Anaphylaxis

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Definition of 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.
A serious allergic reaction that is rapid in onset and might cause death	An acute, potentially fatal, multi-organ system, allergic reaction.				

Fatal anaphylaxis

Prevalence of 0.69 people per million

Medication-induced (M/C, 58.8%), followed by “unspecified” (19.3%), venom (15.2%), and food (6.2%).

Outpatient setting M/C food-induced anaphylaxis/ Inpatient setting M/C drug-induced anaphylaxis

Median time from clinical manifestation to death

30 to 35 min for food, 10 to 15 min for insect venom, and 5 min for IV medications

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Anaphylaxis Epidemiology

Epidemiologic and clinical features of anaphylaxis in Korea

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Background: Little is known about the characteristics of anaphylaxis in Korea or even in Asia.

Objective: To evaluate the incidence of anaphylaxis and the clinical features of patients with anaphylaxis in a Korean tertiary care hospital.

Methods: We performed a retrospective review from January 1, 2000, through July 31, 2006, of 138 patients with anaphylaxis, including inpatients, outpatients, and emergency department visitors, in the Seoul National University Hospital.

Results: Among 978,146 patients, 138 (0.014%) had anaphylaxis. Two cardiopulmonary resuscitations were performed and 1 death occurred. The total mortality rate of anaphylactic patients was 0.0001%. The causes of anaphylaxes were drug (35.3%), food (21.3%), food-dependent exercise-induced (13.2%), idiopathic (13.2%), insect stings (11.8%), exercise induced (2.9%), blood products (1.5%), and latex (0.7%). Radiocontrast media and buckwheat were the leading causes of drug and food anaphylaxis, respectively. The organs most frequently involved in the anaphylaxis were cutaneous (95.7%), cardiovascular (76.8%), and respiratory (74.6%). The most common manifestations were dyspnea (71.3%), urticaria (81.9%), and angioedema (69.4%). Three of 138 patients (2.2%) had biphasic reactions.

Conclusions: The incidence, mortality rate, and clinical features of Korean patients with anaphylaxis were similar to rates for patients from other countries, despite some differences in causative agents.

Ann Allergy Asthma Immunol. 2008;100:31–36.

Table 2. Causes of Anaphylaxis

Cause	No. (%) of patients (N = 138)
Drugs	48 (34.8)
Radiocontrast media	20 (14.5)
Low osmolar radiocontrast media for computed tomography	18 (13.0)
Fluorescein	1 (0.7)
Gadolinium	1 (0.7)
Nonsteroidal anti-inflammatory drugs	11 (8.0)
Antibiotics	8 (5.8)
Cephalosporin	4 (2.9)
Penicillin and derivatives	3 (2.2)
Fluoroquinolone	1 (0.7)
Other	9 (6.5)
Foods	29 (21.0)
Wheat flour	6 (4.3)
Buckwheat	4 (2.9)
Seafood	4 (2.9)
Other	15 (10.9)
Idiopathic	18 (13.0)
Food-dependent exercise-induced anaphylaxis	18 (13.0)
Wheat flour	14 (10.1)
Apple	1 (0.7)
Shrimp	1 (0.7)
Unidentified	2 (1.4)
Insect stings	16 (11.6)
Bee	13 (9.4)
Ant	1 (0.7)
Mosquito	1 (0.7)
Unidentified	1 (0.7)
Exercise-induced anaphylaxis	4 (2.9)
Transfusion-related anaphylaxis	4 (2.9)
Platelet concentrates	4 (2.9)
Latex anaphylaxis	1 (0.7)

Anaphylaxis Epidemiology

Anaphylaxis; 10 Years' Experience at a University Hospital in Suwon

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Background: Anaphylaxis is a systemic hypersensitivity reaction consisting of various etiologies and clinical features. In Korea, reports regarding anaphylaxis are very few. **Objective:** To evaluate the general characteristics and clinical features of anaphylaxis, especially with regard to the severity of it. **Method:** A retrospective study was conducted in inpatients, outpatients and patients encountered at the emergency department at the Ajou University Hospital during 1997～2008. The medical records of a total of 158 patients who met diagnostic criteria for anaphylaxis were reviewed. **Result:** Drugs (51.2%) was the most common cause of anaphylaxis followed by insect stings (25.3%), foods (10.8%) and exercise (6.3%) in our hospital. The common manifestations were dyspnea (70.3%), urticaria (57.6%), dizziness (48.1%) and hypotension (46.2%). There were 65 patients (41.1%) with moderate anaphylaxis and 93 patients (58.9%) with severe anaphylaxis. The patients with older age or underlying cardiovascular disease had more severe anaphylaxis ($P<0.05$, respectively). Although there were no significant correlation between the severity and etiology of anaphylaxis, some drugs such as antibiotics, NSAIDs, and radiocontrast media tended to develop severe anaphylaxis. **Conclusion:** We confirmed that drugs, insect stings, foods, and exercise are the major causes of anaphylaxis. In addition, the patients with older age or a cardiovascular disease had a tendency to develop severe anaphylaxis. **(Korean J Asthma Allergy Clin Immunol 2008;28:298-304)**

Key words: Anaphylaxis, Clinical feature, Severity of anaphylaxis

Table 2. Cause of anaphylaxis

Cause	No. (%) of patients (n=158)
Drug	81 (51.2)
NSAIDs	27 (17.1)
Antibiotics	20 (12.7)
Antibiotics+NSAIDs	10 (6.3)
Radio-contrast media	10 (6.3)
Anesthetics	3 (1.9)
Others	14 (8.9)
Insect stings	40 (25.3)
Bee	30 (19.0)
Ant	7 (4.4)
Unidentified	3 (1.9)
Food	17 (10.8)
Seafood	5 (3.2)
Wheat	3 (1.9)
Buckwheat	3 (1.9)
Others	6 (3.8)
Exercise-induced	10 (6.3)
Food-dependent exercise-induced	5 (3.2)
Idipathic	5 (3.2)

NSAIDs = nonsteroidal anti-inflammatory drugs.

Anaphylaxis Epidemiology

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AAIR
Allergy, Asthma & Immunology Research

Predictors of the Severity and Serious Outcomes of Anaphylaxis in Korean Adults: A Multicenter Retrospective Case Study

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Purpose: Differences in definitions of the condition, relevant triggers, and the geographical locations of study centers, cause estimates of the prevalence of anaphylaxis to vary. Recent epidemiological data indicate that the incidence of anaphylaxis is rising. **Methods:** To investigate the causes and clinical features of anaphylaxis in Korean adults, factors associated with the severity of the condition, and serious outcomes, a retrospective medical record review was performed on adult patients diagnosed with anaphylaxis between 2007 and 2011 in 15 University Hospitals of South Korea. **Results:** A total of 1,806 cases (52% male, age 16-86 years) were reported. Cutaneous symptoms (84.0%), combined with respiratory (53.9%) and/or cardiovascular (55.4%) symptoms, were the most frequent presentations. Using a recognized grading system, 1,776 cases could be classified as either mild, 340; moderate, 690; or severe, 746. Although eliciting factors varied significantly by age, gender, and regional and seasonal factors, drugs (46.5%; including nonsteroidal anti-inflammatory drugs, antibiotics, and radiocontrast media) were the most common cause of anaphylaxis, followed by foods (24.2%), insect stings (16.4%), exercise (5.9%), and unknown etiology (7.0%). All of age, multi-organ involvement, a history of allergic disease, and drug-induced anaphylaxis, were significant predictors of serious outcomes requiring hospital admission or prolongation of hospital stay. Epinephrine auto-injectors were prescribed for 7.4% of reported cases. **Conclusions:** The principal causes of anaphylaxis in Korean adults were drugs, food, and insect stings. Drug-associated anaphylaxis, a history of allergic disease, multi-organ involvement, and older age, were identified as predictors of serious outcomes.

Key Words: Anaphylaxis; adult; epidemiology; multicenter study; severity; serious outcomes

Table 3. Grading of severity according to the cause of anaphylaxis

	Total n=1,776	Mild n=340	Moderate n=690	Severe n=746
Drugs & RCM	827 (46.6%)	99 (29.1%)	334 (48.4%)	394 (52.8%)
NSAIDs	236 (13.3%)	32 (9.4%)	126 (18.3%)	78 (10.5%)
Antibiotics	186 (10.5%)	20 (5.9%)	77 (11.2%)	89 (12.0%)
RCM	214 (12.0%)	27 (7.9%)	58 (8.4%)	129 (17.3%)
Insect stings	291 (16.4%)	121 (35.6%)	90 (13.0%)	80 (10.7%)
Food	430 (24.2%)	72 (21.2%)	176 (25.5%)	182 (24.4%)
Seafood	145 (8.2%)	28 (8.2%)	61 (8.9%)	56 (7.5%)
Wheat	147 (8.3%)	16 (4.7%)	60 (8.7%)	71 (9.5%)
Nuts	29 (1.6%)	3 (0.9%)	12 (1.7%)	14 (1.9%)
Meats	56 (3.2%)	7 (2.1%)	24 (3.5%)	25 (3.4%)
Vegetable	58 (3.3%)	13 (3.8%)	21 (3.0%)	24 (3.2%)
Exercise with/ without food	104 (5.9%)	8 (2.4%)	46 (6.7%)	50 (6.7%)
FDEIA	73 (4.1%)	6 (1.8%)	35 (5.1%)	32 (4.3%)
Exercise	31 (1.7%)	2 (0.6%)	11 (1.6%)	18 (2.4%)
Unknown	124 (7.0%)	40 (11.7%)	44 (6.4%)	40 (5.3%)

RCM, radiocontrast media; NSAID, nonsteroidal anti-inflammatory drug; FDEIA, food-dependent exercise-induced anaphylaxis.

Patterns of Anaphylaxis

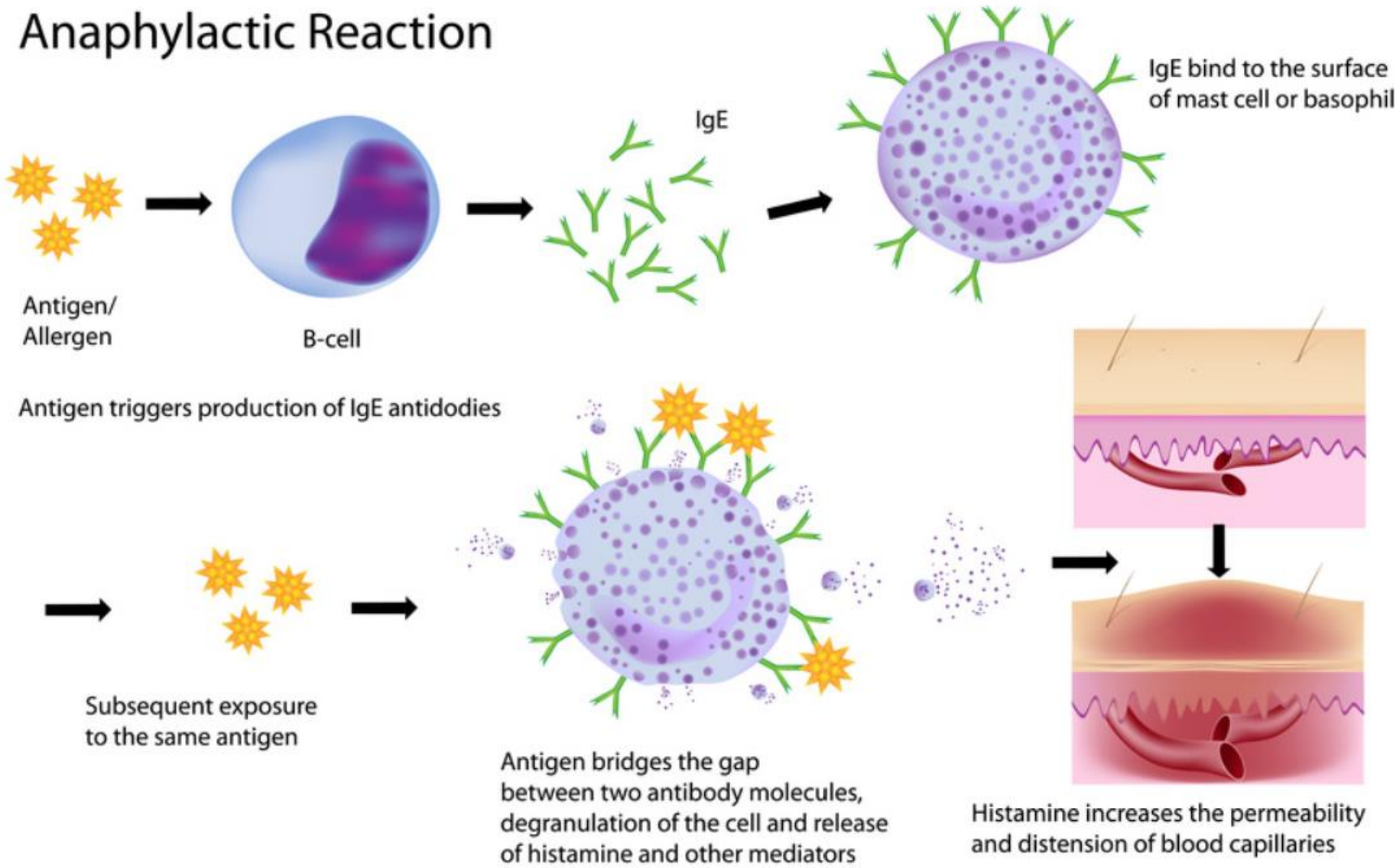
Uniphasic - 70 ~ 90% of anaphylaxis cases, peak 30 to 60 min

resolves over the next hour with no recurrence

Biphasic – recurrence of symptoms hours after resolution of the initial event (Not re-exposure trigger)

Protracted – persistent anaphylaxis, rare reaction lasting for days or even week.

Mechanism of Anaphylaxis



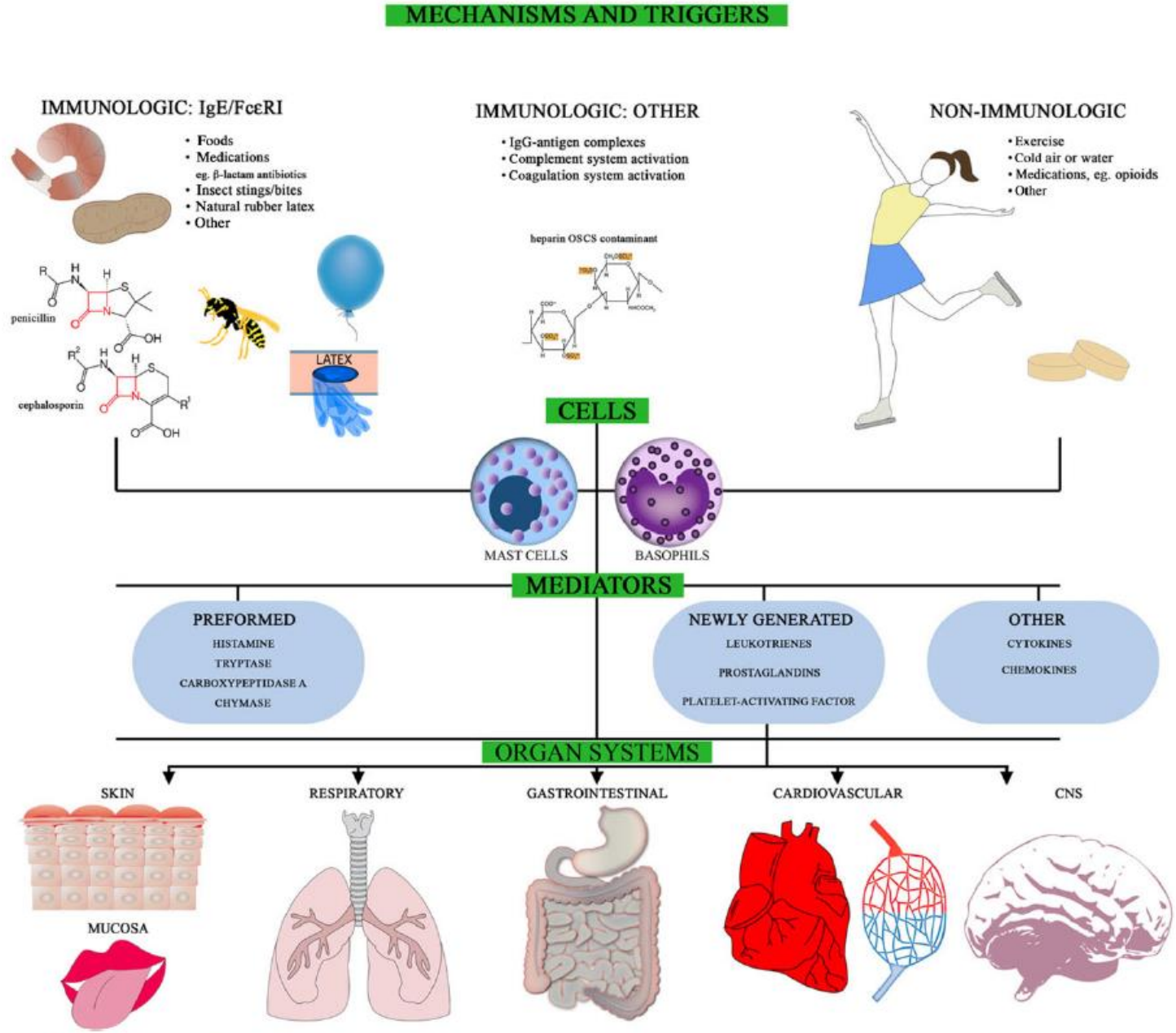
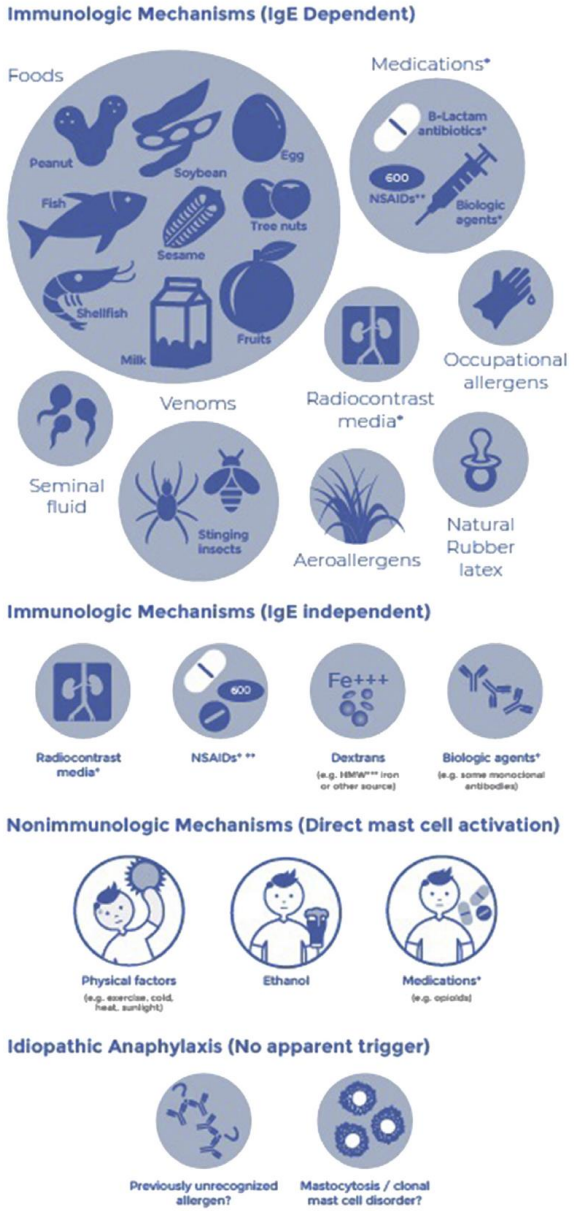


Fig. 3. Pathogenesis of anaphylaxis: mechanisms and triggers, cells, mediators, and organ systems affected.[16] CNS, central nervous system; Ig, immunoglobulin.

Acute Medicine & Surgery 2017; 4: 235–245

Mechanism	Examples	Comments
Immunologic-IgE	Food allergens[a]	8 common food allergens listed below
(Secondary MCD)	Airborne allergens	Animal dander, aerosolized foods, pollen
	Latex	Gloves, catheters, masks, medication vials
	Hymenoptera venom	Honey bee, wasp, yellow jacket, hornet, IFA
	Medication allergy	Antibiotics, biologicals,[b] vaccines, NSAIDs[b]
	Alpha-gal	Mammalian meat (beef, pork, venison, lamb)
	FDEIA	Exercise + food (wheat, nuts, legumes, etc)
	Hormones	Progesterone or estrogens (catamenial)
	Seminal fluid	Postcoital anaphylaxis
	Radiocontrast media[b]	IgE-mediated reactions have been reported
Immunologic-non-IgE	Immune aggregates	Includes immune complexes/complement
	IVIG	From IgG or IgE anti-IgA antibodies
	Aspirin and NSAIDs[b]	Leukotriene-driven and other mechanisms
	Dialysis membranes	
	Radiocontrast media[b]	Complement activation, kinin generation
	Dextrans/HMW iron	
	Biologics[b]	Cytokine inhibitors, omalizumab, etc
	Heparin	Generation of kinins by contaminated
		Chinese heparin
Nonimmunologic		
Direct effects	Opiates, physical	Cold, heat, exercise, sunlight
Primary MCD[c]	MMAS and systemic	Genetic defects affect proliferation or activation of mast cells
MCAS[c]		Can be associated with germline replications of TPSAB1 gene encoding α-tryptase[36]
Idiopathic		Increased mast cell sensitivity/degranulation
		T helper cell 2-cytokine polarization
		Unrecognized allergens
Masqueraders	Munchausen stridor	
	Undifferentiated somatoform anaphylaxis	
	Vocal cord dysfunction	



Acute Medicine & Surgery 2017; 4: 235–245

Clinical feature

Organ system	Presentation	Sequelae
Skin/mucosa	Urticarial eruption	Hypovolemia
(80%-90%)	Angioedema	
	Oropharyngeal	Airway obstruction
	Laryngeal	Stridor
		Airway obstruction
	Intestinal	Abdominal pain
	Flushing	Hypotension
	Pruritus (palms/soles/oral/genitalia)	
Bronchopulmonary	Laryngeal edema	Hoarseness/stridor
(60%-70%)		Dysphonia
	Wheeze/cough	Respiratory failure
		Hypoxemia/cyanosis
	Rhinitis	Nasal obstruction
Cardiac	Vasodilation/reduced SVR	Hypotension/shock
(40%-50%)	Myocardial vasoconstriction	Reduced CO
	Myocardial depression	Myocardial ischemia
		Arrhythmia
		Cardiac arrest
Gastrointestinal	Nausea, vomiting	Dehydration
(40%-50%)	Diarrhea	Hypovolemia
	Intestinal edema	Abdominal pain
Neurological	Dizziness	Syncope
(<15%)	Confusion	Seizures
	Headache	
	Feeling of impending doom	
	Tunnel vision	
Genitourinary	Uterine cramps (♀)	Pain
	Uterine bleeding (♀)	
	Scrotal edema (♂)	Pain
Miscellaneous	Urinary/fecal incontinence	

Prevalence of symptom cluster is showed as percentages (%). CO = cardiac output; SVR = systemic vascular resistance.

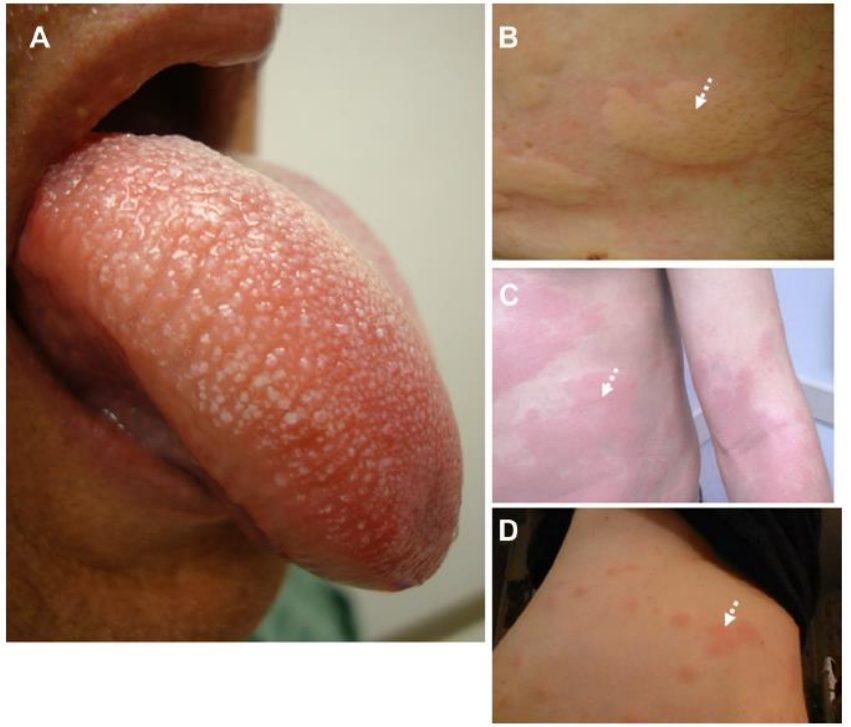


Figure 2 – *Clinical manifestations of anaphylaxis. A, Angioedema of the tongue and oropharynx. B, Discrete urticarial lesions in a patient with acute allergic reaction. C, Coalescent urticaria and diffuse erythema in a patient with a severe systemic allergic reaction. D, Delayed urticarial reactions in response to beef ingestion in an entomologist who had sustained multiple occupation-related tick bites months earlier. White dotted arrows indicate clinical findings.*

CHEST 2018; 153(2):528-543

Diagnosis of Anaphylaxis

Practice paper

World Allergy Organization anaphylaxis guidelines: Summary

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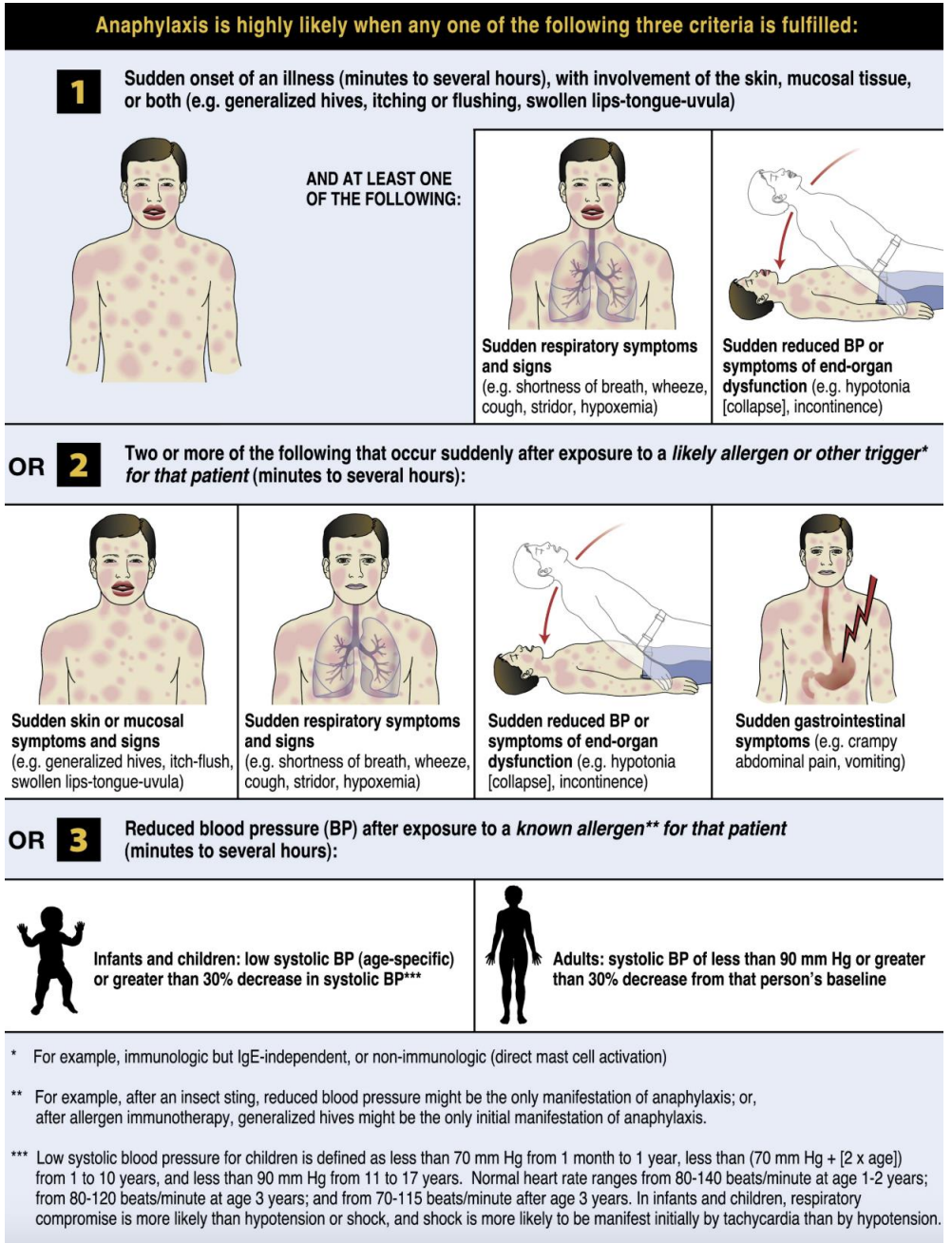
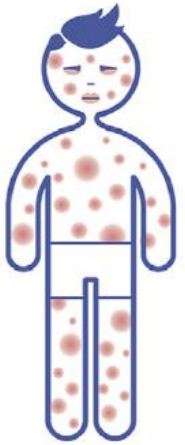


Diagnosis of Anaphylaxis

World Allergy Organization Anaphylaxis Guidance 2020

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. Airway/Breathing: Respiratory compromise.
(e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

B. Circulation: Reduced BP or associated symptoms of end-organ dysfunction.
(e.g. hypotonia [collapse], syncope, incontinence)

C. Other: Severe gastrointestinal symptoms.
(e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens)

2 Acute onset of **hypotension*** or **bronchospasm** or **laryngeal involvement†** after exposure to a known or highly probable allergen for that patient (minutes to several hours), **even in the absence of typical skin involvement.**

Infants and children: low systolic BP (age-specific) or greater then 30% decrease in systolic BP*

Adults: systolic BP of less than 90 mm Hg or greater than 30% drecrease from that person's baseline

or

Bronchospasm

Laryngeal involvement

Differential diagnosis

Common diagnostic dilemmas	Flush syndromes
Acute asthma[a]	Peri-menopause
Syncope (faint)	Carcinoid syndrome
Anxiety/panic attack	Autonomic epilepsy
Acute generalized urticaria[a]	Medullary carcinoma of the thyroid
Aspiration of a foreign body	**Nonorganic Disease**
Cardiovascular (myocardial infarction,[a] pulmonary embolus)	Vocal cord dysfunction
Neurologic events (seizure, cerebrovascular event)	Hyperventilation
Postprandial syndromes	Psychosomatic episode
Scombroidosis[b]	**Shock**
Pollen-food allergy syndrome[c]	Hypovolemic
Monosodium glutamate	Cardiogenic
Sulfites	Distributive[d]
Food poisoning	Septic
Excess endogenous histamine	**Other**
Mastocytosis/clonal mast cell disorders[e]	Nonallergic angioedema
Basophilic leukemia	Hereditary angioedema types I, II, & III
	ACE inhibitor-associated angioedema
	Systemic capillary leak syndrome
	Red man syndrome (vancomycin)
	Pheochromocytoma (paradoxical response)

Diagnosis testing

Tryptase - m/c use

- within 1hour TO 24hour

Histamine (Serum) – 5 to 10 min elevation, but trasient

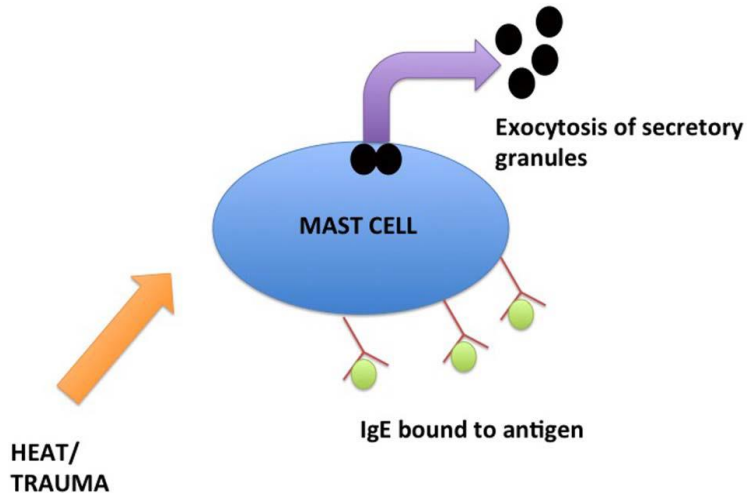
returning to normal within 60 min

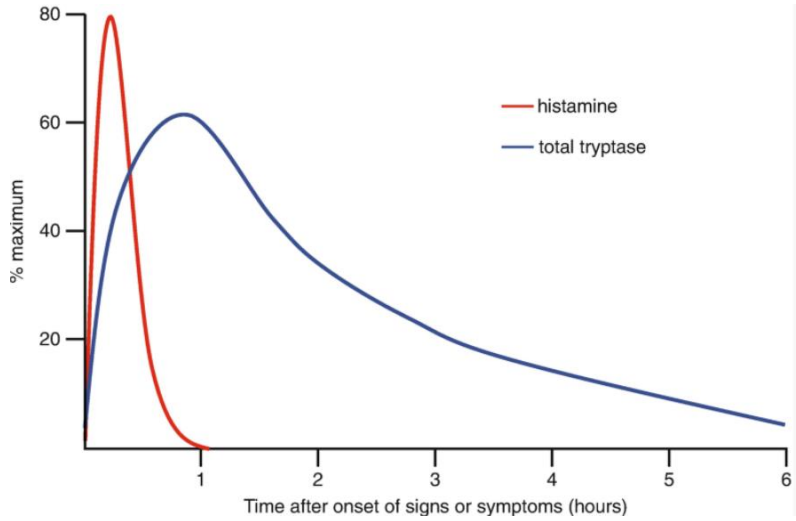
Ig E - levels of different IgE antibodies.

Antibodies are made by the immune system

to protect the body from bacteria, viruses, and allergens.

But this biomarker was not always elevation





Arch Dis Child Educ Pract Ed. 2016;101(5):246-251.

Treatment of anaphylaxis

Epinephrine

1. 1st line drug for anaphylaxis
2. Delaying administration of EN

   → (1) increased reaction severity

   (2) increased morbidity

   (3) greater likelihood of biphasic reactions

   (4) increased risk of fatality
3. But, only 13% received EN (nation-wide data)
4. Serious adverse effects: Ventricular arrhythmias, hypertensive crisis, Pul. Edema
5. Very safe : IM injection

0.01 mg/kg of body weight, to a maximum total dose of 0.5 mg - This is equivalent to 0.5 mL of 1 mg/mL (1:1000)[5] epinephrine (adrenaline)	
Infants under 10 kg	0.01 mg/kg = 0.01 mL/kg of 1 mg/mL (1:1000)
Children aged 1-5 years	0.15 mg = 0.15 mL of 1 mg/mL (1:1000)
Children aged 6-12 years	0.3 mg = 1 mg/mL (1:1000)
Teenagers and adults	0.5 mg = 1 mg/mL (1:1000)

Treatment of anaphylaxis

1. Epinephrine IM (Level of Evidence B) : sole 1st line medication

2. H1-antihistamines (Level of Evidence B)
   (1) relieve itching, flushing, urticarial, angioedema, and nasal and eye symptoms
   (2) cannot inhibit the release of mediators from mast cells and basophils
   (3) Do not prevent or relieve upper airway obstruction, hypotension, or shock

3. H2-antihistamines (Level of Evidence B)
   (1) administered with an H1-antihistamines → decrease in flushing, headache, and other sx.
   (2) recommended in only a few anaphylaxis guidelines
   (3) rapid IV administration of cimetidine has been reported to increase hypotension
   (4) anaphylaxis to ranitidine has been reported

Treatment of anaphylaxis

4. Glucocorticoids (Level of Evidence B)

(1) Switch off transcription of a multitude of activated genes that encode pro-inflammatory proteins

→ potentially relieve protracted anaphylaxis symptoms and prevent biphasic anaphylaxis

(2) These effects have never been proven

(3) Are not lifesaving in initial hours of an anaphylactic episodes

(4) can be considered as second-line medications

Treatment of anaphylaxis

5. Bronchodilators (selective beta-2 adrenergic agonists) (Level of Evidence B)
   (1) Sometimes given as additional Tx. (wheezing, coughing, and shortness of breath)
   (2) Should not be substituted for EN
      a) minimal alpha-1 adrenergic agonist vasoconstrictor effects
      b) do not prevent or relieve laryngeal edema and upper airway obstruction, hypotension, or shock.

Common misconceptions in anaphylaxis

Common 'myths'	What evidence tells us
Myth 1: Anaphylaxis often results in death	Anaphylaxis can be life-threatening, but the majority of reactions do not result in severe outcomes
Myth 2: There are no hives so it can't be anaphylaxis	Cutaneous symptoms (most commonly urticaria or 'hives') are absent in around 10% of anaphylaxis reactions
Myth 3: No trigger for the reaction is identified, therefore it is not anaphylaxis	In around 20% of cases, no trigger is identified; this is known as idiopathic anaphylaxis
Myth 4: Epinephrine is dangerous	Epinephrine given by intramuscular injection into the outer mid-thigh is very safe
Myth 5: Antihistamines can be used to treat anaphylaxis initially; epinephrine is only needed if symptoms worsen	Epinephrine, not antihistamines, is the first-line treatment for anaphylaxis
Myth 6: Corticosteroids prevent delayed or biphasic reactions in anaphylaxis	There is insufficient evidence to support the use of corticosteroids prevent delayed or biphasic reactions in anaphylaxis
Myth 7: Only children who have had anaphylaxis need an epinephrine autoinjector	It is very difficult—if not impossible—to accurately predict who is at risk of severe anaphylaxis
Myth 8: Epinephrine autoinjectors are overprescribed and overused in anaphylaxis	Autoinjectors are underused to treat anaphylaxis in the community
Myth 9: Prescription of an epinephrine autoinjector in isolation is life-saving	Optimal management of food allergic patients and treatment of anaphylaxis has many facets and is not limited to a prescription for an epinephrine autoinjector
Myth 10: MMR and influenza vaccination are contraindicated in patients with previous anaphylaxis to egg	Both vaccines are safe to administer in egg-allergic children, including those with previous anaphylaxis

Arch Dis Child 2019;104:83–90.


B
NDC 49502-500-02
For Allergic Emergencies (Anaphylaxis)
Rx only
EPIPEN 2-PAK®
(epinephrine injection, USP)
Auto-Injectors 0.3 mg
Each carton contains:
Two yellow EpiPen® Auto-Injectors
One grey Trainer
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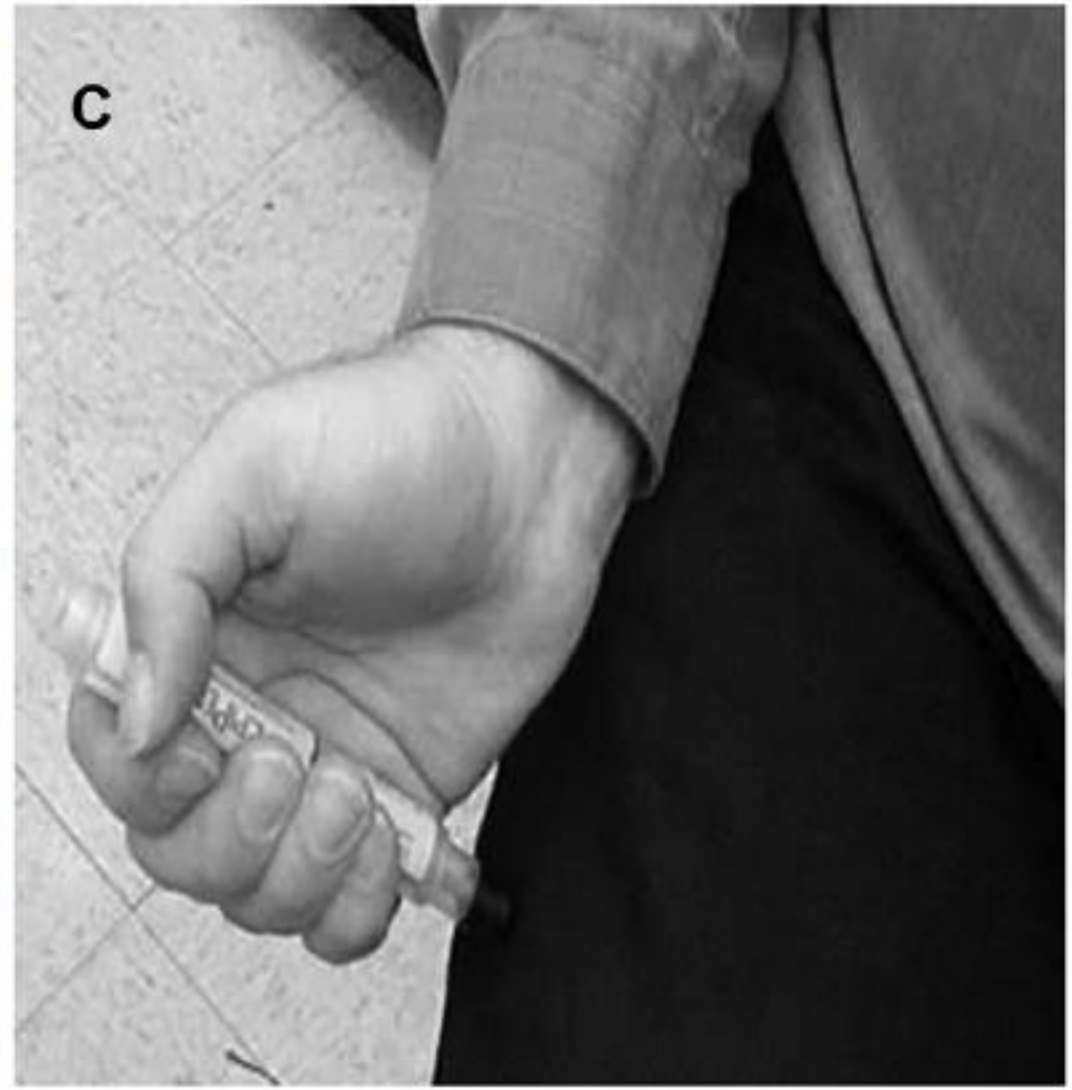
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Thank you