



Chapter 109 – Allergy, Hypersensitivity, Angioedema, and Anaphylaxis Episode Overview

Key Points:

1. A history of sudden urticarial rash accompanied by respiratory difficulty, abdominal pain, or hypotension, strongly favors the diagnosis of anaphylaxis.
2. Epinephrine is the first-line treatment in patients with anaphylaxis: give it immediately.
3. There are no absolute contraindications to the use of epinephrine in the setting of anaphylaxis.
4. Antihistamines and corticosteroids are second- and third-line agents in the management of anaphylaxis and should not replace or precede epinephrine.
5. Consider prolonged observation or admission for patients who:
 - a. Experience protracted anaphylaxis, hypotension, or airway involvement;
 - b. Receive IV epinephrine or more than two doses of IM epinephrine;
 - c. Or have poor outpatient social support.
6. Patients discharged after an anaphylactic event should be prescribed an EpiPen and instructed on its use.
7. Patients with refractory hypotension may require glucagon (receiving beta-blockage) or a continuous IV epinephrine infusion.
8. Non-histaminergic angioedema (non-allergic angioedema) does not typically respond to epinephrine and antihistamines. New drugs, including berinert, icatibant, ecallantide, and Ruconest have been approved for use in HAE. FFP has been used with varying success in HAE, ACID, and ACE inhibitor–induced angioedema.

NOTE: ACID: acquired C1 esterase deficiency (ACED)

Core Questions:

1. List the four types of Gell and Coombs classifications of immune reaction and give examples of each
2. List four etiologic agents causing anaphylaxis by immunologic mechanisms
3. List six mediators of anaphylaxis and their physiologic actions and clinical manifestations
4. Define anaphylaxis, and list the clinical criteria for diagnosis of anaphylaxis
5. List four risk factors for anaphylaxis and increased anaphylaxis severity and mortality
6. Describe a standard treatment protocol for patients with a history of radiocontrast-induced anaphylaxis
7. List 10 differential diagnoses on the DDx for anaphylaxis
8. Outline a treatment algorithm for anaphylaxis
9. Describe management of refractory hypotension in anaphylaxis
10. Compare and contrast the management of angioedema with urticaria and without urticaria
11. List 3 differential diagnoses for kinin-mediated angioedema



Wisecracks:

- 1) List the types of immune reactions and give an example of each
 - 2) Describe 5 mechanism of action of epinephrine in anaphylaxis
 - 3) List 5 IgE-mediated anaphylactic reactions and 5 non-IgE mediated reactions
 - 4) List 6 differential diagnoses for flushing
 - 5) What is the biphasic response?
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Rosen's in Perspective

This chapter covers disease states in which the immune system overreacts against typically harmless agents. These hypersensitivity reactions are manifested in clinical symptoms ranging from mildly inconvenient to fatal.

For practical purposes, let's define some terms:

- **Allergy**
 - Used in this chapter to refer to mast cell–mediated hypersensitivity reactions. For most allergic diseases to occur, predisposed individuals need to be exposed to allergens through a process called sensitization. Substances that elicit an allergic reaction are referred to as allergens, and those that elicit an antibody response (activated by B- and T-cell receptors) are called antigens.
- **Urticaria**
 - A common allergic reaction to foods, drugs, or physical stimuli and is clinically characterized by an erythematous, raised, and pruritic rash.
- **Angioedema**
 - Another important syndrome, mediated by either an allergic (histaminergic) mechanism in response to exposure to foods, drugs, physical stimuli, or a non-allergic (non-histaminergic) mechanism (e.g., hereditary angioedema [HAE], or angiotensin-converting enzyme [ACE] inhibitor). Angioedema is characterized by edema of the subcutaneous or submucosal tissues, which can cause airway compromise if the tongue or larynx is involved.
- **Anaphylaxis**
 - A life-threatening systemic allergic reaction characterized by acute onset and multiorgan involvement.

Check out the first few pages of the chapter if you want a review on the immune system!

[1] List the four types of Gell and Coombs classifications of immune reaction and give an example of each

So there are four types, I use the mnemonic ACID to help my little brain remember this immunology stuff!



Essentially, it's these four categories that are used to classify hypersensitivity reactions

- **“ACID”**
 - **Acute IgE**
 - Anaphylaxis
 - **Cell-cytotoxic**
 - Blood transfusion reaction
 - **Immune complex**
 - SLE
 - **Delayed**
 - No antibodies involved - EM, SJS, TENS

Refer to box 109.1 in Rosen's 9th Edition for the table summarized below describing the Gell and Coombs classification of immune reactions

Type of Immune Reaction	Definition
<p>TYPE I: IMMEDIATE HYPERSENSITIVITY</p>	<ul style="list-style-type: none"> • Binding of multivalent antigens to IgE on the surface of mast cells and basophils leads to degranulation of mediators • In previously sensitized individuals, the reaction develops quickly (minutes). This type of hypersensitivity reaction is seen in allergic diseases (e.g., hay fever, allergic asthma, urticaria, angioedema, and anaphylaxis) • Nonimmunologic (anaphylactoid) reaction refers to the direct release of preformed mediators of mast cells independent of IgE
<p>TYPE II: CYTOTOXIC ANTIBODY REACTION</p>	<ul style="list-style-type: none"> • Antibody (IgM, IgG) binding of membrane-bound antigens leads to cytotoxicity and cell lysis of cells through the complement or mononuclear cell system (macrophages, neutrophils, and eosinophils). • This type of reaction is seen in transfusion reaction and Rh incompatibility.
<p>TYPE III: IMMUNE COMPLEX–MEDIATED REACTION</p>	<ul style="list-style-type: none"> • Binding of antibody (IgM, IgG) to antigens forms soluble immune complexes, which are deposited on vessel walls, causing a local inflammatory reaction (Arthus reaction) leading to inflammation and tissue injury • This type of reaction is seen in systemic lupus erythematosus and serum sickness (after antithymocyte globulin administration).
<p>TYPE IV: CELL-MEDIATED DELAYED HYPERSENSITIVITY</p>	<ul style="list-style-type: none"> • Sensitized lymphocytes (TH1 cells) recognize the antigen, recruit additional lymphocytes and mononuclear cells to the site, and start the inflammatory reaction. No antibodies are involved. • This type of reaction is seen in contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.



[2] List four etiologic agents causing anaphylaxis by immunologic mechanisms

In up to 60% of adults and 10% of children - no inciting agent is identified!

Refer to box 109.3 in Rosen’s 9th Edition for the table summarized below describing the etiologic agents causing anaphylaxis

Agents of Anaphylaxis	Examples
IMMUNOLOGIC MECHANISMS (IgE-DEPENDENT)	<ul style="list-style-type: none"> • Foods: Egg, peanut, tree nut, milk, fruits, shellfish, soybean, sesame • Medications: Antibiotics, NSAIDs, chemotherapeutic agents, immunomodulators • Insect stings: Hymenoptera venoms, fire ant stings • Natural rubber latex • Hormones: Insulin, methylprednisolone, parathormone, estradiol, progesterone, corticotropin • Local anesthetics: Mostly ester family (procaine, tetracaine, benzocaine) • RCM (radiocontrast) • Occupational allergens: Enzymes, animal protein, plant protein • Aeroallergens: Pollen, dust, spores, pet dander
IMMUNOLOGIC MECHANISMS (IgE-INDEPENDENT)	<ul style="list-style-type: none"> • RCM (radiocontrast) • NSAIDs* • Dextrans • Biologic agents: Monoclonal antibodies, immunomodulators <p>*Aspirin exacerbated respiratory distress (AERD) and NSAID-induced respiratory distress syndromes are unique in individuals with a history asthma or allergic rhinitis and are not considered anaphylactic reactions.</p>
NON-IMMUNOLOGIC MECHANISMS (DIRECT MAST CELL ACTIVATIONS)	<ul style="list-style-type: none"> • Physical factors: Exercise, cold, heat, sunlight • Ethanol • Medications: Some opioids
IDIOPATHIC (NO APPARENT TRIGGER)	VARIABLE NUMBER OF POTENTIAL TRIGGERS

[3] List six mediators of anaphylaxis and their physiologic actions and clinical manifestations

Refer to table 109.1 in Rosen’s 9th Edition for the table summarized below describing mediators of anaphylaxis and their physiologic actions



Here are a couple familiar mediators:

- **Histamine**
- **Leukotrienes**
- **Prostaglandins**
- **Tryptase**
- **Cytokines**
- **Chemokines**

In general, the more rapid an anaphylaxis reaction occurs after an exposure, the more likely it is to be severe and potentially fatal.

Most of these symptoms are due to increased vascular permeability/vasodilation leading to distributive shock states; stimulation of nerve endings; decreased cardiac output; smooth muscle contraction

Specific Organ System	Clinical Manifestation
Upper Resp. Tract	<ul style="list-style-type: none"> ● Rhinitis ● Laryngeal edema
Lower Resp. Tract	<ul style="list-style-type: none"> ● Bronchospasm
Cardiovascular	<ul style="list-style-type: none"> ● Tachycardia ● Hypotension ● Shock ● Syncope ● Dysrhythmias ● Cardiac Arrest
Integument	<ul style="list-style-type: none"> ● Urticaria ● Pruritus ● Warmth ● Flushing ● Angioedema
Eyes	<ul style="list-style-type: none"> ● Conjunctivitis
Gastrointest. Tract	<ul style="list-style-type: none"> ● Dysphagia ● Abdominal cramping ● Nausea/Vomiting ● Diarrhea ● Tenesmus
Central Nervous S.	<ul style="list-style-type: none"> ● Sense of impending doom ● Restlessness ● Anxiety
Heme	<ul style="list-style-type: none"> ● Disseminated Intravascular Coagulopathy
Genitourinary Tract	<ul style="list-style-type: none"> ● Urinary incontinence

[4] Define Anaphylaxis, and list the clinical criteria for diagnosis of anaphylaxis

Rosen’s Definition: “...a life-threatening systemic allergic reaction characterized by acute onset and multi-organ involvement.”



Refer to box 109.5 in Rosen’s 9th Edition for the comprehensive summary of the clinical criteria for the diagnosis of anaphylaxis

Here are the criteria in an abbreviated form - three criteria:

- **Acute onset - minutes/hours of skin and/or mucosal tissue involvement WITH EITHER**
 - Resp. compromise (“glottis and down”)
 - Blood pressure drop (syncope/incontinence)
- **Exposure to a likely allergen, with acute symptomatology, with two of the four signs and symptoms:**
 - Skin-mucosa
 - Respiratory system
 - Blood pressure drop
 - GI symptoms
- **Acutely reduced BP after exposure to a known allergen for that patient**

Important Notes:

- Skin and mucosal tissue are one organ system, AND the lips-tongue-uvula are all part of the mucosal tissue NOT the respiratory tract!
- Nasal congestion, sneezing, ocular itching, and tearing are also common complaints.
- Patients with laryngeal edema often complain of hoarseness, throat tightness, or stridor.

[5] List four risk factors for anaphylaxis and increased anaphylaxis severity and mortality

Refer to box 109.2 in Rosen’s 9th Edition for the comprehensive summary of the risk factors for anaphylaxis, severity of anaphylaxis, and mortality related to anaphylaxis

Risk Factors for Anaphylaxis
<ul style="list-style-type: none">● Age and sex<ul style="list-style-type: none">○ Pregnant women, infants, teenagers, elderly● Route of administration<ul style="list-style-type: none">○ Parenteral > oral● Higher social economic status● Time of the year<ul style="list-style-type: none">○ Summer and fall (the outdoor seasons)● History of atopy● Emotional stress● Acute infection● Physical exertion● History of mastocytosis



Risk Factors for Increased Anaphylaxis Severity and Mortality

- Extremes of age
- Very young (under-recognition)
- Elderly
- Comorbid conditions
- Cardiovascular disease (heart failure, ischemic heart disease, hypertension)
- Pulmonary disease (asthma, obstructive airway disease)
- Others
- Concurrent use of anti-hypertensive agents, specifically beta-blockers and angiotensin-converting enzyme (ACE) inhibitors
- Concurrent use of cognition-impairing drugs (e.g., alcohol, recreational drugs, sedatives, tranquilizers)
- Recent anaphylaxis episode

[6] Describe a standard treatment protocol for patients with a history of radiocontrast-induced anaphylaxis

Refer to box 109.4 in Rosen's 9th Edition for the summary of a standard protocol for patients with a history of radiocontrast–induced anaphylaxis

The pathophysiologic mechanism of anaphylactic reactions to RCM is unknown, but it is believed to be non-immunologic (non-IgE). Clinically, the risk for severe adverse reaction with ionic and nonionic contrast materials is less than 1%.

Standard Treatment Protocol for Patients with Hx of RCI Anaphylaxis

- Prednisone 50 mg by mouth given 13 hours, 7 hours, and 1 hour before the procedure
- Consider an H2 antagonist, such as ranitidine 150 mg by mouth given 3 hours before the procedure
- Diphenhydramine 50 mg PO given 1 hour before the procedure
- Consider ephedrine 25 mg by mouth given 1 hour before the procedure

[7] List 10 differential diagnoses on the DDX of anaphylaxis

Refer to box 109.6 in Rosen's 9th Edition for the comprehensive differential diagnosis for anaphylaxis

- **Shock states:**
 - Septic, hypovolemic, cardiogenic (MI), distributive, obstructive (PE)



- **ALLA and NALLA (allergic angioedema or non-allergic angioedema [HAE, AC1ED, ACE-IAA])**
- **Less life-threatening things:**
 - **Flush syndrome**
 - MSG, sulfites, scombroidosis, alcohol
 - Mastocytosis
 - Carcinoid tumour
 - Perimenopause
 - **Panic attack**
- **Miscellaneous**
 - Hypoglycemia
 - Red man syndrome
 - Vocal cord dysfunction syndrome
 - Pheochromocytoma
 - Asthma attack
 - Syncope

[8] Outline a treatment algorithm for anaphylaxis

The majority of the morbidity and mortality associated with anaphylaxis is caused by acute respiratory failure or cardiovascular collapse. There is no evidence that second line agents improve overall outcome!

- **Remove Any Trigger (stinger, medication)**
 - MOVE
 - ABC's!! Airway!!
 - Call for Epinephrine - all other drugs can wait!!
- **First-line Agent**
 - Epinephrine is the first-line medication and should be given immediately at the first suspicion of an anaphylactic reaction.
 - Adult: 0.3 to 0.5 mg IM* (1 :1000 concentration) in anterolateral thigh every 5 to 10 minutes as necessary
 - Pediatric: 0.01 mg/kg IM (1 :1000 concentration) in anterolateral thigh every 5 to 10 minutes as necessary
 - Alternatively, epinephrine (EpiPen, 0.3 mL; or EpiPen Jr, 0.15 mL) can be administered into anterolateral thigh
 - NEVER GIVE EPINEPHRINE SUBCUTANEOUSLY
- **Bolus Crystalloid**
- **Second-line Agents**
 - Antihistamines
 - Diphenhydramine:
 - Adults: 50 mg IV or 50 mg oral
 - Pediatric: 1 mg/kg IV or oral
 - Ranitidine:



- Adult: 50 mg IV (150 mg oral)
- Pediatric: 1 mg/kg IV or oral
- Aerosolized Beta-agonists (if bronchospastic)
- Combivent (albuterol and ipratropium)
- Glucocorticoids (No Benefit in the Acute Management)
- Methylprednisolone:
 - Adult: 125 to 250 mg IV
 - Pediatric: 1 to 2 mg/kg IV
- Prednisone/prednisolone:
 - Adult: 40 to 60 mg oral
 - Pediatrics: 1 to 2 mg/kg oral
- **Observation and Disposition**
 - Consensus guidelines note that patients who respond well to treatment and experience total resolution of symptoms can be discharged home after an observation period of approximately **4 to 8 hours**.
 - Consider prolonged observation or hospitalization for patients who:
 - Present with protracted anaphylaxis, hypotension or airway involvement;
 - Receive IV epinephrine or more than two doses of IM epinephrine;
 - Have poor outpatient social support.

NOTE: The benefits of epinephrine in anaphylaxis outweigh any risks. There are no absolute contraindications to the use of epinephrine. It is the drug of choice for the treatment of anaphylaxis!

[9] Describe management of refractory hypotension in anaphylaxis

For refractory hypotension in anaphylaxis:

- **Consider Continuous IV Epinephrine Drip**
 - Dilute 1 mg (1 mL 1:1000) in 1000 mL of normal saline or D5W to yield a concentration of 1 µg/mL
 - Dosing
 - Adults: 1 to 10 µg/minute IV (titrated to desired effect)
 - Pediatrics: 0.1 to 1.5 µg/kg/minute IV (titrated to desired effect)
- **Other Vasopressors to Consider**
 - Dopamine: 5 to 20 µg/kg per minute continuous IV infusion (titrated to desired effect)
 - Norepinephrine: 0.05 to 0.5 µg/kg per minute (titrated to desired effect)
 - Phenylephrine: 1 to 5 µg/kg per minute (titrated to desired effect)
 - Vasopressin: 0.01 to 0.4 units/min (titrated to desired effect)
- **For Patients Receiving Beta-Blockade**
 - Glucagon: 1 to 5 mg IV over 5 minutes, followed by 5 to 15 µg/min continuous IV infusion (adult dosing)
 - Consider IV Insulin 1unit/kg infusion (off label, used for BB overdoses)



[10] Compare and contrast the management of angioedema with urticaria and without urticaria

Urticaria appears as papules or wheals that consist of central swelling with surrounding reflex erythema, and it is associated with itching or a burning-type sensation. These lesions are a result of mediators (predominantly histamine) released from mast cells. They tend to occur on the extremities and trunk and are usually transient, with skin often returning to its normal appearance within 24 hours.

There are also several types of inducible urticaria including cold contact, delayed pressure, heat contact, solar, aquagenic, cholinergic, and contact urticaria.

NOTE: Urticaria is an allergic presentation commonly encountered in the ED and is characterized by the presence of wheals (hives), angioedema, or both. Angioedema is characterized by edema of the subcutaneous or submucosal tissues, commonly involving the face, mouth, lips, tongue, extremities, and genitalia. Patients more commonly present with pain and pressure, not pruritus. Of particular concern is when the tongue, posterior pharynx, or larynx is involved, which could progress to airway obstruction and compromise.

Angioedema is mediated either by:

- **An allergic (histaminergic) mechanism in response to an exposure to foods, drugs or physical stimuli, or ALLA**
 - Treatment:
 - If the case meets anaphylactic criteria, treat as such!
 - In cases that do not meet the criteria for anaphylaxis, antihistamines are considered the first-line treatment.
 - Second-generation H1-antihistamines, such as cetirizine, loratadine, and fexofenadine, are the preferred agents, and up to fourfold the conventional dose may be considered.
 - Because 15% of the histamine receptors in skin are H2, the addition of an H2-antihistamine (e.g., ranitidine) may also be beneficial.
 - A short course of oral corticosteroids (e.g., prednisone) may be considered as a second-line therapy.
- **A non-allergic (non-histaminergic) mechanism (e.g., HAE, AC1D, idiopathic or ACE inhibitor), or NALLA**
 - Treatment:
 - Do not typically respond to epinephrine, antihistamines, or steroids
 - However, anyone with airway threatening angioedema and no prior history on hand should be treated with the standard anaphylaxis treatment!
 - These are difficult airways, don't fall into the CICV blackhole!
 - Berinert is human plasma derived C1-esterase inhibitor (C1-INH) concentrate and is approved for treatment of HAE in the United States. The dose is 20 units/kg IV.



- Ecallantide is a kallikrein inhibitor that is administered as three separate 10 mg subcutaneous injections for a total of 30 mg.
- Icatibant is a bradykinin 2-receptor inhibitor that is administered as a single subcutaneous injection of 30 mg.
- Conestat alfa (Ruconest) is a recombinant C1-INH concentrate that is given IV at a dose of 50 units/kg.
- For ACE inhibitor–induced angioedema, the treatment is mainly supportive. The medication should be discontinued and the patient instructed not to take any ACE inhibitor in the future. There are reports of FFP being used with success in severe cases of ACE inhibitor–induced angioedema.

NOTE: Hospitalization must be considered for patients with continued angioedema of the sublingual area, tongue, soft palate, pharynx, or larynx

NOTE: Fresh frozen plasma (FFP), has been reported to be efficacious in treating acute attacks; however, there are reports of exacerbation of angioedema with administration of FFP.

[11] List 3 differential diagnoses for kinin-mediated angioedema

This is the NALLA form....

Non-histaminergic (non-allergic) angioedema is typically a result of elevated bradykinin levels. This classification includes:

- HAE with or without C1 esterase inhibitor deficiency
- Acquired C1 esterase inhibitor deficiency (AC1D)
- ACE inhibitor–induced
- Idiopathic angioedema

NOTE: The lack of C1 inhibitor causes activation of the kallikrein-kinin system, increasing the consumption of kininogen, resulting in increased production of bradykinin (a potent peptide vasodilator).

In the setting of ACE inhibitor–induced angioedema, the inhibition of ACE, one of the main inactivators of bradykinin, results in increased bradykinin levels. ACE inhibitor–induced angioedema has a predilection for the face, often involving the, lips, eyelids, tongue, larynx, or pharynx. The highest incidence occurs in the first month of therapy but has been reported to occur as many as 10 years after therapy was initiated.

Wisecracks:

[1] List the types of immune reactions and give an example of each

Refer to box 109.1 in Rosen's 9th Edition for the table summarized below describing the Gell and Coombs classification of immune reactions



Type of Immune Reaction	Definition
TYPE I: IMMEDIATE HYPERSENSITIVITY	<ul style="list-style-type: none"> • Binding of multivalent antigens to IgE on the surface of mast cells and basophils leads to degranulation of mediators • In previously sensitized individuals, the reaction develops quickly (minutes). This type of hypersensitivity reaction is seen in allergic diseases (e.g., hay fever, allergic asthma, urticaria, angioedema, and anaphylaxis) • Nonimmunologic (anaphylactoid) reaction refers to the direct release of preformed mediators of mast cells independent of IgE
TYPE II: CYTOTOXIC ANTIBODY REACTION	<ul style="list-style-type: none"> • Antibody (IgM, IgG) binding of membrane-bound antigens leads to cytotoxicity and cell lysis of cells through the complement or mononuclear cell system (macrophages, neutrophils, and eosinophils). • This type of reaction is seen in transfusion reaction and Rh incompatibility.
TYPE III: IMMUNE COMPLEX-MEDIATED REACTION	<ul style="list-style-type: none"> • Binding of antibody (IgM, IgG) to antigens forms soluble immune complexes, which are deposited on vessel walls, causing a local inflammatory reaction (Arthus reaction) leading to inflammation and tissue injury • This type of reaction is seen in systemic lupus erythematosus and serum sickness (after antithymocyte globulin administration).
TYPE IV: CELL-MEDIATED DELAYED HYPERSENSITIVITY	<ul style="list-style-type: none"> • Sensitized lymphocytes (TH1 cells) recognize the antigen, recruit additional lymphocytes and mononuclear cells to the site, and start the inflammatory reaction. No antibodies are involved. • This type of reaction is seen in contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

[2] Describe 5 mechanism of epinephrine in anaphylaxis

Epinephrine derives its therapeutic value from its combined alpha-adrenergic and beta-adrenergic actions:

Receptor Stimulation	Physiologic Response
Alpha-1	<ul style="list-style-type: none"> • Vasoconstriction • Increased PVR • Decreased mucosal edema
Beta-1	<ul style="list-style-type: none"> • (+) Inotropy and (+) chronotropy
Beta-2	<ul style="list-style-type: none"> • Mast cell/basophil stabilization • Bronchodilation



These combined effects result in decreased mediator release from mast cells and basophils, which improves hives and bronchospasm, decreases mucosal edema and swelling, and reverses systemic hypotension. Epinephrine therefore works directly to improve the clinical features most commonly observed in an anaphylactic reaction.

[3] List 5 IgE-mediated anaphylactic reactions + 5 non-IgE mediated reactions

Refer to box 109.3 in Rosen’s 9th Edition for the table summarized below describing the etiologic agents causing anaphylaxis

Agents of Anaphylaxis	Examples
IMMUNOLOGIC MECHANISMS (IgE-DEPENDENT)	<ul style="list-style-type: none"> • Foods: Egg, peanut, tree nut, milk, fruits, shellfish, soybean, sesame • Medications: Antibiotics, NSAIDs, chemotherapeutic agents, immunomodulators • Insect stings: Hymenoptera venoms, fire ant stings • Natural rubber latex • Hormones: Insulin, methylprednisolone, parathormone, estradiol, progesterone, corticotropin • Local anesthetics: Mostly ester family (procaine, tetracaine, benzocaine) • RCM • Occupational allergens: Enzymes, animal protein, plant protein • Aeroallergens: Pollen, dust, spores, pet dander
IMMUNOLOGIC MECHANISMS (IgE-INDEPENDENT)	<ul style="list-style-type: none"> • RCM (radiocontrast) • NSAIDs* • Dextrans • Biologic agents: Monoclonal antibodies, immunomodulators <p>*Aspirin exacerbated respiratory distress (AERD) and NSAID-induced respiratory distress syndromes are unique in individuals with a history asthma or allergic rhinitis and are not considered anaphylactic reactions.</p>
NON-IMMUNOLOGIC MECHANISMS (DIRECT MAST CELL ACTIVATIONS)	<ul style="list-style-type: none"> • Physical factors: Exercise, cold, heat, sunlight • Ethanol • Medications: Some opioids
IDIOPATHIC (NO APPARENT TRIGGER)	VARIABLE NUMBER OF POTENTIAL TRIGGERS



[4] List 6 differential diagnoses for flushing

- Flushing associated with food
 - Alcohol
 - MSG
 - Sulfites
 - Scombroidosis
- Carcinoid tumor
- Peri-menopause
- Thyrotoxicosis
- Basophilic leukemia
- Mastocytosis (systemic mastocytosis and urticaria pigmentosa)
- Vasointestinal peptide tumors

[5] What is the biphasic response?

Up to 20% of patients may experience a biphasic reaction defined as a reoccurrence of symptoms without re-exposure to the triggering agent. Most of these reactions occur within 8 hours but have been reported as far out as 72 hours. The majority will again respond to the appropriate treatment, and recent literature suggests that clinically important biphasic reactions and fatalities are actually much rarer than previously reported.

Biphasic reactions are more common in patients who have a history of asthma, ingest the allergen, or present with laryngeal edema, wheezing, or gastrointestinal symptoms.

Glucocorticoids have no immediate role in the acute management of anaphylaxis and should be considered as third line interventions. Their onset of action typically does not occur for several hours, and they should not be administered before first and second line treatments. They may, however, provide benefit by preventing protracted symptoms or a biphasic reaction, but this has never been proven. Currently, there are no studies that have specifically evaluated the role of glucocorticoids in the treatment of anaphylaxis.

Shout-out to the SGEM #57:

<http://thesgem.com/2013/12/sgem57-should-i-stay-or-should-i-go-biphasic-anaphylactic-response/>