by directly applying fresh fish to her skin followed by a prick-puncture to introduce the fish antigen; the fish tested included Alaskan King Salmon

(from the same distributor where she had purchased the salmon which had presumably elicited the prior reactions), farm-raised salmon, wild pink salmon, and Sockeye (red salmon), as well as histamine and saline controls. Only histamine elicited a significant wheal-and-flare response within 15 minutes of testing.

Fish Borne Parasites and Anaphylaxis – *Anisakis*

Two months after the initial evaluation and with avoidance of salmon during this interval, her peripheral blood eosinophilia had resolved (absolute peripheral blood eosinophils were now 190 cells/ μ L). At this point, we were convinced that the salmon was the source of the antigen leading to anaphylaxis, but it was unlikely that the meat of the fish was responsible for her reaction. We, therefore, questioned if a parasitic infestation of the fish, as opposed to the fish meat itself, was the source of antigen causing her allergic reaction. *Anisakis* is a parasite found in salt-water fish and crustaceans, and the third stage larval form of this parasite can infect fish, like salmon. Ingestion of parasite-contaminated seafood can cause severe allergic reactions in *Anisakis*-sensitized individuals (Figure 1).^{12, 13} *Anisakis* infection can also cause anisakiasis in humans.

Specific IgE to the fish parasite, *Anisakis simplex*, a genus of parasitic nematodes, was measured, and our patient had a markedly elevated sIgE of 47.10 kU/L and an IgG of 29.0 kU/L to *Anisakis* parasite, the latter probably reflecting previous exposures to the parasite antigen. These test results supported the notion that our patient had IgE antibody to *Anisakis*, and this fish-borne parasite was the cause of the reactions when she ate parasite infected salmon. Because the reaction to salmon had occurred on three separate occasions and the sIgE to *Anisakis* was markedly elevated, we did not feel a food challenge was necessary to confirm sensitivity to this allergen.¹⁴

Anisakis is a rare, but known cause of anaphylaxis. Since anisakiasis was originally described in 1960 as a cause of anaphylaxis, cases have been described in Europe, Asia, Africa, and North and South America, including the United States.¹⁵ This infestation demonstrates an intriguing interaction between the parasitic infection of fish which can then lead to allergic sensitization and an allergic reaction when the parasite-infected fish is eaten. The mechanism of these reactions is immunologic as antigen-IgE interactions trigger mast cell mediator release.

Primary infection with *Anisakis* often induces significant eosinophilic inflammation with clinical symptoms including nausea, abdominal pain, vomiting and diarrhea. In severe cases, anisakiasis can lead to bronchospasm and/or anaphylactic shock with hypotension when the IgE-sensitized patient is exposed to the infested fish.¹⁶ In the case of our patient, she had both eosinophilia, possibly reflecting a parasitic infestation, and anaphylaxis as manifested by gastrointestinal upset and hypotension/syncope following ingestion of the parasitic antigen. Management of acute parasitic infestation with anisakiasis may include anti-helminthics, analgesics, and supportive care.¹² In most cases, however, human infestation with this parasite is self-limited.

Once sensitized to the protein of the parasite, allergic reactions to *Anisakis* proteins can occur in the absence of an acute infection if parasite containing fish products are inhaled,

directly contacted (as seen in fish handlers), or, as in the case of our patient, consumed. Notably, most cases of *Anisakis simplex* allergy occur in middle-aged adults without a prior history of atopy.¹³ Epidemiologic studies demonstrate that workers who process fish are at increased risk of becoming sensitized to *Anisakis*, and that sensitization is an important risk factor for allergic disease.¹⁶ *Anisakis simplex* larval forms are small, but can be seen by the naked eye (Figure 2).

The diagnosis of allergic sensitization to this parasite relies on a clinical history of exposure, a positive specific IgE titer or skin prick test to *Anisakis*, and negative specific IgE or skin tests to the fish or seafood that was eaten.¹² It should be noted that *Anisakis* research has shown elevations in sIgE to *Anisakis* can occur as a normal response to the parasite, even in those without allergic symptoms.¹⁷ It has also been demonstrated that the allergens are inactivated by pepsin and, in most patients, larva must be viable to illicit allergic symptoms in sensitized individuals.¹⁸

In the case of our patient, the most striking clue was the strong, but inconsistent, association between her anaphylaxis and ingestion of salmon but no evidence of IgE antibody to salmon as well as a negative skin test response even when salmon meat was used for testing. In the evaluation of anaphylaxis in patients like ours, it is necessary to realize that the antigen causing the allergic reaction may not be the fish meat but rather a parasite in the fish, and ingestion of the salmon, as in this case, served simply as a carrier for the allergen.

Avoiding reactions to ingestion of fish with live *Anisakis* can be achieved by deep freezing (at -20°C for at least 24 hours) or cooking at 60°C for 10 minutes or longer.¹² Many patients sensitized with *Anisakis* tolerate frozen or well-cooked fish, however a small percentage of individuals are sensitized to heat-stable antigens and remain at risk for allergic reactions even with properly cooked fish.¹² Interestingly, the majority of reported cases of anisakidosis in the United States are due to Pacific salmon, as was the case with our patient.¹³

Our patient has subsequently avoided all ocean fish and trout, which feed on ocean crustaceans and has had no additional anaphylactic reactions. She eats fresh water fish, such as perch, walleye, and white fish, without any allergic reactions. She carries an auto-injectable epinephrine to treat any accidental ingestions which may lead to severe reactions. [Table 4]

Conclusion

Anaphylaxis can be prevented by allergen avoidance, which underscores the importance of identifying the causative allergen. In our patient, the causative allergen was not readily apparent even though the ingestion of salmon seemed the obvious provocative food. When such individuals are evaluated, and the obvious food “allergen” is not readily identified, clinicians should consider the possibility that parasites may exist in fish and be both the sensitizing and provocative allergen. Like Troy, it was not the Trojan horse that led to the downfall of this city, but rather the warriors within this horse. For our patient, it was the hidden parasite, *Anisakis*, not the salmon, that caused her anaphylaxis.

Acknowledgments

Jose R. Quintans, MD, PhD

References

1. Simons FE. Anaphylaxis. *J Allergy Clin Immunol*. 2010; 125:S161–81. [PubMed: 20176258]
2. Steinke JW, Platts-Mills TA, Commins SP. The alpha-gal story: lessons learned from connecting the dots. *J Allergy Clin Immunol*. 2015; 135:589–96. [PubMed: 25747720]
3. Schwartz LB, et al. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest*. 1989; 83(5):1551. [PubMed: 2468689]
4. Schwartz LB, et al. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. *N Engl J Med*. 1987; 316(26):1622. [PubMed: 3295549]
5. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol*. 2012; 157:215–25. [PubMed: 22041891]
6. Schwartz LB, Irani AM. Serum tryptase and the laboratory diagnosis of systemic mastocytosis. *Hematol Oncol Clin North Am*. 2000; 14(3):641. [PubMed: 10909044]
7. Greenberger PA, Ditto AM. Chapter 24: Anaphylaxis. *Allergy Asthma Proc*. 2012; 33(Suppl 1):S80–3. [PubMed: 22794697]
8. Ring J, et al. Anaphylaxis. *Chem Immunol Allergy*. 2014; 100:54–61. [PubMed: 24925384]
9. Fenny N, Grammer LC. Idiopathic anaphylaxis. *Immunol Allergy Clin North Am*. 2015; 35:349–62. [PubMed: 25841556]
10. Hungerford, James. Scombroid Poisoning: A Review. *Toxicon*. 2010; 56:2, 231–243.
11. Pennotti R, et al. Ciguatera and scombroid fish poisoning in the United States. *Foodborne Pathol Dis*. 2013; 10:1059.
12. Nieuwenhuizen NE, Lopata AL. Allergic reactions to Anisakis found in fish. *Curr Allergy Asthma Rep*. 2014; 14:455. [PubMed: 25039016]
13. Audicana MT, Kennedy MW. Anisakis simplex: from obscure infectious worm to inducer of immune hypersensitivity. *Clin Microbiol Rev*. 2008; 21:360–79. table of contents. [PubMed: 18400801]
14. Wood, RA. Oral food challenge testing. In: Adkins, NF., JrBochner, BS.Burks, AW.Busse, WW.Holgate, ST.Lemanske, RF., Jr, OHehir, RE., editors. Middleton's Allergy Principles and Practice. 8th. Philadelphia, PA: Elsevier; 2014. p. 1357-1364.
15. Nieuwenhuizen NE, Lopata AL. Anisakis—a food-borne parasite that triggers allergic host defences. *Int J Parasitol*. 2013; 43:1047–57. [PubMed: 23994604]
16. Nieuwenhuizen N, Lopata AL, Jeebhay MF, Herbert DR, Robins TG, Brombacher F. Exposure to the fish parasite Anisakis causes allergic airway hyperreactivity and dermatitis. *J Allergy Clin Immunol*. 2006; 117:1098–105. [PubMed: 16675338]
17. Daschner A, Cuellar C, Rodero M. The Anisakis allergy debate: does an evolutionary approach help? *Trends Parasitol*. 2012; 28:9–15. [PubMed: 22079162]
18. Baeza ML, et al. *Anisakis simplex* allergy: a murine model of anaphylaxis induced by parasitic proteins displays a mixed Th₁/Th₂ pattern. *Clin Exp Immunol*. 2005; 142:433–440. [PubMed: 16297154]

Figure 1.
Life cycle of *Anisakis simplex* including accidental human hosts. Source: CDC-DPDx.
(From <http://www.cdc.gov/dpdx/anisakiasis/index.html>)

Figure 2. White arrows point to circular black swirls which represent *Anisakis simplex* L3 in the flesh of a hake. Source: Clin Microbiol Rev 2008, 21(2):360

Table 1

Target organs and effects of anaphylaxis

Skin	Flushing, erythema, pruritus, urticaria, angioedema
Respiratory	Upper airway – rhinitis, upper airway angioedema Lower airway – bronchospasm
Cardiovascular	Hypotension, light-headedness (pre-syncope), syncope, dysrhythmias, angina
Gastrointestinal	Nausea, cramping, diarrhea, vomiting
Central Nervous System	Headache, confusion, altered level of consciousness, tunnel vision, seizure

Table 2**Critical Criteria for Diagnosing Anaphylaxis**

Anaphylaxis is highly likely when any *one* of the following three criteria is fulfilled:

- 1** Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissues, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
And at least one of the following:
    - a.** Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    - b.** Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
  - 2** Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
    - a.** Involvement of skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    - b.** Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    - c.** Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
    - d.** Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
  - 3** Reduced BP after exposure *to known allergen for that patient* (minutes to several hours):
    - a.** Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP^{*}
    - b.** Adults: systolic BP less than 90 mm Hg or greater than 30% decrease from their baseline
-

From Sampson HA et al. Second symposium on the definition and management of anaphylaxis. *J Allergy Clin Immunol* 2006;117: 391–7.

PEF, Peak expiratory flow; BP, blood pressure.

^{*} Low systolic BP for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Table 3**Pathophysiologic Classification of Anaphylaxis****IgE DEPENDENT, IMMUNOLOGIC**

Foods
 Drugs
 Insect stings and bites
 Exercise (food dependent)
 Other causes

IgE INDEPENDENT, IMMUNOLOGIC

Immune aggregates
 IgG anti-IgA
 Cytotoxic
 Disturbance of arachidonic acid metabolism
   Aspirin
   Other nonsteroidal antiinflammatory drugs
 Activation of kallikrein-kinin contact system
   Dialysis membranes
   Radiocontrast media
 Multimediator recruitment
   Complement
   Clotting
   Clot lysis
   Kallikrein-kinin contact system
 Other causes

NONIMMUNOLOGIC

Direct mediator release from mast cells and basophils
   Drugs, e.g., opiates
   Physical factors, e.g., cold and sunlight
 Exercise
c-kit Mutation (D816V)
 Mastocytosis
 Other causes

IDIOPATHIC

From Brown GA, Kemp SF, Lieberman PL. Anaphylaxis. In: Middleton's Allergy Principles and Practice 8th ed. Adkinson F Jr, Bochner Bs, Burks AW, Busse WW, Holgate ST, Lemanske RF Jr, O'Hehir RE editors. Vo. 2 2014 pp. 1237–1259.

Table 4

Preventing recurrence of anaphylaxis

1) Identification	- Identify trigger based on history and available testing
2) Medication	- Auto-injectable epinephrine - Antihistamine for less severe reactions
3) Education	- Anaphylaxis Action Plan - Stress strict avoidance of allergen - Management of co-morbidities, especially asthma and cardiovascular disease - Patient awareness of drugs that may interfere with epinephrine use (i.e. beta blockers)