Flushing Away Common Allergy Misconceptions

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Presenter Disclosure

- **Dr. McKibbin:**
  - **Speakers Bureau/Honoraria: ALK, AstraZeneca, Novartis, Valeo**
- **Dr. Zaborniak:**
  - **Speakers Bureau/Honoraria: AstraZeneca, Regeneron**
- **Marc Geirnaert:**
  - **no disclosures**

Mitigating Potential Bias

- Not applicable

Equity Commitment

- In preparing for this presentation, I have considered the Health Equity Resource for Presenters provided by the conference planning committee.

- This was provided to help presenters reflect on how these topics and content can have good effects or bad effects on people or populations that are underserved.

Learning Objectives

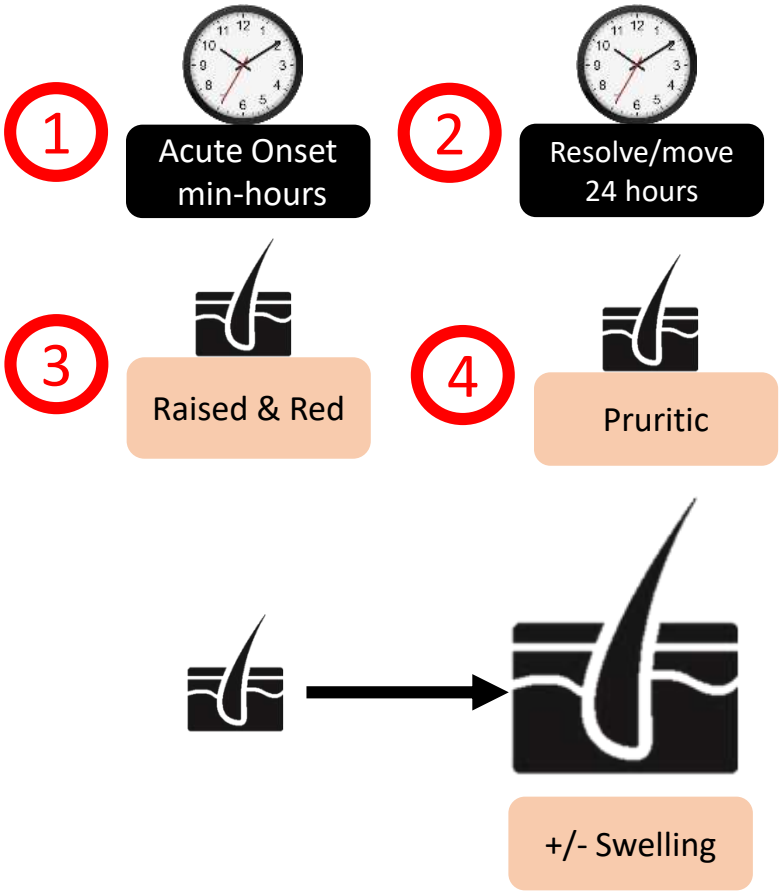
- Describe anaphylaxis and explain why epinephrine is the drug of choice for the treatment of anaphylaxis.
- Differentiate between anaphylaxis and infusion-related reaction.
- List common drugs used in oncology and hematology that cause infusion-related reactions and describe how to manage subsequent doses.

Anaphylaxis & its Treatment

Lundy McKibbin, BSc, MD, FRCPC
Cortext or HSC paging (any time)

Urticaria
(hives)

Hives



℞

1. 2nd Gen AH

Up to 4 tablets daily

Reactine (Cetirizine)
10-40mg po daily prn
Allegra (Fexofenadine)
Aerius (Desloratadine)
Claritin (Loratadine)
Rupall (Rupatadine)
Blexten (Bilastine)

Antihistamines do NOT SAVE LIVES!
(they only stop itchiness)

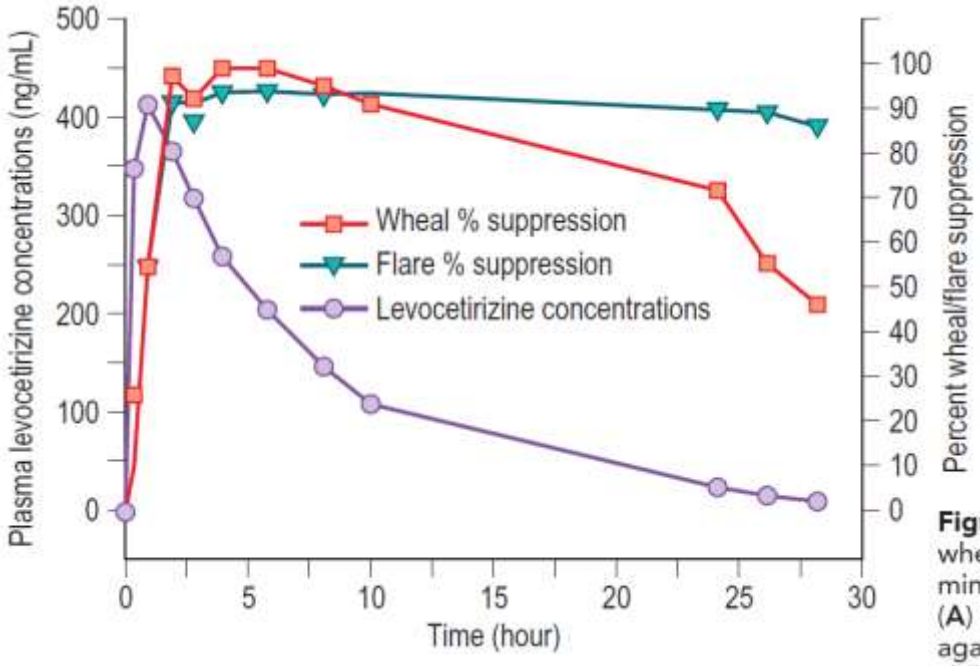


Figure 94-8 Levocetirizine plasma concentrations and effect on the wheals and flares (erythema) produced by skin prick tests with histamine phosphate 1 mg/mL. Mean plasma levocetirizine concentrations (**A**) and mean wheal and flare percent suppression (**B**) are plotted against time before and after ingestion of levocetirizine 5 mg by children age 6 to 11 years. Compared with predose values, wheals were significantly suppressed from 1 to 28 hours, inclusive, and flares were also significantly suppressed from 1 to 28 hours, inclusive (data not shown). *(From Simons FER, Simons KJ. Levocetirizine: pharmacokinetics and pharmacodynamics in children age 6 to 11 years. J Allergy Clin Immunol 2005;116:355-61.)*

Adison, N. Middleton's Allergy: Principles and Practice. 8th edition. 2014.

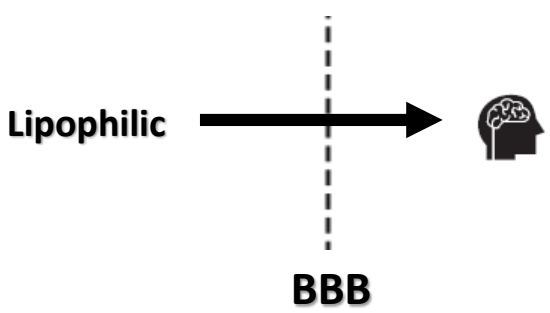
TABLE 94-3 H_1 Antihistamines: Pharmacokinetics and Pharmacodynamics in Healthy Adults

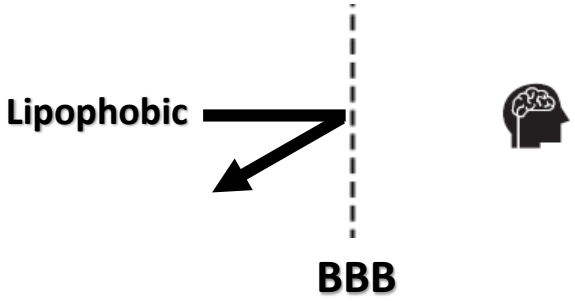
Medication	Time to Maximum Plasma Concentration (t_{max}, hr) after Single Dose	Terminal Elimination Half-life ($t_{1/2}$, hr)	Clinically Relevant Drug–Drug Interactions*	Onset of Action (hr)†	Duration of Action (hr)
ORALLY ADMINISTERED H_1 ANTIHISTAMINES					
FIRST (OLD) GENERATION					
Chlorpheniramine‡	2.8 ±0.8	27.9 ±8.7	Possible	3	24
Diphenhydramine‡	1.7 ±1.0	9.2 ±2.5	Possible	2	12
Doxepin‡	2	13-17	Possible	n/a	n/a
Hydroxyzine‡	2.1 ±0.4	20.0 ±4.1	Possible	2	24
SECOND (NEW) GENERATION					
Bilastine	1.2	14.5	Unlikely	2	24
Cetirizine	1.0 ±0.5	6.5-10	Unlikely	0.7	≥24
Desloratadine	1-3	27	Unlikely	2-2.6	≥24
Fexofenadine*	1-3	11-15	Unlikely	1-3	24
Levocetirizine	0.8 ±0.5	7 ±1.5	Unlikely	0.7	>24
Loratadine (metabolite: descarboethoxyloratadine)	1.2 ±0.3 (1.5 ±0.7)	7.8 ±4.2 (24 ±9.8)	Unlikely	2	24
Rupatadine	0.75-1.0	6 (4.3-14.3)	Unlikely	2	24

Adison, N. Middleton's Allergy: Principles and Practice. 8th edition. 2014.

TABLE 94-2 H_1 Antihistamines: Chemical and Functional Classification

CHEMICAL CLASS	FUNCTIONAL CLASS	
	First (Old) Generation	Second (New) Generation





Non-selective

H_1 selective

Adison, N. Middleton's Allergy: Principles and Practice. 8th edition. 2014.

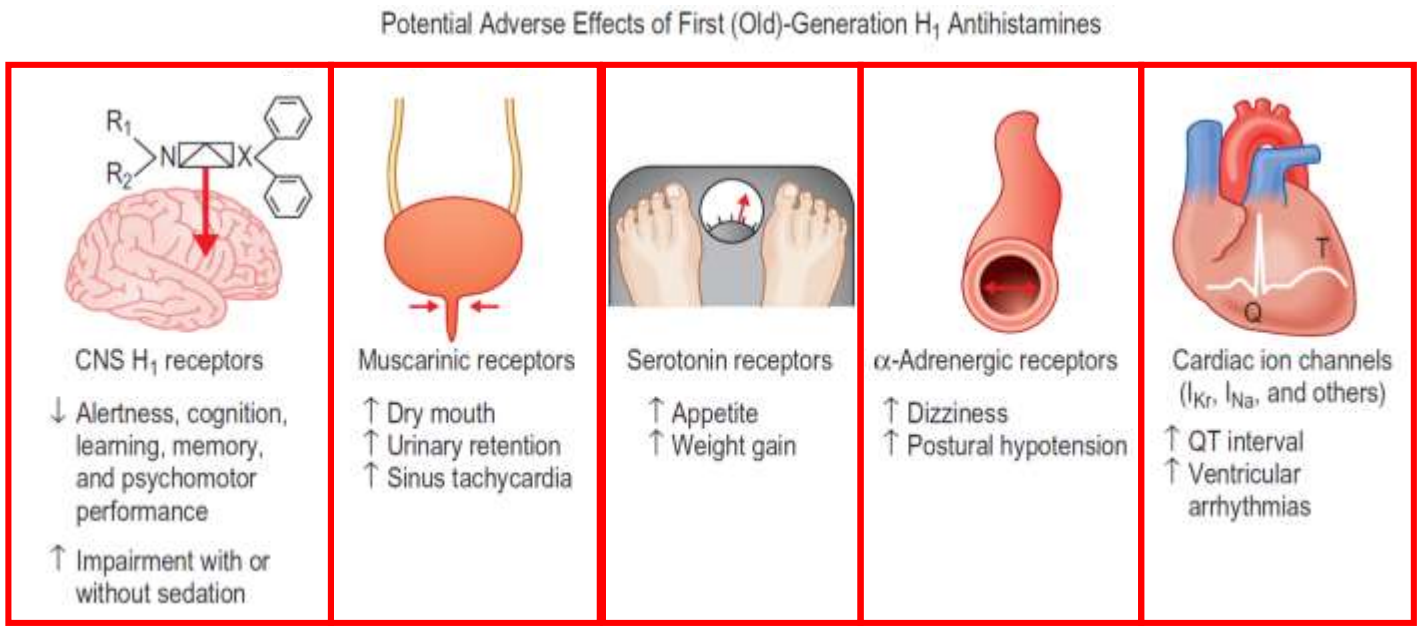


Figure 94-15 Mechanisms associated with potential adverse H_1 antihistamine effects. First (old)–generation H_1 antihistamines cross the blood-brain barrier and occupy central nervous sytem *(CNS)* H_1 receptors, as documented by means of positron emission tomography. High H_1-receptor occupancy correlates directly with impairment of CNS function, with or without accompanying sedation. These medications also may cause adverse effects through other mechanisms, such as their antimuscarinic and antiserotonin effects. I_{Kr}, Rapid component of the delayed outward rectifying potassium channel; I_{Na}, rapid component of the inward rectifying sodium channel. *(From Simons FER, Simons KJ. Histamine and H_1-antihistamines: celebrating a century of progress. J Allergy Clin Immunol 2011;128:1139-50.)*

Adison, N. Middleton's Allergy: Principles and Practice. 8th edition. 2014.

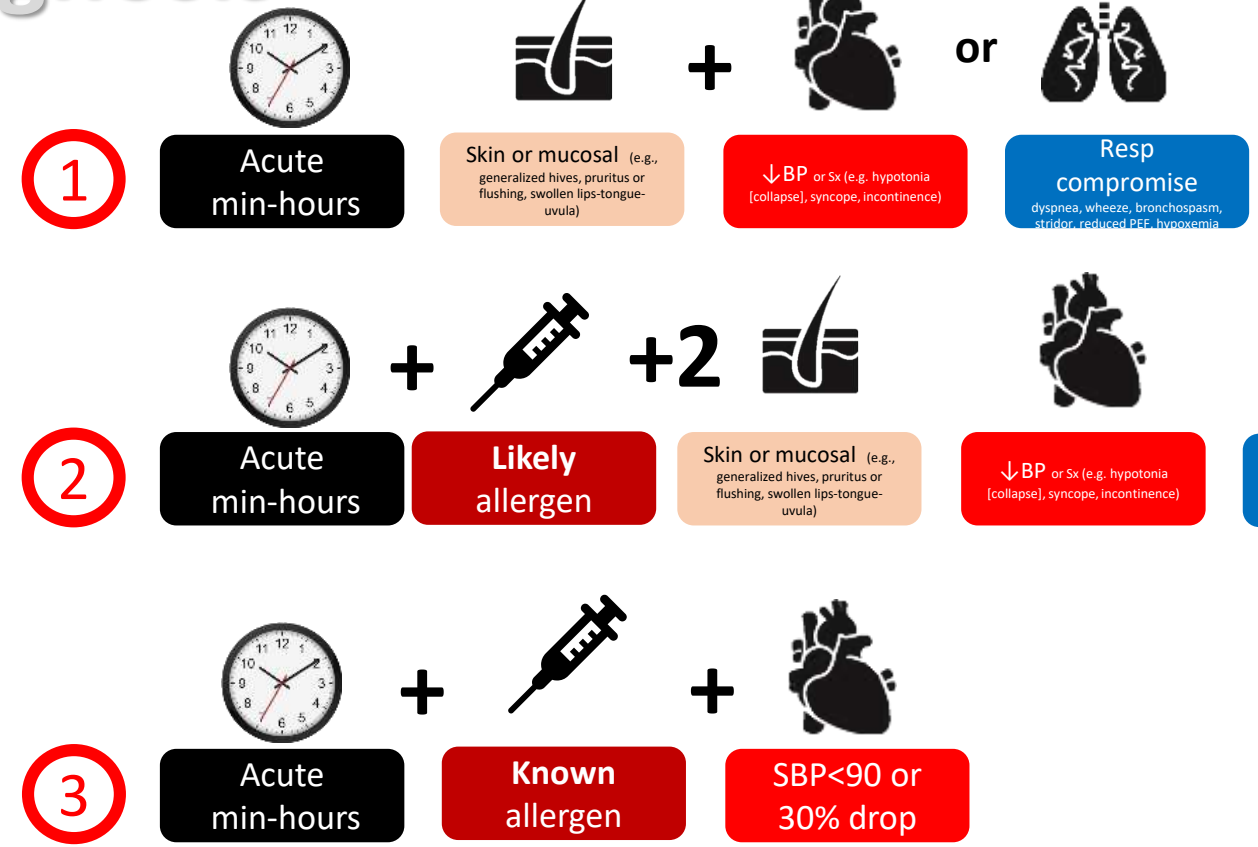
- **Less effective** than second generation antihistamines
- **Sedation** confounds assessment (↓ LOC: from Benadryl or anaphylaxis?)
- **Not a sleeping aid** as it impairs REM (restorative) sleep, leaving patients more tired
- **Can even cause hypotension**
- **Cognitive impairment**
  - Drivers did worse than those beyond alcohol limit
  - Long-term cognitive effects (including Alzheimer's)
- **Promotes Cardiac Arrhythmias** (prolonged QT)

You will **NEVER** save someone's life by giving Benadryl

Anaphylaxis

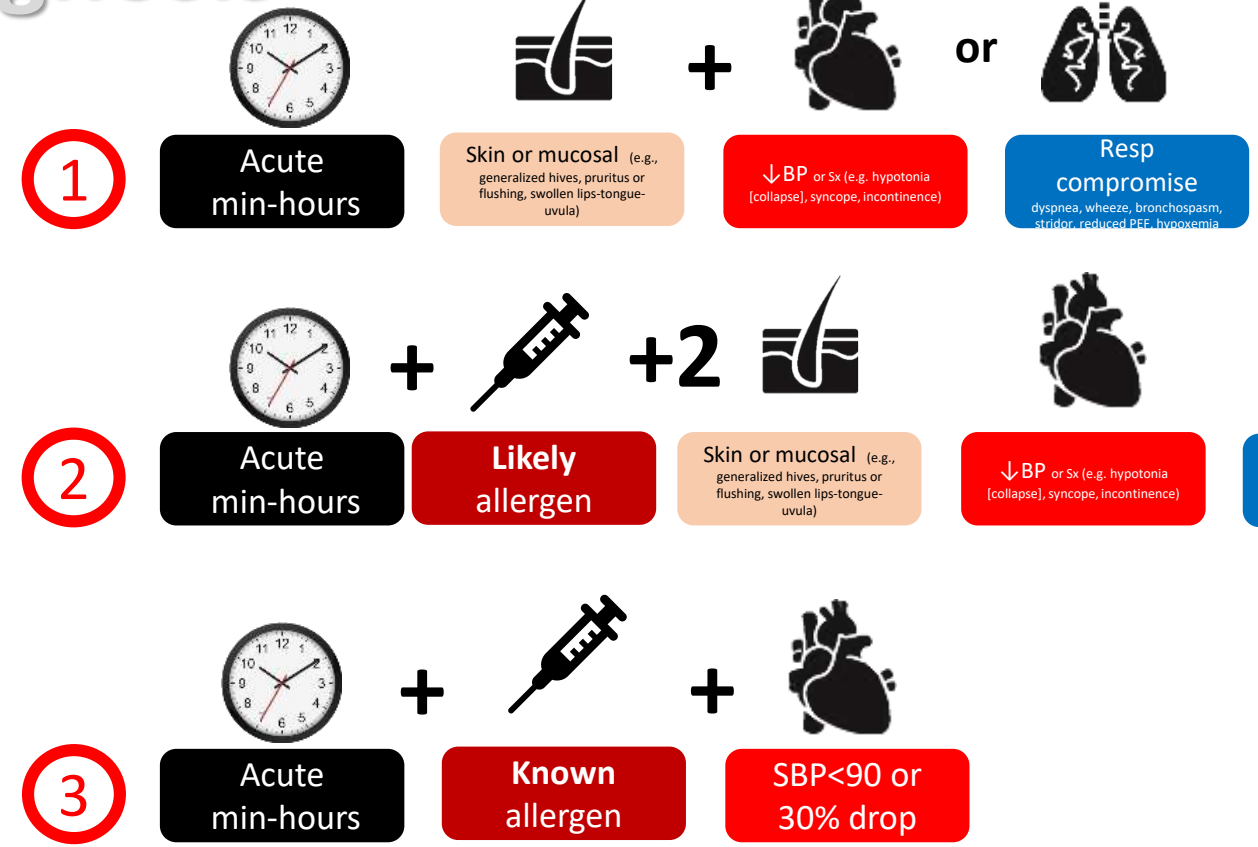
Diagnosis

Anaphylaxis



Diagnosis

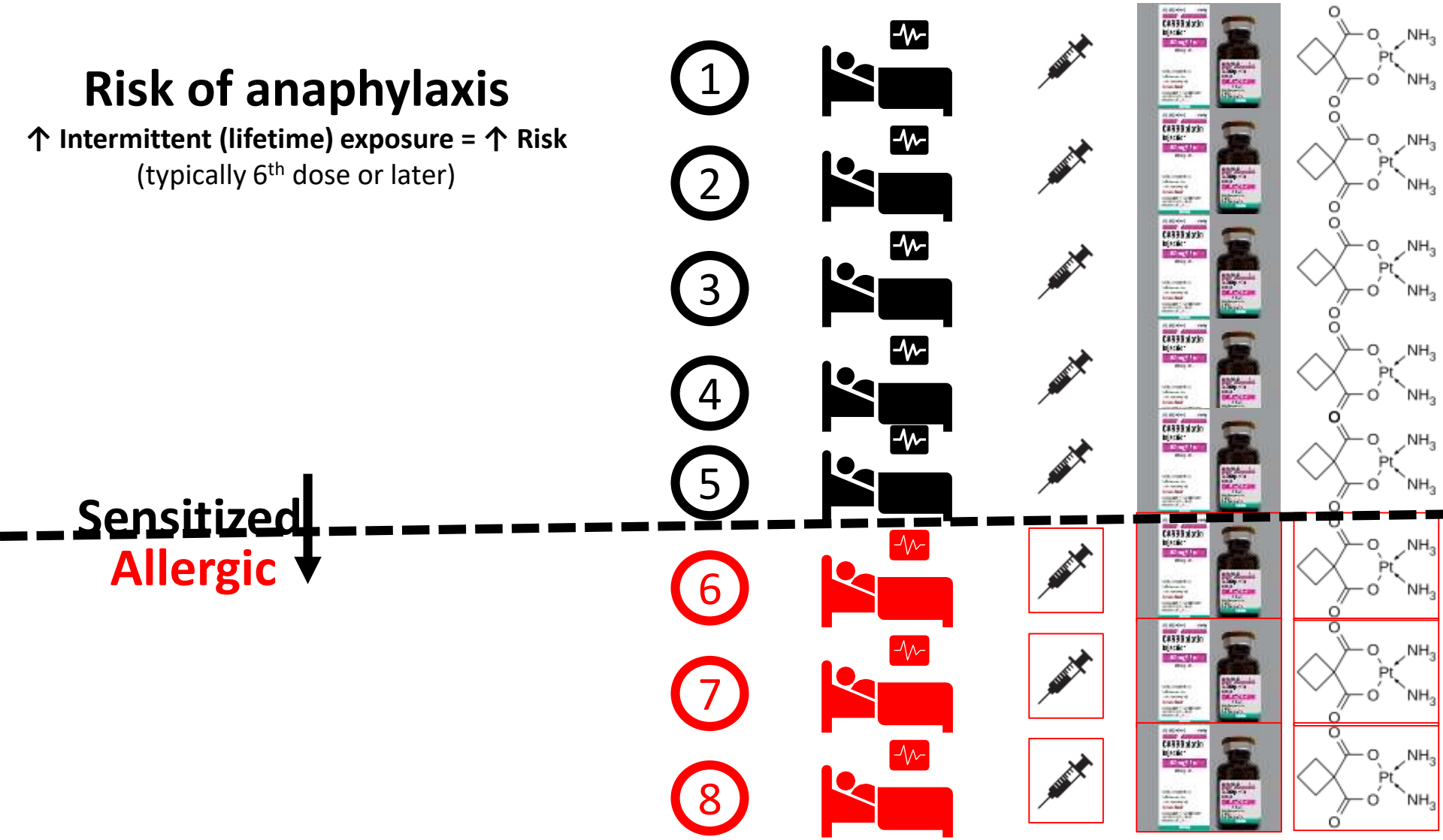
Anaphylaxis



Risk of anaphylaxis

↑ Intermittent (lifetime) exposure = ↑ Risk

(typically 6th dose or later)



How do you **treat** possible **anaphylaxis?**

① Epinephrine

0.5mg IM lateral thigh (1mg/mL)

② Epinephrine

0.5mg IM lateral thigh (1mg/mL)

③ Epinephrine

IM or send to ED for IV Initial: 0.1 mcg/**kg**/minute **(IV conc. 0.1mg/mL)**

IM > SQ

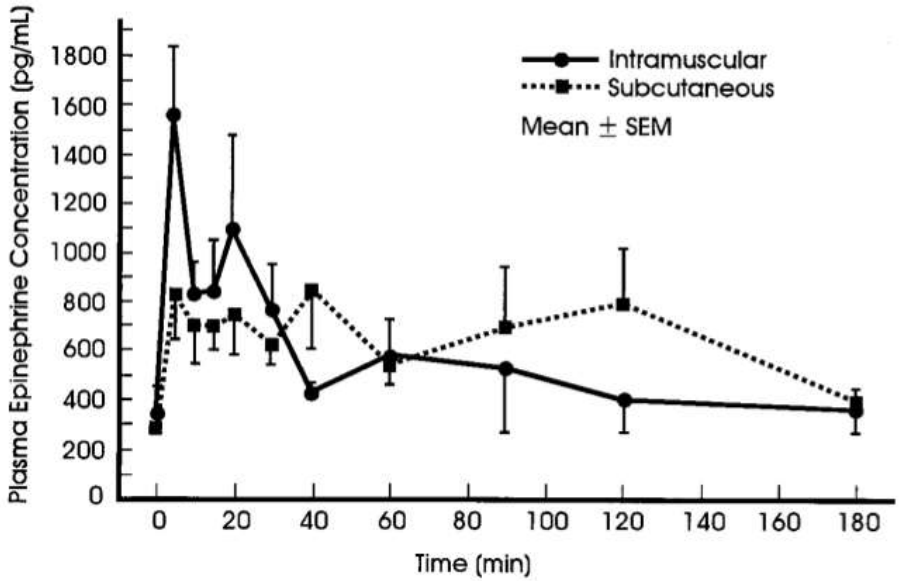


FIG. 1. Mean plasma epinephrine concentration versus time plot after injection of epinephrine subcutaneously in nine children and after injection of epinephrine intramuscularly in eight children.

Simons et al. J Allergy Clin Imunol. Vol 101, number 1, Part 1

↓BP

- **Epinephrine** 0.01 mg/kg (max 0.5 mg) IM q5– 20 min as necessary (consider **Glucagon** if on β Blocker)
- **IV fluids**
- **Supine, elevate legs** (~500mL bolus)
- **Vasopressors**
- **Glucocorticoids** –minimal evidence, but may prevent biphasic symptoms

Resp compromise

dyspnea, wheeze, bronchospasm, stridor, reduced PEF, hypoxemia

- **O_2**
- Inhaled **β_2 agonist** for **bronchospasm**

Skin or mucosal (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

- **Antihistamine** for **cutaneous** symptoms

- up to **20%** (huge over estimate) have a **biphasic** course: recurrence after a 1-8 hour asymptomatic period.

NB: recent literature demonstrates the steroids do not prevent biphasic reaction (not an important therapy for anaphylaxis)

How do you **treat** possible **anaphylaxis?**

Epinephrine

Treat early: delayed or no epinephrine increases risk of death.

Pointers on Desensitization

- Must be IgE mediated
- Contraindicated in SCARs (e.g. SJS, TEN, DReSS)
- Temporary
  - e.g. A patient desensitized to ASA who misses ASA for 2 days, must repeat lengthy desensitization

Anaphylaxis vs. Infusion Reaction

(in less than 10 minutes)

Contact information:
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Anaphylaxis vs. Infusion Reaction

Housekeeping

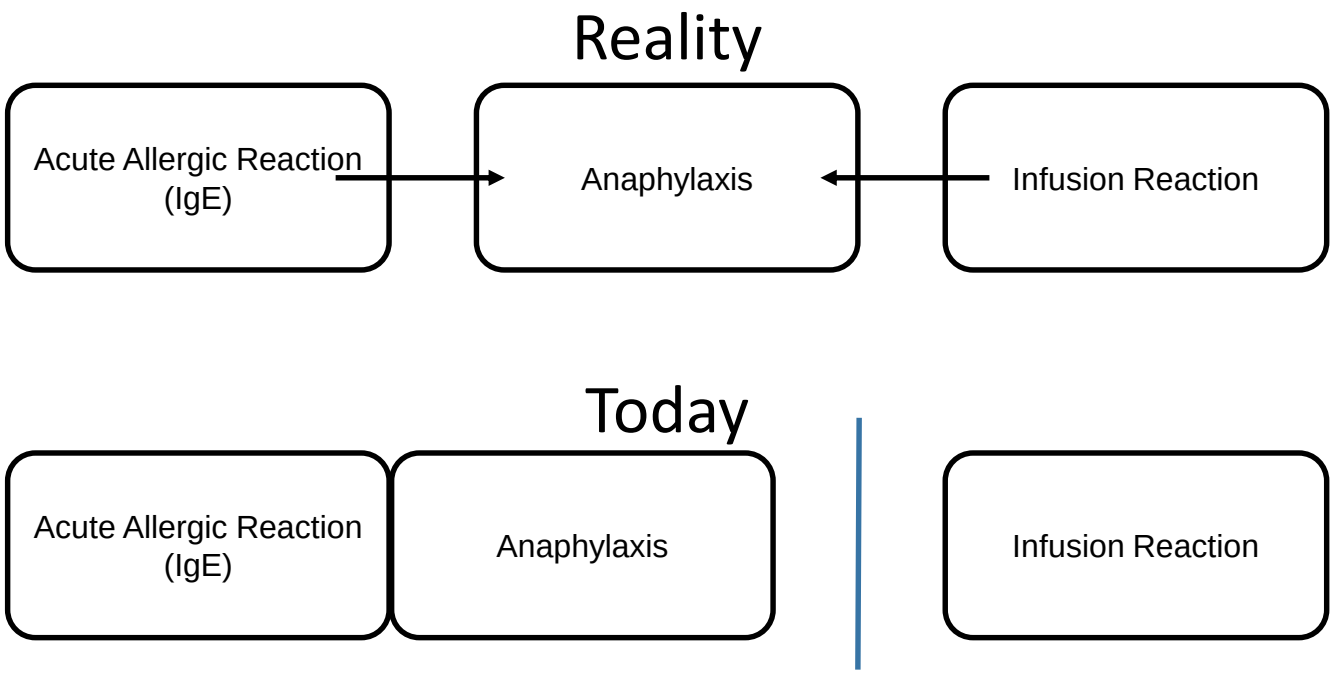
Oversimplification for today…

- Acute allergic reaction
  - IgE antibody mediated activation of mast cells
- Infusion reaction
  - Adverse reaction during (or shortly following) infusion
- Anaphylaxis
  - Acute-onset and systemic response from a variety of mechanisms

Crespo A, Forbes L, Gallo-Hershberg D, et al. Management of Cancer Medication-Related Infusion Reactions CancerCare Ontario: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/60646

Anaphylaxis vs. Infusion Reaction

Disclaimer



Anaphylaxis vs. Infusion Reaction

Definitions

Anaphylaxis

WAO 2011 (1)	EAACI 2013 (2)	AAAAI/ACAAI 2010 (11)	ASCIA 2016 (16)	NIAID 2006 (13)	WHO ICD-11 2019 (14)
A serious life-threatening generalized or systemic hypersensitivity reaction.	A severe life-threatening generalized or systemic hypersensitivity reaction.	An acute life-threatening systemic reaction with varied mechanisms, clinical presentations, and severity that results from the sudden release of mediators from mast cells and basophils.	Any acute onset illness with typical skin features (urticarial rash or erythema/flushing, and/or angioedema), PLUS involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms; or Any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.	Anaphylaxis is a serious allergic reaction that involves more than one organ system (for example, skin, respiratory tract, and/or gastrointestinal tract). It can begin very rapidly, and symptoms may be severe or life-threatening.	Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes.

Cardona et al. World Allergy Organization Journal (2020) 13:100472
http://doi.org/10.1016/j.waojou.2020.100472

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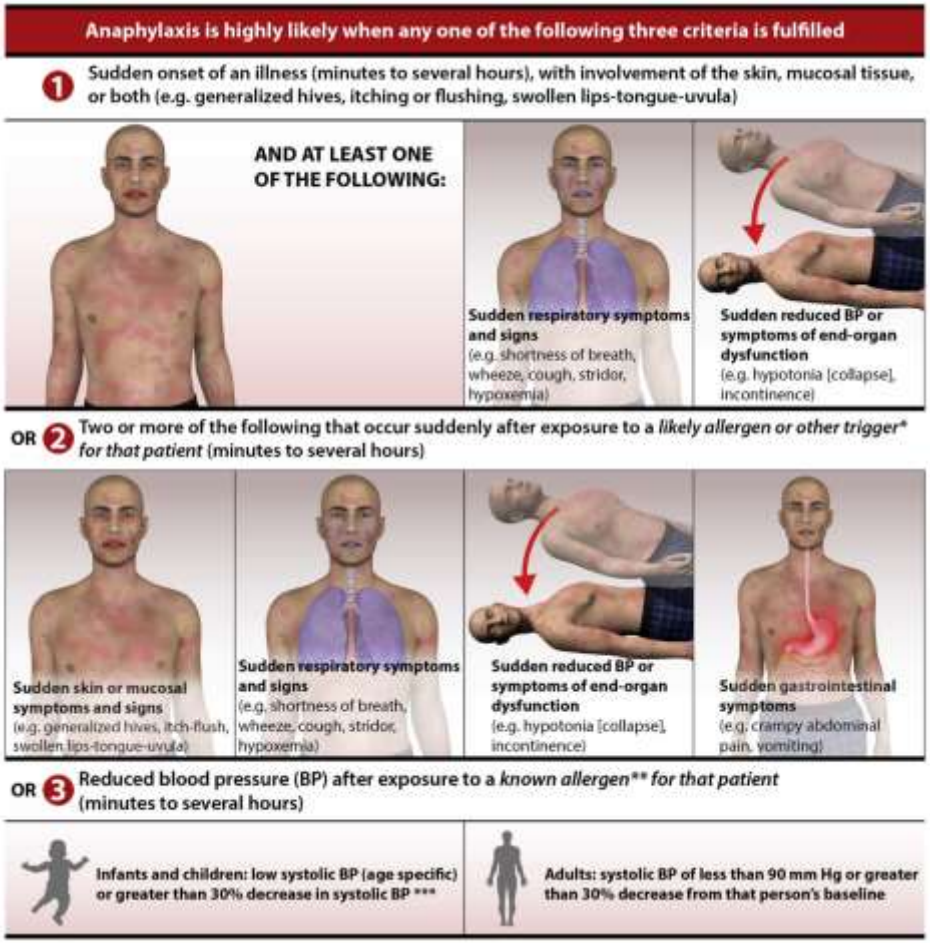
Anaphylaxis vs. Infusion Reaction

Definitions

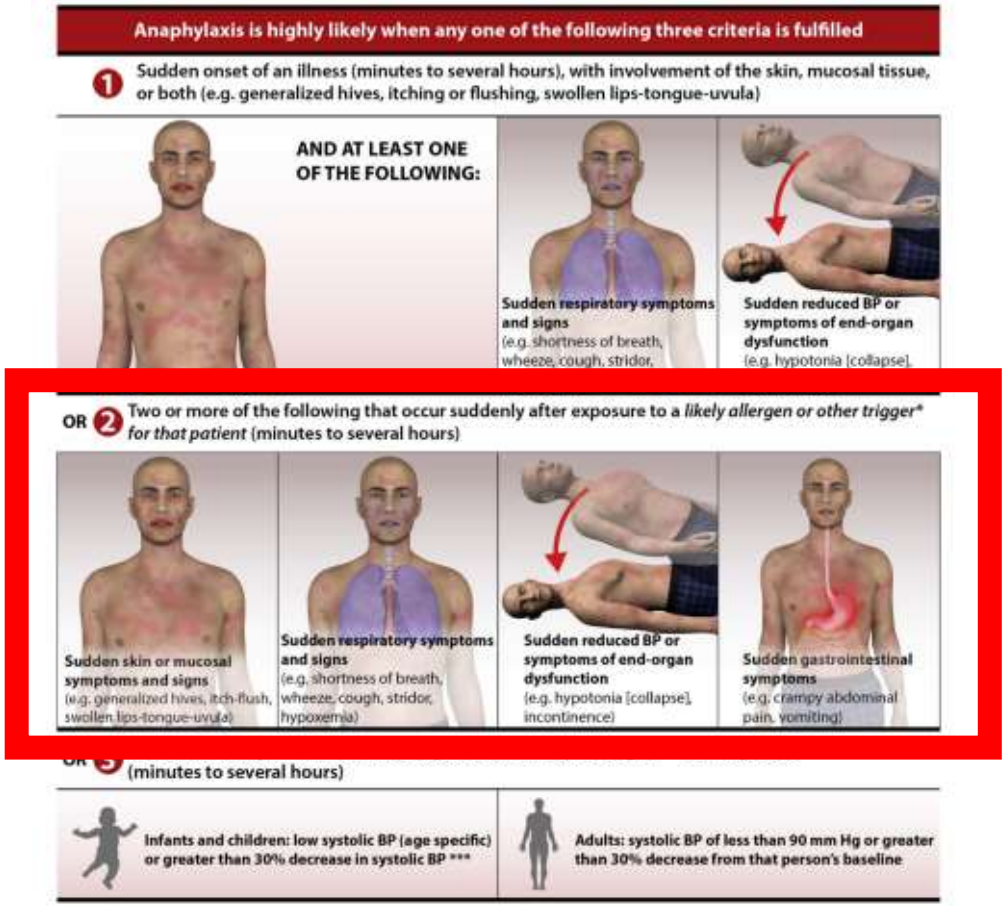
Anaphylaxis criteria is **not** a definition

Anaphylaxis criteria



Shaker MS, et al., Anaphylaxis-a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. 2020 Apr;145(4):1082-1123.

Anaphylaxis criteria



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Anaphylaxis vs. Infusion Reaction

Definitions

Infusion Reaction

- Poorly defined
  - Not explained by the known toxicity profile of the drug
  - Can affect any organ system
  - Range from mild to severe / life-threatening
  - Generally no “proven” immunological mechanism
  - No validated means of lab or allergy skin testing for confirmation

Anaphylaxis vs. Infusion Reaction

Definitions

Infusion Reaction Mechanisms

- Antibody dependent and independent mechanisms
  - Fcgamma receptor on neutrophils and basophils
  - Anaphylatoxin induced mast cell activation
  - Complement activation
  - Cytokine release
  - Direct mast cell activation

Bernard Yu-Hor Thong, et al., Prevention of Drug Hypersensitivity Reactions: Prescreening and Premedication, The Journal of Allergy and Clinical Immunology: In Practice, Volume 9, Issue 8, 2021, Pages 2958-2966

Anaphylaxis vs. Infusion Reaction

Comparison of symptoms

	Infusion Reaction	Anaphylaxis
Skin	Flushing, itching, rash	Urticaria, angioedema
Cardiovascular	HR, BP, syncope	Tachycardia, hypotension, LOC
Respiratory	Dyspnea, chest pain, hypoxia	Cough, dyspnea, wheeze, hypoxia, nasal congestion
Gastrointestinal	N/V/D, pain	N/V/D
Other	Back/abdo pain, fever/chills	Impending doom, tunnel vision

Anaphylaxis vs. Infusion Reaction

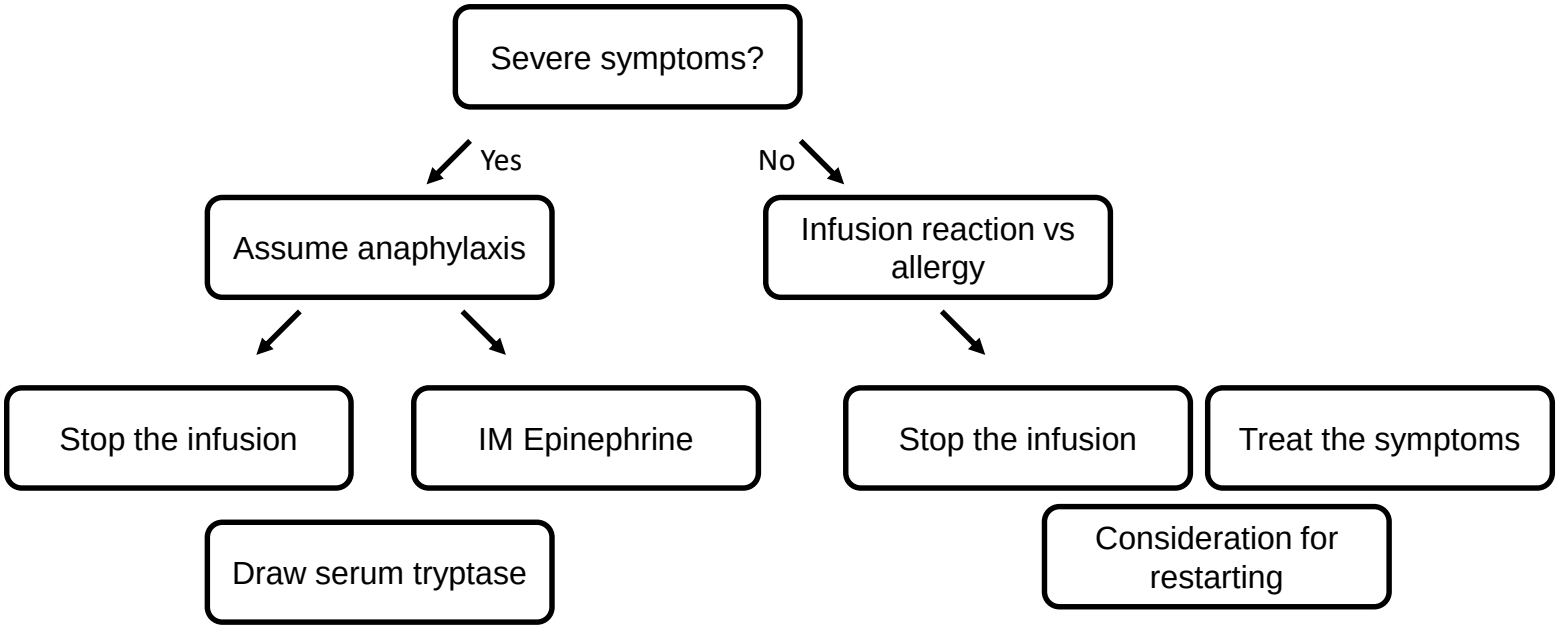
Comparison of symptoms

	Infusion Reaction	Anaphylaxis
Timing	Often 1st infusion	Further into treatment
Tryptase	Not elevated	Often elevated (< 3 hours)
Re-exposure	Pre-treatment Infusion time	Desensitization
Allergy skin testing	Negative	Positive (ideally)

Anaphylaxis vs. Infusion Reaction

Summary

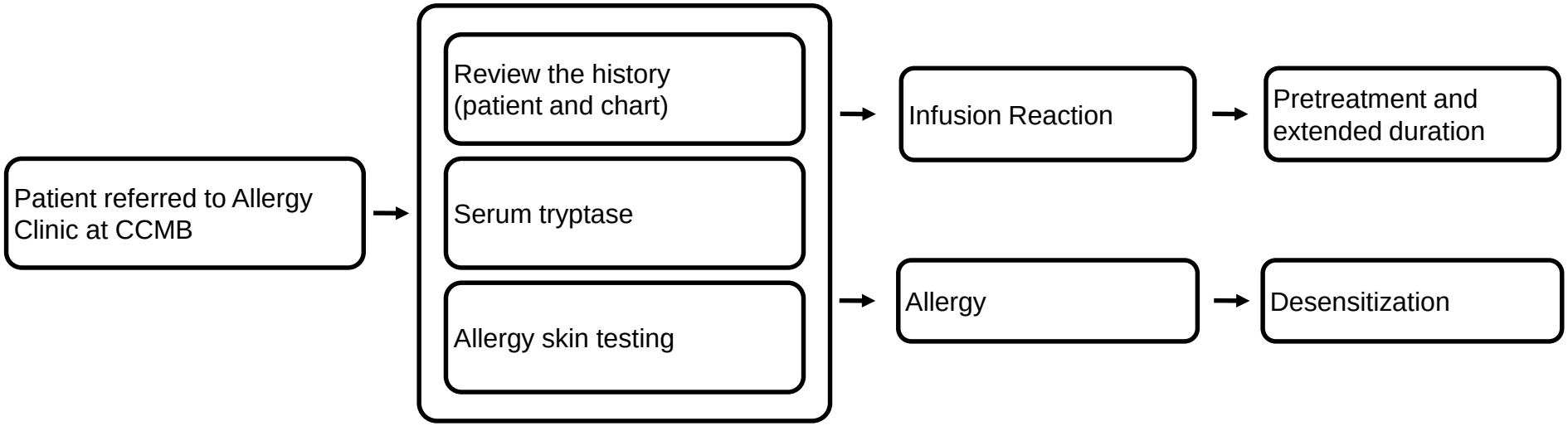
Practically speaking, when seeing an acute reaction occurring…



Anaphylaxis vs. Infusion Reaction

Summary

Once we have the luxury of time…



Carboplatin

- Carboplatin incidence of hypersensitivity reactions increases with the number of doses administered
- 27% incidence in patients who receive 7 cycles or more
- Approximately half of reactions observed are moderate to severe
- **Very important**: platinum ***sensitive*** ovarian cancer patients are at risk as they have already received prior exposure to carboplatin
- Referral to allergy for recommendations if patient experiences moderate to severe (i.e. desensitization)

Oxaliplatin

- Hypersensitivity reactions occurs within minutes to hours from start of infusion
- Mostly after 6th dose administered
- Cutaneous symptoms occur in 45%, respiratory in 42% and cardiovascular/anaphylaxis rarely
- Increase infusion time from 2 to 4 hours
- Pre-medicate with antihistamines. Can also consider aspirin and montelukast
- Grade 3 or 4 reactions: may require desensitization

Etoposide

- Hypersensitivity reactions to etoposide reported in 1 to 3% of patients
- Most reactions occur within 10 minutes from the start of the infusion
- For rechallenge in patients who had mild to moderate hypersensitivity reactions:

i) pre-medicate with antihistamines (i.e. cetirizine 20mg) and steroids (i.e. dexamethasone)

ii) Slow infusion rate: administer over 2 hours

Trastuzumab

- Mostly infusion-related reactions but anaphylaxis can occur (0.25% of patients)
- Usually occurs with first infusion
- Re-challenge should include Histamine-1 (H1) blocker and dexamethasone (i.e. cetirizine 20mg oral and dexamethasone 12mg oral/IV)
- Keep infusion time over 90 minutes on re-challenge

Rituximab

- Hypersensitivity reactions are highest on first infusion
- Onset is usually within 30 minutes to 2 hours from first infusion
- When re—challenging start at a reduced rate and gradually increase. For example, if infusion-reaction occurred at rate of 50 mg/hour, you would want to start at 25 mg/hour and gradually increase every 30 minutes
- Ensure pre-medications are optimized

Cetuximab

- 90% of severe infusion reactions occur on first infusion
- Severe infusion reactions: rapid onset of airway obstruction, hypotension, myocardial infarction and/or cardiac arrest.
- Fatal anaphylactic reactions may occur despite the use of prophylactic reactions
- Grade 1-2 infusion reactions: increase infusion time on subsequent doses
- Grade 3-4 infusion reactions: discontinue

Avelumab

- Majority of infusion-related reactions are low grade
- Most reactions occur during drug administration or shortly after infusion is complete
- Majority occurring at initial infusion
- Rarely observed after the first 4 infusions of avelumab
- Re—challenge: increase infusion duration from 60 minutes to 120 minutes

Pembrolizumab

- Grade 1 or 2 infusion-related reactions: pre-medicate with acetaminophen and antihistamine (i.e. acetaminophen 650mg orally and cetirizine 20mg orally) prior to each infusion
- Consider increasing infusion time (i.e. from 30 minutes to 60 minutes)

Nivolumab

- Grade 1 or 2 infusion-related reactions: pre-medicate with acetaminophen and antihistamine (i.e. acetaminophen 650mg orally and cetirizine 20mg orally) prior to each infusion
- Increase duration of nivolumab infusion from 30 minutes to 60 minutes
- Grade 3 or 4: allergy consultation

Sacituzumab govitecan

- Hypersensitivity reactions within 24 hours of dose occurred in 37% of patients.
- Grade 3 or 4 occurred in 2%. Incidence of hypersensitivity reactions leading to permanent discontinuation is low (0.3%).
- If patient experiences infusion-related reactions, then do not shorten the infusion time (i.e. keep at 3 hours) and ensure optimization of pre-medications

Docetaxel

- Infusion-related reactions usually occur on the first or second infusion
- Usually occurs early in the infusion (within first 10 minutes)
- For grade 1 to 2 reactions: re-challenge with docetaxel at a slower rate and add other pre-medications (i.e. cetirizine 20mg).
- It is important that patient take dexamethasone twice daily the day before and in the morning of docetaxel treatment

Paclitaxel

- Infusion-related reactions usually occur on the first or second infusion
- Usually occurs early in the infusion (within first 10 minutes)
- For grade 1 to 2 reactions: re-challenge with paclitaxel at a slower rate
- Instead of dexamethasone IV for 1 dose prior to paclitaxel, consider dexamethasone orally evening prior and morning of paclitaxel infusion

Take Home Messages

- Epinephrine is an important drug for anaphylaxis
- Allergy clinic is established at CCMB and is here to help with hypersensitivity reactions (all routes of administration)
- In some instances, desensitization protocols are required to help patient receive full doses of their chemotherapy
- Contact us: we are happy to help!

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- Each drug monograph