MONTANAPHYLAXIS: 
THE ULTIMATE ALLERGIC EMERGENCY
Dan Atkins, M.D.

LEARNING OBJECTIVES

• Define anaphylaxis
• List the most common causes of anaphylaxis
• Describe the common clinical symptoms of anaphylaxis
• Discuss the treatment of anaphylaxis


DEFINITIONS

• Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance.

• Anaphylaxis is a serious allergic reaction that is sudden in onset and may cause death.

ANAPHYLAXIS: CLINICAL CRITERIA FOR DIAGNOSIS

Anaphylaxis is highly likely when any ONE of the following three criteria are fulfilled

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, 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)

ANAPHYLAXIS: CLINICAL CRITERIA FOR DIAGNOSIS

2. Two or more of the following that occur rapidly after exposure to a likely allergy for that patient (minutes to hours)

a. Involvement of the 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 (e.g. hypotonia (collapse), syncope, incontinence)

d. Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

ANAPHYLAXIS: CLINICAL CRITERIA FOR DIAGNOSIS

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 of less than 90 mmHg or greater than 30% decrease in that person’s baseline
**MECHANISMS & TRIGGERS**

**Immunologic mechanisms: IgE-dependent**
- Foods: peanuts, tree nuts, shellfish, fish, milk, egg, sesame
- Food additives & contaminants
- Medications: antibiotics, NSIADS, biological agents
- Venoms: stinging insects
- Natural rubber latex
- Occupation allergens
- Seminal fluid
- Inhalants: animal dander, grass pollen (rare)
- Immunotherapy (insect venom, inhalant allergens)
MECHANISMS & TRIGGERS

Immunologic mechanisms: IgE-independent

- Radiocontrast media
- Dextran
- Infliximab

MECHANISMS & TRIGGERS

Non-immunologic mechanisms

- Physical factors
  - Exercise
  - Cold or heat
  - Sunlight/UV radiation
- Ethanol
- Medications: opioids

COMMON CAUSES OF NON-IGE-MEDIATED REACTIONS

- Multimediator complement activation/contact system activation
  - RCM, ethylene oxide gas on dialysis tubing, ACE inhibitor given during renal dialysis, protamine
- Nonspecific mast cell degranulation
  - Opiate, muscle relaxant, idiopathic anaphylaxis, physical factors such as exercise, heat, cold
- Immune aggregates
  - IVIG, dextran
- Cytotoxic
  - Transfusion reactions to cellular elements
- Psychogenic
  - Factitious, undifferentiated somatoform idiopathic anaphylaxis

Kemp SF. Immunology and Allergy Clinics of America 21:611,2001
### MECHANISMS & TRIGGERS

**Idiopathic anaphylaxis**
- Hidden or previously unrecognized allergens?
- Mastocytosis/clone mast cell disorder

### EPIDEMIOLOGY

- Lifetime prevalence: 0.05% to 2%
- Prevalence increasing in younger people
- Under-diagnosed - especially 1st episode
- Underreported, miscoded
  - 1% of ED visits for acute systemic allergic reactions
  - ED records review: 57% of likely episodes of food anaphylaxis were not diagnosed as anaphylaxis

Simons FER. JACI 2010; 21:611

### RISK FACTORS

- **Race:**
  - No effect on incidence
- **Geographic location:**
  - No effect other than exposure to the allergen (eg. fire ant exposure in southern US)
- **Gender**
  - Females: RCM, intramuscular relaxants, aspirin & latex more common
  - Males: Insect sting reactions more common
- **Age**
  - Children and adolescents: food-induced anaphylaxis
  - Adults: reactions to RCM, dextran, general anesthetics & hymenoptera stings
RISK FACTORS

- Atopy
  - Reactions to food, latex, exercise, RCM & idiopathic anaphylaxis
  - NOT considered a risk factor for insect sting or medication-induced anaphylaxis

- Asthma
  - Not associated with an increased risk of anaphylaxis
  - Increased risk for fatality

PATIENT FACTORS INCREASING RISK OF SEVERITY AND FATALITY

- Age
  - Infants: recognition, lack of appropriate epinephrine auto-injector dose
  - Adolescents & young adults: risk-taking behaviors
  - Elderly: medications, co-morbid disease, venom reactions more severe

SYMPTOMS AND SIGNS OF INSECT STING REACTIONS IN ADULTS AND CHILDREN

<table>
<thead>
<tr>
<th>SYMPTOM OR SIGN</th>
<th>FREQUENCY (%)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ADULTS</td>
<td>CHILDREN</td>
</tr>
<tr>
<td>Cutaneous only</td>
<td>15</td>
<td>60*</td>
</tr>
<tr>
<td>Urticaria/angioedema</td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td>Dyspnea/wheezing</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Throat tightness/hoarseness</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Dizziness/hypotension</td>
<td>60*</td>
<td>10</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>30*</td>
<td>5</td>
</tr>
</tbody>
</table>

In Kaplan AP (ed): Allergy, New York, Churchill Livingstone, 1985
PATIENT FACTORS INCREASING RISK OF SEVERITY AND FATALITY

• Comorbidities
  – Asthma, other respiratory disease
  – Cardiovascular disease
  – Allergic rhinitis, eczema
  – Mastocytosis/clonal mast cell disorders
  – Depression
  – Thyroid disease

• Concurrent medications/chemical use
  – Effect recognition
    □ β-Blockers and ACE inhibitors

• Other factors
  – Exercise
  – Acute infection
  – Menstrual cycle
  – Emotional stress
  – Occupation (bee keeping)
  – Increased baseline serum tryptase levels
  – Reduced PAF AH activity, increased PAF levels
  – Reduced level of ACE activity, increased bradykinin levels

ANAPHYLAXIS: CAUSES OF DEATH

Respiratory Arrest
  • Upper airway
    – Laryngeal edema
  • Lower airway
    – Severe, refractory bronchospasm

Shock
  • Vasodilation with volume redistribution leading to pulseless electrical activity
  • Dysrhythmia due to release of anaphylactic mediators in the myocardium
LESSONS FOR MANAGEMENT OF ANAPHYLAXIS FROM A STUDY OF FATAL REACTIONS
Pumphrey RSH. Clin Exp Allergy 2000; 30:1144-50

Analysis of anaphylactic deaths in the UK since 1992
• The median time to cardiorespiratory arrest for venom allergy after being stung was 15 minutes (range 4 – 120 minutes)
• The median time to cardiorespiratory arrest for food allergy was 30 minutes after food ingestion (range 6 – 360 minutes)

ANAPHYLAXIS: CAN WE TELL WHO IS AT RISK OF A FATAL REACTION?
Pumphrey R. Current Opinion in Allergy and Clinical Immunology 4:285-290, 2004

Analysis of anaphylactic deaths in the UK since 1992
• First time reactions resulting in fatality
  – 23 of 34 insect sting reactions
  – 17 of 24 antibiotic reactions
  – 10 of 10 contrast media reactions
  – 4 of 6 non-steroidal anti-inflammatory drug reactions
• Challenge testing with a reduced dose is unlikely to warn of anaphylaxis without causing it

ANAPHYLAXIS: CAN WE TELL WHO IS AT RISK OF A FATAL REACTION?
Pumphrey R. Current Opinion in Allergy and Clinical Immunology 4:285-290, 2004

Analysis of anaphylactic deaths in the UK since 1992
• Recurrent reaction
  – Could not find evidence that reactions are more severe with each subsequent exposure
  – Severe previous reactions were associated with a severe recurrence
  – Those dying of food allergy had usually had previous reactions that were not typically severe
• Asthma and food allergy
  – Optimal asthma control is important for those with asthma and food allergy
### CLINICAL MANIFESTATIONS OF ANAPHYLAXIS

<table>
<thead>
<tr>
<th>Signs/symptoms</th>
<th>Incidence (%)</th>
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<tbody>
<tr>
<td>Urticaria and angioedema</td>
<td>88</td>
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<tr>
<td>Upper airway edema*</td>
<td>56</td>
</tr>
<tr>
<td>Dyspnea and wheezing</td>
<td>47</td>
</tr>
<tr>
<td>Flush*</td>
<td>46</td>
</tr>
<tr>
<td>Dizziness, syncope, and hypotension</td>
<td>33</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>30</td>
</tr>
<tr>
<td>Rhinitis*</td>
<td>16</td>
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<tr>
<td>Headache*</td>
<td>15</td>
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<tr>
<td>Substernal pain*</td>
<td>6</td>
</tr>
<tr>
<td>Itch without rash*</td>
<td>4.5</td>
</tr>
<tr>
<td>Seizure*</td>
<td>1.5</td>
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</tbody>
</table>

*Symptom or sign not reported in all four series

### BIPHASIC ANAPHYLACTIC REACTIONS IN PEDIATRICS

<table>
<thead>
<tr>
<th>Signs/symptoms</th>
<th>Incidence (%)</th>
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</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>94</td>
</tr>
<tr>
<td>Urticaria, angioedema, flushing, warmth</td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td></td>
</tr>
<tr>
<td>Upper airway:</td>
<td>78</td>
</tr>
<tr>
<td>Throat tightness or itching, oropharyngeal edema, drooling, stridor</td>
<td>58</td>
</tr>
<tr>
<td>Lower airway</td>
<td></td>
</tr>
<tr>
<td>Chest tightness or wheezing</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Arrhythmias, hypotension, poor capillary refill, weak pulses</td>
<td>30</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>27</td>
</tr>
<tr>
<td>Neurological</td>
<td>27</td>
</tr>
<tr>
<td>Generalized: diaphoresis, tingling, impending doom</td>
<td>14</td>
</tr>
</tbody>
</table>


### DIFFERENTIAL DIAGNOSIS

- Anaphylaxis
- Common entities
  - Acute generalized urticaria
  - Acute asthma
  - Syncope
  - Panic attack
  - Foreign body aspiration
  - Cardiovascular event (MI, PE)
  - Neurologic event (seizure, stroke)
DIFFERENTIAL DIAGNOSIS

- Flush Syndromes
  - Carcinoid
  - Perimenopause
  - Chlorpropamide – alcohol
  - Autonomic epilepsy
  - Medullary thyroid carcinoma

- Postprandial syndromes
  - Pollen-food allergy syndrome
  - Scombroidosis
  - MSG
  - Sulfites

DIFFERENTIAL DIAGNOSIS

- Other forms of shock
  - Hypovolemic
  - Cardiogenic
  - Distributive
  - Endotoxic

- Excess exogenous production of histamine syndromes
  - Systemic mastocytosis, urticaria pigmentosa, basophilic leukemia
  - Acute promyelocytic leukemia (tretinoin treatment)
  - Hydatid cyst

DIFFERENTIAL DIAGNOSIS

- Nonorganic disease
  - Panic attacks
  - Vocal cord dysfunction syndrome
  - Munchausen’s stridor
  - Globus hystericus
  - Undifferentiated somatoform anaphylaxis
DIFFERENTIAL DIAGNOSIS

- Miscellaneous
  - Nonallergic angioedema
  - Red man syndrome (vancomycin)
  - Pheochromocytoma
  - Progesterone anaphylaxis
  - Urticarial vasculitis
  - Hyper-IgE urticaria syndrome
  - Idiopathic systemic capillary leak syndrome

CLINICAL COURSE

- Uniphasic
- Biphasic
  - Recurrence up to ? hours later
- Protracted
  - Hours to days

SCREENING FOR ANAPHYLAXIS?

- Antigen-specific IgE levels
  - Screening of sera from blood banks reveals measurable antigen-specific IgE in a large number of patients (insect venom, latex)
    - Insect venom sensitization ranges from 9-32%
    - Not predictive of severity of reaction
- Skin testing
  - Asymptomatic sensitivity
  - Size of skin test does not predict the severity of the reaction
  - Fatal and near fatal reactions to insect stings can occur in patients with negative skin tests
SCREENING FOR ANAPHYLAXIS?

- Basophil histamine release
  - Spontaneous or allergen-triggered in vitro basophil histamine release does not correlate with reaction severity

- Many anaphylactic reactions occur on first known exposure
  - Approximately 75% reactions to peanuts and tree nuts occur on first known exposure
  - 50% of fatal reactions to insect stings occur on the first known sting

NATURAL HISTORY OF INSECT STING ALLERGY

Natural history of insect sting allergy showing the risk of systemic reaction to a sting in untreated patients (solid line) and during and after treatment in patients who received VIT for a duration of either 1 to 2 years (dotted line) or for a mean of 6 years (dashed line)


FOOD ALLERGY:

- Natural History
  - 75% of cow’s milk allergic children and 80% of egg allergic children eventually become tolerant
  - Most wheat and soy allergy children also become tolerant
  - Approximately 20% of young children sensitized to peanut and about 15% of tree nut allergic children outgrow their sensitivity

Sampson HA J Allergy Clin Immunol 1999; 103:981-9
MANAGEMENT OF ANAPHYLAXIS: OVERVIEW

EMERGENCY CARE:
- Epinephrine
- Consider: Initial CPR
- Oxygen
- Antihistamines H1 & H2
- IV fluids
- Vaspressors
- Inhaled bronchodilators
- Intubation or tracheostomy


LABS DURING ACUTE ANAPHYLAXIS

- Plasma histamine level
  - Obtain sample within 15 minutes to 1 hour of symptom onset
  - Large bore needle, keep at 4C, spin and freeze plasma quickly
  - 24 hr urine histamine and N-methylhistamine

- Total tryptase level
  - Obtain blood sample within 15 minutes to 3 hours of symptom onset
  - Consider comparing level during reaction with level obtained at baseline
  - Can measure tryptase in postmortem serum

Kemp SF & Lockey RF. J Allergy Clin Immunol 2002;110:341-8

MANAGEMENT OF ANAPHYLAXIS: IMMEDIATE INTERVENTION

- Assessment of airway, breathing, circulation and mentation
- Administer aqueous epinephrine
  - Intramuscularly, 1:1000 dilution into anterolateral thigh (vastus lateralis).
    - Adults: 0.3-0.5 ml
    - Children: 0.01 mg/kg; maximum dose of 0.3 mg
    - Repeat every 5 minutes as indicated
  - Intravenously, dilute 0.1-0.3 ml of 1:1000 aqueous epinephrine in 10 ml of normal saline (1:100,000 to 1:33,000 dilution)
    - Administer dose over several minutes
    - Repeat as necessary if not responding to injected epinephrine and fluid volume resuscitation
    - Continuous hemodynamic monitoring is required

Kemp SF & Lockey RF. J Allergy Clin Immunol 2002;110:341-8
Absorption of epinephrine is faster after intramuscular than subcutaneous injection

Simon FER. JACI 2004;113:837-44

MANAGEMENT OF ANAPHYLAXIS:

EPINEPHRINE USE: SPECIFIC MEASURES

• Inject aqueous epinephrine 1:1000, ½ dose (0.1-0.2 mg) at the reaction site after sting or injection to delay absorption

• Inhaled or nebulized epinephrine for laryngeal edema
  – Not to be used in lieu of IM epinephrine

Kemp SF & Lockey RF. J Allergy Clin Immunol 2002;110:341-8

TREATMENT OF REACTION

ANTIHISTAMINE OR EPINEPHRINE?

• Antihistamines
  – Helpful for cutaneous symptoms such as itching, flushing and urticaria
  – Minimal, if any, relief for GI or respiratory symptoms
  – Do not relieve upper airway edema or hypotension
  – Do not prevent explosive release of histamine or other mediators
  – Onset of activity of ingested antihistamine does not occur for 40 to 60 minutes, maximal activity in 4 hrs

MANAGEMENT OF ANAPHYLAXIS: ISSUES RELATED TO EPINEPHRINE USE

- Narrow therapeutic range
- Many physicians don’t know how to use an autoinjector
- When to prescribe one? When to use it?
- Many patients don’t carry them
  - Are we treating ourselves by prescribing one?
  - More don’t carry when they know the allergen that causes symptoms
- Patients often can’t remember how to use an autoinjector even after instruction
  - Need to review use at each office visit

MANAGEMENT OF ANAPHYLAXIS: ISSUES RELATED TO EPINEPHRINE USE

- Parents of infants with syringes and an ampule of epinephrine can’t draw up doses quickly or accurately
- When to go from one dose to the next?
- Give epinephrine IM, not subcutaneous
- Outdated autoinjector, use or not?
- Inhaled epinephrine does not work for treatment of systemic reactions in children
- Sublingual epinephrine tablets in the future?
**POTENTIAL REASONS EPINEPHRINE MIGHT NOT WORK IN ANAPHYLAXIS**


- **Patient/caregiver/physician**
  - Rapid progression of anaphylaxis
  - Epinephrine given too late
  - Wrong route or faulty technique
- **Epinephrine related**
  - Dose issues
    - Dose too low
    - Optimal dose not available
  - Route/site not optimal
    - IM versus subcutaneous versus inhaled
    - Self-injection device versus ampule and syringe
  - Past expiration date
- **Other**
  - Individual not supine
  - On medications that interfere with response to epinephrine

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**EPINEPHRINE: ADVERSE EFFECTS**

<table>
<thead>
<tr>
<th>Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td>Fear</td>
<td>Angina</td>
</tr>
<tr>
<td>Restlessness</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Pallor</td>
<td>Sudden increase in blood pressure</td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
</tr>
</tbody>
</table>

- Increased risk of adverse effects of epinephrine
  - Certain pre-existing cardiovascular, central nervous system, or thyroid disorders
  - Use of monoamine oxidase inhibitors (block metabolism)
  - Use of tricyclic antidepressants, cocaine (prolong duration of action)

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**MANAGEMENT OF ANAPHYLAXIS: GENERAL MEASURES**

- Place subject in a recumbent position and elevate the lower extremities
- Establish and maintain airway (endotracheal tube or cricothyroidotomy)
- Administer oxygen at 6 to 8 L/min
- Administer normal saline intravenously for fluid replacement and venous access
- If severe hypotension, rapidly infuse volume expanders
- If allergen was injected, tourniquet above the reaction site to decrease absorption
- If ingested allergen consider administration of activated charcoal

Kemp SF & Lockey RF. J Allergy Clin Immunol 2002;110:341-8
MANAGEMENT OF ANAPHYLAXIS:
ANTIHISTAMINES

• H<sub>1</sub> antihistamine: Diphenhydramine
  – Adult: 50 mg or more in divided doses orally or IV with maximum dose of 400 mg per day
  – Children: 1 mg/kg per dose with 5 mg /kg/day and maximum dose of 300 mg per day

• H<sub>2</sub> antihistamine
  – Ranitidine, diluted to 20 ml in 5% dextrose and given IV over 5 minutes
    • Adults: 50 mg (can also use cimetidine 4 mg/kg)
    • Children: 12.5 – 50 mg (1mg/kg)

Kemp SF & Lockey RF. J Allergy Clin Immunol 2002;110:341-8

MANAGEMENT OF ANAPHYLAXIS:
ANTIHISTAMINES

– Most often used medication in the treatment of anaphylaxis

– Combined use of H<sub>1</sub> and H<sub>2</sub> antagonists should be considered

– May be helpful for stabilization of blood pressure as well as for cutaneous symptoms (not proven)

MANAGEMENT OF ANAPHYLAXIS:
REFRACTORY HYPOTENSION

Dopamine

• 400 mg in 500 ml of 5% dextrose in water IV at rate of 2-20 mcg per kg per min.

• Titrate rate to maintain adequate blood pressure

• Continuous hemodynamic monitoring is required

Kemp SF & Lockey RF. J Allergy Clin Immunol 2002;110:341-8
MANAGEMENT OF ANAPHYLAXIS: BRONCHOSPASM

- Nebulized bronchodilator
  - Albuterol 2.5-5 mg in 3 ml saline OR
  - Levalbuterol 0.63-1.25 mg unit dose
  - Repeat as necessary

- If no response to β-agonist consider
  - Aminophylline 5 mg/kg IV over 30 minutes
    - Adjust dose for age, disease state, or current theophylline use

Kemp SF & Lockey RF. J Allergy Clin Immunol 2002;110:341-8

MANAGEMENT OF ANAPHYLAXIS: SYSTEMIC GLUCOCORTICOSTEROIDS

- Systemic glucocorticosteroids
  - Methylprednisolone 1-2 mg/kg per 24 hours
  - Not acutely helpful, but might prevent prolonged or recurrent reactions

Kemp SF & Lockey RF. J Allergy Clin Immunol 2002;110:341-8

MANAGEMENT OF ANAPHYLAXIS: COMPLICATED BY β-BLOCKER THERAPY

- Characteristics
  - Refractory to treatment
    - Profound hypotension
    - Bradycardia + AV nodal block
    - Severe sustained bronchospasm, urticaria or angioedema

- Treatment
  - Usual approach, consider the following
    - No cimetidine, could decrease β-blocker clearance, use ranitidine
    - Atropine for heart block and refractory bronchospasm
    - Glucagon 1-5 mg (20-30 mcg/kg in children, maximum dose of 1 mg) administered IV over 5 minutes, followed by infusion of 5-15 mcg/min
    - Watch for aspiration, may cause nausea and emesis

Kemp SF & Lockey RF. J Allergy Clin Immunol 2002;110:341-8
Patient presents with history consistent with allergic reaction to food, drug, or insect sting

Complete history & physical examination:
Findings consistent with allergic reaction

Was there a systemic reaction?

Yes
No

Provide:
- Symptomatic treatment if only local symptoms present
- Consider referral to an Allergist

Provide:
- Self-injectable epinephrine and antihistamine
- Education about avoidance
- Referral to an Allergist

Skin testing and/or laboratory testing and/or challenge if indicated

Nonpharmacologic Management
- Patient education
  - Prevention
  - Allergen avoidance
  - Natural history of disease
  - Response to accidental exposure
  - Action plan
  - When and how to use medications
  - When to seek medical care
  - Therapeutic options

Pharmacologic Management
- Immunotherapy, if available
- Medications for treatment of acute reactions
- Treatment of other allergic disease (asthma)

Accurate diagnosis

Long-term Management
Long-term Management

• Periodic follow-up visits
  • Discuss accidental exposures
  • Assess for any change in level of sensitivity
  • Skin tests or laboratory testing, if indicated
  • Response to immunotherapy, if provided
  • Review and revise Anaphylaxis Action Plan
  • Review availability and knowledge of medications
  • Assess impact on lifestyle
  • Discuss new therapies or innovations
  • Answer questions
  • Decide on timing of next visit