6208.06 ALLERGIC REACTIONS

INTRODUCTION

Allergic (hypersensitivity) reactions are most often secondary to an exaggerated immune system response to an otherwise harmless foreign antigen. Antigens are proteins found on the surface of cells; antigens that cause hypersensitivity reactions, are referred to as allergens. Common allergens are peanuts, tree nuts, milk, insect stings and medications. **Anaphylaxis** is an extreme systemic and life-threatening form of hypersensitivity.

Most **allergy and anaphylaxis** are **Type I Hypersensitivity reactions** where a person exposed to an allergen inappropriately produces IgE antibodies specific to that trigger. This initial exposure doesn't usually result in symptoms but primes the body to respond the next time the allergen is seen. It is not known why this immune response occurs in certain individuals, but it is believed to be a combination of genetic and environmental factors.

When next exposed to the allergen, specific IgE antibodies will be released; these then attach to mast cells, which cause a release of histamine, prostaglandins and several types of interleukins. These chemical mediators are responsible for producing the urticaria and flushing, angioedema (rapid swelling of the deep dermis, mucosa and subcutaneous tissue) and the more severe manifestations of allergic reactions.

Non-immune Anaphylaxis, previously referred to as an "anaphylactoid" reaction, is triggered by mechanical/direct activation and degranulation of mast cells, as opposed to IgE-mediated activation. Such non-immune reactions may occur secondary to ambient temperature, exercise, or the administration of radiocontrast dyes, ASA, NSAIDS, or opioids for example. Signs, symptoms, and treatment options are the same as with any other anaphylactic reaction.

"Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death. Severe anaphylaxis is characterized by potentially life-threatening compromise in breathing and/or the circulation, and may occur without typical skin features or circulatory shock being present." (World Allergy Organization, 2019).

In Canada, 1 person per 3 million population dies each year due to anaphylaxis. The most common cause of these deaths is failure to recognize anaphylaxis resulting in a delay in administration of epinephrine. Symptoms can progress rapidly, one study of fatal food allergies showed that the median time from onset of symptoms to cardiac arrest was only 30 minutes. **Early recognition and epinephrine administration is paramount in anaphylaxis.**

There are multiple definitions of anaphylaxis in the literature and our understanding has evolved over time. All definitions of anaphylaxis include:

- **rapid** onset (within 2 hours of exposure to a known trigger)
- compromise in **breathing** and/or **circulation** and/or extreme **GI** symptoms
- may or may not involve the classic **skin** findings (urticarial rash and flushing)
- may or may not include circulatory **shock**

Peds Pearl
Adolescents with history of peanut or tree nut allergy are at particularly high risk of severe anaphylaxis (Campbell 2014).

SAFETY

Some allergic reactions can be caused by animal bites or stings. It is important for clinicians to ensure the animal/insect is not a threat to themselves.

In some cases of allergic reactions, the patient may require treatment with nebulized medications, leading to aerosolized particles. Clinicians should use appropriate personal protective equipment.

Many patients with a history of allergies will have their own epinephrine auto-injector. Be aware that it is a common error for patients and responders to attempt to use the auto-injector upside down. This deploys the epinephrine dose into the users thumb, placing them at risk for ischemia and necrosis. It is important to ensure the auto-injector is being used correctly by referring to the directions on the device. Another error that can be made when using when using an auto-injector is that it is not left in the muscle long enough. If the auto-injector does not appear to have any effect, this may be the cause.

6208.06 ALLERGIC REACTIONS

ASSESSMENT

The clinician must quickly recognize the presence of anaphylaxis as this indicates that immediate life-supporting management interventions are necessary. It may not always be obvious that anaphylaxis is present, such as when the patient has a decreased level of consciousness or shock. A clinician may be alerted to the possibility of anaphylaxis when the focused history includes exposure to a known food or medication allergen within the last 2 hours.

On history and physical exam, consider all the various systems that may be involved and assess accordingly. Urticaria and angioedema are the most common presenting symptoms, followed by respiratory manifestations. Nausea, vomiting, and diarrhea are common after ingested allergens. Refer to Table 1 for a list of signs and symptoms of allergic reactions categorized by body system.

Table 1: Manifestations of allergic reactions by body system (adapted from Arnold & Williams, 2011)

Dermatologic/mucosal Periorbital swelling/erythema, injected (red) conjunctiva, swelling of the tongue and lips, urticaria, pruritis, flushing, swelling
Respiratory **Upper airway:** rhinorrhea, sneezing, throat constriction, dry cough, difficulty breathing, swallowing, or speaking, changes in voice, stridor, cyanosis **Lower airway:** wheeze or cough, chest tightness, tachypnea
Cardiovascular Tachycardia, diaphoresis, hypotension, shock
Gastrointestinal Nausea, vomiting, abdominal cramps, diarrhea
Neurologic Headache, dizziness, confusion, tunnel vision, loss of consciousness
Psychological Anxiety, metallic taste, paresthesia in extremities, feeling of “impending doom”

The patient may not have had a reaction before and may not know the inciting allergen or that symptoms they're experiencing are allergy-related. If the patient does have a history of allergy or anaphylaxis, it's helpful to inquire how severe these reactions were (e.g. How did they present? Did they need to be intubated? etc.) For example, if a person had a life-threatening reaction to an insect sting in the past and now presents within minutes after an insect sting, then treatment (i.e. epinephrine) should be started right away rather than wait for symptoms to occur as clinical deterioration can be rapid.

Peds Pearl

Parents are sometimes hesitant to give their child epinephrine and will often activate EHS first. If anaphylaxis is apparent or the child has history of anaphylaxis and a recent exposure to the same allergen, give epi right away.

The most severe reactions commonly present with airway, respiratory, and hemodynamic compromise indicated by the presence of laryngeal or airway edema, bronchoconstriction (wheezing and/or decreased air entry), tachycardia, hypotension, and an altered level of consciousness. These symptoms may be isolated or involve multiple systems.

Patients at risk of Severe Anaphylaxis (Campbell 2014, Shaker 2020)

(1) peanut and tree nut allergy, especially adolescents
(2) pre-existing respiratory or cardiovascular disease
(3) asthma
(4) delayed administration of epinephrine
(5) previous biphasic anaphylactic reactions*
(6) advanced age
(7) mast cell disease
(8) cardiovascular disease

*a biphasic reaction is one in which the symptoms reappear after treatment without re-exposure to the allergen.

The clinician should assess the airway early for stridor, voice changes, a barking cough, or a feeling of ‘tightness’ in the throat. Assess the lips, tongue, and if possible back of the throat for swelling. Any of these signs and symptoms may indicate impending airway obstruction. It is also critical to monitor the patient closely in case such findings evolve during the course of care.

Peds Pearl

Obtain vitals with the child in a position of comfort. For young children, have the child seated in the parent's lap. As always, recall normal vs abnormal pediatric vital signs for different age children.

Pediatric Heart Rate

Age	Low	Normal	High
0 to <3 mo	<95	110 - 160	>180
3 to <6 mo	<105	120 - 160	>180
6 to <12 mo	<100	110 - 150	>160
1 to <4 y	<75	85 - 140	>145
4 to <10y	<60	70 - 115	>125
≥ 10y	<45	60 - 100	>105

Pediatric Definition of Hypotension*

*Defined as <5th percentile for age

Age	Systolic BP (mmHg)
Term neonate (0-28 days)	<60
Infants (29 days - <12 mo)	<70
Children (1 - <10 years)	<70 + (age in years x 2)
Children (>10 years)	<90

Source: American Heart Association Inc.

Determine the time the exposure occurred, the time the symptoms began, and how quickly they may still be evolving. Anaphylactic reactions usually begin within 15 minutes of exposure to an allergen and though symptoms vary, patients with a history of anaphylaxis often present with similar symptoms each time. If the patient received epinephrine prior to arrival of the clinician, determine the time it was given. Rapidly worsening symptoms are a concerning finding and should prompt the clinician to immediately give a repeat injection, prepare for a difficult airway and prepare for further shock management with an epinephrine infusion.

An accurate history and physical exam will help the clinician differentiate between an allergic reaction and anaphylaxis vs. something else with a similar presentation. Presentations such as asthma, upper airway obstruction due to a variety of other etiologies, shock due to another cause, vasovagal syncope, and panic attacks may be confused with allergic reactions and vice versa.

When no obvious signs of anaphylaxis are present, a more detailed history should be obtained. Ask about possible exposures to the most common allergens such as food, drugs, or insect stings. Also ask about any other (possibly new or changed) exposures including detergents, lotions, beauty products, clothing, latex, animals, pollen or grass/tree exposures, etc. The patient may have had a similar reaction in the past and in some cases may already know they have an allergy to a particular substance. If the patient has an altered level of consciousness, obtain a history from bystanders/friends/family members.

MANAGEMENT

Early recognition of anaphylaxis is key. Recall that a patient can have anaphylaxis without having a rash or hypotension. Once anaphylaxis is identified, epinephrine must be given immediately. Epinephrine stabilizes mast cells, thereby preventing further histamine release. It also reduces the life-threatening airway swelling and hypotension in anaphylaxis by causing vasoconstriction and bronchodilation. Early administration of intramuscular (IM) epinephrine reduces the risk of death and reduces the need for multiple doses of epinephrine in the patient's overall care.

Key point: Life-threatening anaphylaxis can occur in absence of rash or hypotension. Once anaphylaxis is recognized, give epinephrine IM immediately.

The patient should be removed from the source of the allergen if possible. Where feasible, have the patient wash their hands in the event of a mild/moderate reaction of unknown etiology. This will reduce the risk of recontamination from an allergen that may be on the hand. Anyone who may come into contact with the patient (e.g. family) should also be asked to wash their hands. Plain water and hand sanitizers are not effective in removing allergens.

The clinician should be careful that the patient does not become exposed to any medical supplies which they may be allergic to (e.g. latex-based products, alcohol-based swabs, medication preservative agents, etc.)

When administering any medication, it is important for the clinician to differentiate between patients who

6208.06 ALLERGIC REACTIONS

have adverse effects due to medications and those with allergies to them (in which case it would not be appropriate for them to receive that medication). For example, a patient may state they have an allergy to morphine because it makes them nauseous, however this is an adverse effect of the medication, not an allergy. If a patient states they have an allergy to a medication, ask questions to determine exactly what happens when they receive that particular substance.

Since aggressive medical management of anaphylaxis is so important, a detailed discussion of epinephrine is included here. The quickest and safest way to give epinephrine in anaphylaxis is via the IM route. It is paramount to recognize differences in epinephrine concentration and to never give epinephrine 1 mg/mL (i.e. epi 1:1000) via the intravenous or intraosseous route. Errors in epinephrine dosing have contributed to deaths in anaphylaxis. Only epinephrine 0.1 mg/mL (i.e. epi 1:10,000), commonly referred to as cardiac epi, should be ever be used for IV administration. The 1 mg/mL (1:1000) concentration is only to be given IM.

Key point: Never give epinephrine 1 mg/mL (epi 1:1000) formulation via the intravenous or intraosseous route.

Epinephrine is given IM whenever there are signs of airway obstruction, respiratory compromise, hemodynamic symptoms OR persistent severe GI symptoms (Adults - **PEP 2 supportive**; Pediatrics - **PEP 3 supportive**). If any of these symptoms are present in the context of an exposure to a potential allergen, epinephrine 0.01 mg/kg to a max of 0.5 mg should be given in the lateral thigh. For most adults, the usual dose will be 0.5 mg IM in the lateral thigh. Careful attention should be paid to the clinical response to the first injection. Repeat IM injections should be given if minimal or no response within 5-10 minutes up to 3 times. If symptoms are very severe at onset or it is determined a second injection is required, an IV epinephrine infusion should be prepared and started if the symptoms are persistent after 3 IM doses of epinephrine.

Pediatric Epinephrine Dosing Guide

Weight (kg)	Epinephrine dose (1 mg/mL) amp	Epinephrine Auto-injector Dose
5-10	0.1 mg	0.15 mg (EpiPen® Junior)
11-15	0.15 mg	
16-20	0.2 mg	
21-25	0.25 mg	0.3 mg (EpiPen®)
26-30	0.3 mg	
31-35	0.35 mg	
36-40	0.4 mg	
41-45	0.45 mg	
≥46	0.5 mg	

Epinephrine can cause mild symptoms similar to fight or flight response (e.g. anxiety, heart racing, flushing, etc.) or more severe life threatening ventricular dysrhythmias, myocardial infarction, hypertension or intracerebral hemorrhage. The latter is more often associated with epinephrine IV bolus doses. Having said that, for patients with severe anaphylaxis unresponsive to IM injections, an IV epinephrine infusion can be life-saving.

To safely prepare an IV epinephrine infusion, ensure only cardiac epinephrine [i.e. the 0.1 mg/mL (1:10,000) formulation] is used. Add 0.5 mg (5 mL of 1:10,000 cardiac epinephrine) to a 500 mL bag of normal saline. The result is a 1 mcg/mL solution. Start the infusion at 0.1 mcg/**kg**/min. This can be titrated to effect at 2 mcg/min up to 10 mcg/min (Shaker, 2020).

Airway management

Patients with allergic reactions involving the respiratory system should receive oxygen as required to maintain an SpO_2 of at least 92%.

If there is airway obstruction secondary to angioedema, the airway is managed in keeping with principles discussed in the EHS 6200 Adult Airway Management CPG%. IM epinephrine is first line therapy for upper airway obstruction due to anaphylaxis. Other adjunctive treatment for upper airway obstruction such as inhalations must occur AFTER IM epinephrine is given.

Decision to proceed with intubation must take into account transport time to receiving hospital, and

rapidity with which upper airway obstruction is occurring. If obstruction is imminent despite aggressive medical management (as above), and transport time is "long", a preemptive attempt at an awake intubation is warranted. Significant difficulty should be predicted, therefore the clinician should be prepared to promptly perform a surgical airway should intubation, as well as ventilation and oxygenation with BVM become impossible. Extraglottic devices are unlikely to be of assistance in the setting of angioedema. If medical management and BLS airway maneuvers allow for adequate "temporizing" of oxygenation and ventilation, and transport time is relatively short, further airway interventions should be deferred until arrival at hospital.

Adjunct Medications

Diphenhydramine (Benadryl) is an H1 anti-histamine and should be given to all **adult** patients who receive epinephrine for a suspected anaphylactic reaction (**PEP 2 supportive**), as well as patients with less severe, non-life threatening allergic reactions (**PEP 1 supportive**). It will often improve pruritis and rash but it will not reverse airway changes or affect hypotension. It should not be used alone in anaphylaxis.

Peds Pearl

Diphenhydramine is no longer recommended for use in children due to side effects including sedation, memory issues and a small chance of dystonic reactions. Parents may give their children a second generation antihistamine such as cetirizine (Reactine) if they have it.

If a patient with an allergic reaction develops signs of bronchoconstriction (e.g. wheezes) salbutamol should be administered **(PEP white)**.

Hemodynamic Supportive Care

Anaphylaxis can cause widespread vasodilation, and therefore a relative depletion of intravascular volume, which can quickly lead to shock and hypotension. For patients who are hypotensive or showing signs of shock, give IM epinephrine first and then an IV bolus of normal saline (20 mL/kg) should be administered rapid push over 5-10 minutes and repeated as required if there is ongoing hemodynamic instability **(PEP 3 supportive)**. If hypotension persists despite fluid bolus and 3 doses of epinephrine IM, vasopressor support in the form of epinephrine infusion should be considered for further hemodynamic support.

Subsequent ED Management

Subsequent ED management includes the same principles and medications as outlined above. Ranitidine may be administered as an additional anti-histamine (blocks H2 receptors), and a steroid may be given to help suppress an ongoing reaction or prevent reoccurrences over the next few days. If epinephrine is administered either by the patient, the prehospital clinician, or in the ED, the patient requires observation in the ED to ensure symptoms do not reoccur after the effects of the epinephrine have subsided. The ED is also an important opportunity to counsel regarding potential future allergen exposures, ensure patient has an epinephrine auto injector and arrange follow-up if required. These are all important considerations should a patient refuse transport after epinephrine administration.

Cardiac Arrest

Anaphylaxis can progress very quickly if not treated right away, for example, one review of fatal anaphylactic reactions showed a median time between onset of symptoms and death being 30 minutes for food allergens, 15 minutes for stings and less than 5 minutes for allergies to IV medications. If cardiac arrest occurs in anaphylaxis despite optimal treatment, aggressive resuscitation should occur. If within the catchment area of the Halifax Infirmary, consider contacting the HI early in the resuscitation to plan for potential extracorporeal membrane oxygenation (ECMO).

TRANSFER OF CARE

It is important to provide pre-arrival information to receiving hospitals for patients with airway or hemodynamic compromise.

All relevant details to the receiving facility in terms of time of exposure, initial presentation, treatment rendered, time of epinephrine administration (patient's own and/or administration by clinician), and patient's response to treatment.

CHARTING

In addition to the mandatory fields it is important to document the following in the ePCR text fields:

- ✓ Time of allergen exposure
- ✓ Initial patient presentation

6208.06 ALLERGIC REACTIONS

- ✓ Treatment provided before and after clinician arrival
- ✓ Time/dose/route of epinephrine administration (before and/or after clinician arrival)
- ✓ Post-intervention vital signs
- ✓ Reassessment findings

Key Points – Allergic Reactions

Treat allergic reactions and anaphylaxis early!

Allergic reactions can be immediate or delayed; high risk if they are a non-transport

Symptoms can progress rapidly and become life-threatening (reassess frequently)

An accurate history, physical exam, and frequent reassessment will help differentiate between an acute allergic reaction and other etiologies

KNOWLEDGE GAPS

The safety and efficacy of pre-hospital administration of H2 inhibitors and corticosteroids is unknown at this time.

EDUCATION

As management depends on the severity of the reaction, it is important for clinicians to recognize the acuity of mild/moderate/severe allergic reactions.

It is also important for clinicians to be aware of the escalation of epinephrine from IM to an IV infusion for patients who are unresponsive to IM doses. Clinicians should be aware of when escalation is required and know how to correctly set up an infusion.

QUALITY IMPROVEMENT

Anaphylaxis is a time-sensitive management therefore recording accurate time stamps on the ePCR in terms of allergen exposure time and epinephrine administration time is important.

Documentation of epinephrine administration prior to clinician arrival (e.g. by school staff, MFR, bystander, etc.) is an important piece of information in order to measure the quality of the system.

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PEP 3x3 TABLES for ALLERGIC REACTIONS

Throughout the EHS Guidelines, you will see notations after clinical interventions (e.g.: **PEP 2 neutral**). PEP stands for: the Canadian **P**rehospital **E**vidence-based **P**rotocols Project.

The number indicates the Strength of cumulative evidence for the intervention:
1 = strong evidence exists, usually from randomized controlled trials;
2 = fair evidence exists, usually from non-randomized studies with a comparison group; and
3 = weak evidence exists, usually from studies without a comparison group, or from simulation or animal studies.

The coloured word indicates the direction of the evidence for the intervention:
Green = the evidence is supportive for the use of the intervention;
Yellow = the evidence is neutral;
Red = the evidence opposes use of the intervention;
White = there is no evidence available for the intervention, or located evidence is currently under review.

PEP Recommendations for Allergic Reaction Interventions, as of 2021/05/27. PEP is continuously updated. See: https://emspep.cdha.nshealth.ca/ for latest recommendations, and for individual appraised articles.

Mild Allergic Reaction

Recommendation		RECOMMENDATION FOR INTERVENTION			
		SUPPORTIVE (Green)	NEUTRAL (Yellow)	AGAINST (Red)	NOT YET GRADED (White)
STRENGTH OF EVIDENCE FOR INTERVENTION	1 (strong evidence exists)	• Diphenhydramine			
	2 (fair evidence exists)				
	3 (weak evidence exists)				

6208.06 ALLERGIC REACTIONS

Anaphylaxis

Recommendation		RECOMMENDATION FOR INTERVENTION			
		SUPPORTIVE (Green)	NEUTRAL (Yellow)	AGAINST (Red)	NOT YET GRADED (White)
STRENGTH OF EVIDENCE FOR INTERVENTION	1 (strong evidence exists)	• H2 Blocker with Diphenhydramine			• Beta Agonist-Nebulized • Dopamine Infusion • Glucagon • Intubation • Steroid
	2 (fair evidence exists)	• Diphenhydramine • Epinephrine			
	3 (weak evidence exists)	• Crystalloid Infusion			

Pediatric Anaphylaxis

Recommendation		RECOMMENDATION FOR INTERVENTION			
		SUPPORTIVE (Green)	NEUTRAL (Yellow)	AGAINST (Red)	NOT YET GRADED (White)
STRENGTH OF EVIDENCE FOR INTERVENTION	1 (strong evidence exists)				• Beta Agonist-Nebulized • Crystalloid Infusion • Diphenhydramine • Glucagon • Inotrope • Steroid
	2 (fair evidence exists)				
	3 (weak evidence exists)	• Epinephrine			

6208.06 ALLERGIC REACTIONS

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