



Urticaria and Angioedema. Hereditary

Angioedema. Food allergy

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SIGNIFICANCE

Quality of life is substantially reduced

Disturbance with sleep, daily activities, social interaction, work productivity, emotional well-being

High socioeconomic impact from the direct (medication and healthcare visits)

Indirect costs (absence from or reduced efficiency while at work)

DEFINITION

Urticaria is a disease characterized by the development of wheals (hives), angioedema, or both.

The skin lesions are:

- pruritic
- erythematous
- typically last less than 24 hours without leaving residual marks

Acute urticaria is defined as outbreaks of urticarial lesions that do not persist beyond 6 weeks.

Chronic urticaria is defined as the recurrence of hives on a near daily basis for more than 6 weeks.

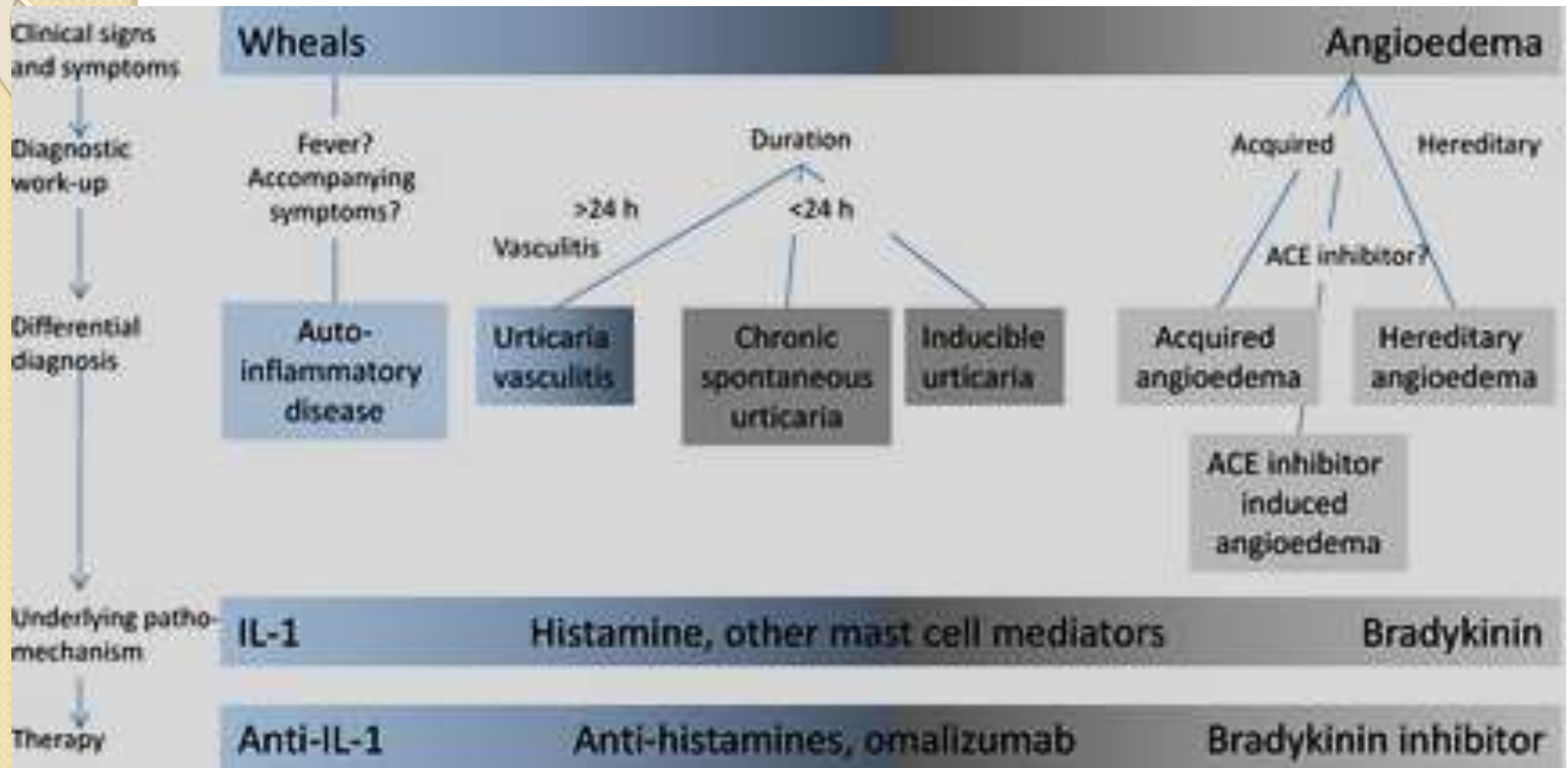
Chronic Spontaneous Urticaria

Spontaneous appearance of itchy wheals, angioedema, or both, for at least 6 weeks

Self limiting disorder persisting for 2–5 years in the majority of cases

20% of patients suffer for more than 5 years

PATHOPHYSIOLOGY



PATHOPHYSIOLOGY

Urticaria is a mast-cell-driven disease

Activation of cutaneous mast cells

Mediators

histamine

cytokines

platelet-activating factor (PAF)

serotonin

proteases

proteoglycans

Result in

sensory nerve activation

vasodilation

plasma extravasation
lesions

cell recruitment to urticarial

PATHOPHYSIOLOGY

Mast cell stimulation leading to acute and chronic urticaria
can be caused by:

IgE-mediated reaction

autoimmunity

direct mast cell activation
metabolism

arachidonic acid

infections

systemic diseases

IgE Mediated

Foods (e.g., peanuts, tree nuts, wheat, soy, milk, egg, shellfish, fish)

Inhalants (e.g., animal dander, pollen)

Insect sting or bite (Hymenoptera venom, fire ants)

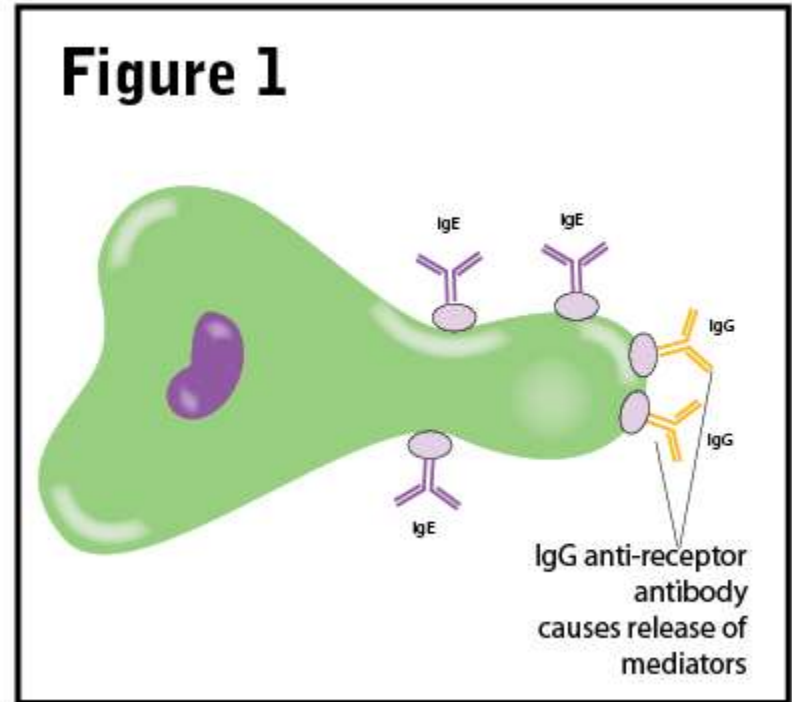
Medications (e.g., beta-lactam antibiotics, sulfa-containing medications)

Contactants (e.g. latex, animal saliva)

Autoimmune Mediated

Anti-FcεRI antibody

Anti-IgE antibody



*Education and research fund
advisor theasthmacenter.org*

Direct Mast Cell Activated

Neuromuscular blocking agents (e.g.,
succinylcholine, pancuronium, atracurium)

Opioid narcotics (e.g., morphine)

Radiocontrast media

Vancomycin

Signs and Symptoms

Urticaria is characterized by the appearance of wheals or hives:

central swelling, pruritus, and evanescent nature

Hives are usually very itchy

Range in size from a few millimeters to the size of a hand

Signs and Symptoms

Wheals usually fade after a few hours, but can be replaced by new ones elsewhere on the body!!!!!!

The skin returns to normal as soon as the wheals fade

Acute Urticaria

The rash appears suddenly and is most severe after 8-12 hours, but usually goes away within 24 hours (although it can occasionally last for 48 hours)

Systemic Diseases

Autoimmune disorders (e.g., systemic lupus erythematosus)

Cryoglobulinemia

Neoplasia



Acute

Less than 6 weeks

Chronic

More than 6 weeks

Recurrent of hives, with or without angioedema, on >3 days/week persisting for ≥ 6 weeks

Chronic Urticaria

- Chronic
 - More than 6 weeks
- Recurrent of hives, with or without angioedema, on > 3 days/week persisting for ≥ 6 weeks*

*Evaluation of a Guidelines-Based Approach to the Treatment of Chronic Spontaneous Urticaria; J Allergy Clin Immunol Pract 2018;6:177-82

- Urticaria : sudden appearance of wheals, angioedema, or both.
- 3 typical features:
 - central swelling of variable size, surrounded by a reflex erythema
 - itching or sometimes burning
 - fleeting nature, usually resolve within 1–24 h.

Classification

- Inducible
 - Symptomatic dermographism
 - Cold urticaria
 - Delayed pressure urticaria
 - Solar urticaria
 - Heat urticaria
 - (Vibratory angioedema)
 - Cholinergic urticaria
 - Contact urticaria
 - Aquagenic urticaria
 - Food/Drug induced : rare
- Spontaneous : idiopathic (CSU or CIU)
 - Autoantibody Associated Urticaria or Chronic autoimmune urticaria(CAU) is the subset of CIU

*The diagnosis and management of acute and chronic urticaria: 2014 update;J Allergy Clin Immunol 2014;133:1270-7.

Approach to Chronic Urticaria

- Consider other disease mimick urticaria
 - Urticarial vasculitis : primary autoimmune
 - Urticarial like dermatoses : pregnancy
 - Autoimmune progesterone induced dermatitis
 - Urticarial pigmentosa
 - Mastocytoma
 - Telangiectasia maculans eruptiva perstans
 - Erythema Multiforme
 - Bullous pemphigoid
 - Polymorphous light eruption

The diagnosis and management of acute and chronic urticaria
: 2014 update; J Allergy Clin Immunol 2014;133:1270-7.

Urticaria Pigmentosa

- Most common skin manifestation of CM
- Differs significantly between children and adults
 - Children : tan to brown papules and less commonly as macules, 1.0 - 2.5 cm
 - Adult : reddish-brown macules and papules, usually < 0.5 cm in diameter



Mastocytoma

- Solitary mastocytomas are tan-brown nodules
- Generally before 6 months of age
- Trauma to mastocytomas has been associated with systemic symptoms such as flushing and hypotension



Erythema Multiforme



- Highly regular, circular, wheal-like erythematous papule or plaque that persists for ≥ 1 week
- usually acral, often mucosal disease (EM major)
- Classic target or iris lesion
- Typical target lesions
 1. Dusky central disk, or blister
 2. More peripherally, infiltrated pale ring
 3. Erythematous halo

Dermatitis Herpetiformis

- Erythematous papule, an urticaria-like plaque, or, most commonly, a vesicle
 - DDX to papular urticaria
- Symmetrically on extensor surfaces
- Localized stinging, burning, or itching
- Granular IgA deposits at dermal papilla



Approach to Chronic Urticaria

- Consideration of various possible cause
 - Inducible? : Physical urticaria
 - Rarely, IgE-mediated reactions from foods, drugs, or other allergens might result in CU
 - Infection : viral infection (HBV, HCV, EBV, and HSV), H.pylori, parasitic infections
 - Mostly unidentified
- Part of other systemic conditions

The diagnosis and management of acute and chronic urticaria
: 2014 update; J Allergy Clin Immunol 2014;133:1270-7.

BOX 38-1 DIFFERENTIAL DIAGNOSIS OF URTICARIA/ANGIOEDEMA

ACUTE (<6 WEEK)

- Drug reaction
 - Immunoglobulin E (IgE) mediated
 - Metabolic—idiosyncratic
 - Cellular immunity
- Food reactions
 - IgE mediated
 - Non-IgE mediated (e.g., scorpion poisoning)
- Intravenous administration
 - Blood products
 - Contrast agents
 - Intravenous γ globulin
- Infection
 - Viral in children
 - Infectious mononucleosis or hepatitis B prodrome
 - ? Bacterial in children

PHYSICAL

- Individual lesions last <2 hours
 - Cold urticaria
 - Cholinergic urticaria
 - Dermatographism
 - Local heat urticaria
 - Aquagenic urticaria
 - Cold-induced cholinergic urticaria
 - Cold-dependent dermatographism
- Lesions last >2 hours
 - Delayed pressure urticaria
 - Vibratory angioedema
 - Familial cold-induced syndromes, usually with fever

CHRONIC (>6 WEEK)

- Autoimmune, often with antithyroid antibodies
- Idiopathic
- Urticarial vasculitis
 - Idiopathic—skin only
 - Associated with other connective tissue disease
- Familial febrile syndromes with urticaria-like rash
- Schnitzler's syndrome

Urticaria Related Systemic Conditions

- **Complement-mediated or immunologic basis**
 - Specific complement component deficiencies
 - Cryoglobulinemia (eg, HCV, CLL)
 - Immune-complex mediated : serum sickness
- **CNTD**, such as SLE, juvenile rheumatoid arthritis, dermatomyositis and polymyositis, Sjogren syndrome, Still disease
- **Thyroid disease** (hypothyroidism, hyperthyroidism)
- **Neoplasms** (particularly lymphoreticular malignancy and lymphoproliferative disorders)

The diagnosis and management of acute and chronic urticaria
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Urticaria Related Systemic Conditions

- **Endocrine disorders** (eg, ovarian tumors)
- **Hormonal therapies** (OCP use)
- **Autoinflammatory disease** : Schnitzler's disease
- **Gleich syndrome**
- **Hypereosinophilic syndrome** : esp. in lymphocytic HES but can occur all subtypes
- **Mast cell activation disorder**
 - **EIA_n, FDEIA_n** : Exercise induced anaphylaxis, food dependent exercise induced anaphylaxis

The diagnosis and management of acute and chronic urticaria
: 2014 update; J Allergy Clin Immunol 2014;133:1270-7.



Inducible Urticaria : Physical Urticaria

Physical Urticaria

- If last < 2 hours → usually physical urticaria
 - The main exception is delayed pressure urticaria, last 12–36 hours and appear 3–6 hours after the initiating stimuli

Dermographism

- Most common form of physical urticaria
- Not associated with atopy
- Delayed dermographism : 3–6 hr after stimulation (with or without immediate reaction)
 - may be associated with delayed pressure urticaria
- Last 24–48 hours
- Cold-dependent dermographism
- ↑Histamine, tryptase, SP, and VIP, but not calcitonin gene-related peptide

Darier sign



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Delayed Pressure Urticaria

- Erythematous, deep, local swellings, often painful
- 3-6 hours after sustained pressure applied
 - Sitting on a hard chair, under shoulder straps and belts, on the feet after running, and on the hands after manual labor
- may be associated with fever, chills, arthralgias, myalgias, ↑ESR and leukocytosis

Vibratory Urticaria

- Typical symptom is hives across the back when toweling off after a shower (in the absence of dermatographism)
- Autosomal dominant
 - Heritable form often is accompanied by facial flushing
- Association with cholinergic urticaria
- After several years of occupational exposure to vibration
- ↑Plasma histamine

Cold Urticaria

- Acquired and inherited forms
 - Familial form is rare
- Attacks occur within minutes after exposures
 - Changes in ambient temperature
 - Direct contact with cold objects
- Hypotension, syncope may occur (by drowning)
- Primary acquired (idiopathic) form may have headache, hypotension, syncope, wheezing, palpitations, N/V, and diarrhea
- Secondary acquired : circulating cryoglobulins, cryofibrinogens, cold agglutinins, and cold hemolysins, esp. in children with infectious mononucleosis

Cold Urticaria

- Passive transfer of cold urticaria by intracutaneous injection of serum or IgE to normal recipient
- Complement has no role in primary acquired cold urticaria
- Cold challenge in secondary acquired form can provoke a cutaneous necrotizing venulitis with complement activation

Ice cube place on volar forearm 5 min → removed (re-warm skin) → erythema and pruritis within 2-4 minutes
→ wheal within 10 minutes indicate a positive test



Delayed Cold Urticaria

- Erythematous, edematous, deep swellings
- 9–18 hours after cold challenge
- Cold immersion does not release histamine,
- Cannot be passively transferred
- Mast cells are not degranulated, neither complement proteins nor Ig are detected

Cholinergic Urticaria

- Distinctive, pruritic, small, 1- to 2-mm wheals that surrounded with large areas of erythema
- ↑Core BT, eg. warm bath, prolonged exercise, or fever
- Aged 23–28 years, ↑prevalence of atopy
- Abnormal pulmonary function during experimental exercise or after the inhalation of acetylcholine (most are asymptomatic)
- Most : Positive autologous sweat skin tests, positive for satellite lesion on methacholine skin test(nonfollicular distribution)
- Negative autologous sweat skin tests, negative for satellite lesion on methacholine skin test (follicular in distribution)



Cholinergic urticaria observed in a patient after 15 minutes of exercise in a warm room

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Cold-induced Cholinergic Urticaria

- Unusual variant
- Typical “cholinergic” appearing lesions occur with exercise, but only if the person is chilled
 - Exercise outside on a winter’s day
- Ice cube test and methacholine skin test are both negative

Local Heat Urticaria

- Develop within minutes after exposure to locally applied heat
- ↑ Incidence of atopy
- Familial delayed form of local heat urticaria (occurred in 1–2 hr after challenge and lasted up to 10 hr)



Solar Urticaria

- Develop within minutes after exposure to sun or artificial light sources
- Headache, syncope, dizziness, wheezing, and nausea are systemic features
- ↑ Incidence of atopy
- Usually idiopathic
- May be associated with SLE, polymorphous light eruption

Solar Urticaria

- Passively transferred with serum, suggesting a role for IgE antibody
- Ag on skin irradiated with the appropriate wave length of light → complement activation and release of C5a



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Adrenergic Urticaria

- Wheals surrounded by a white halo
- Develop during emotional stress
- Elicited by the intracutaneous injection of norepinephrine



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Contact Urticaria


- Direct contact with a variety of substances
- IgE mediated or nonimmunologic
- Proteins from latex : prominent cause of IgE-mediated
 - Cross-reactivity to fruits

Aquagenic Urticaria

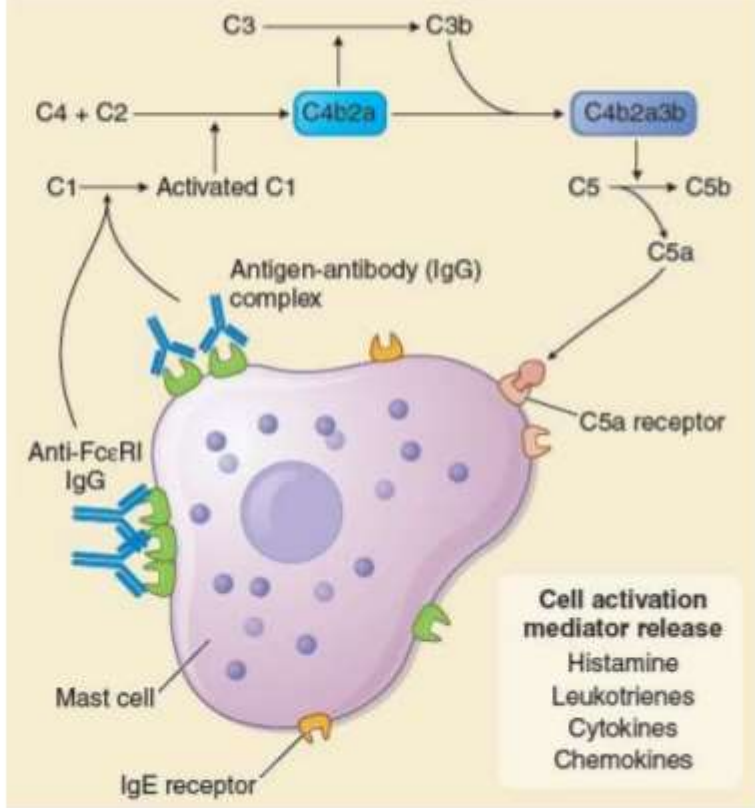
- Pruritus alone or, more rarely, urticaria
- Water of any temperature
- Reminiscent of cholinergic urticaria
- Aquagenic pruritus without urticaria is usually idiopathic
 - also occurs in elderly persons with dry skin
 - in patients with polycythemia vera, Hodgkin's disease, MDS, and HES
- Should evaluate for hematologic disorder

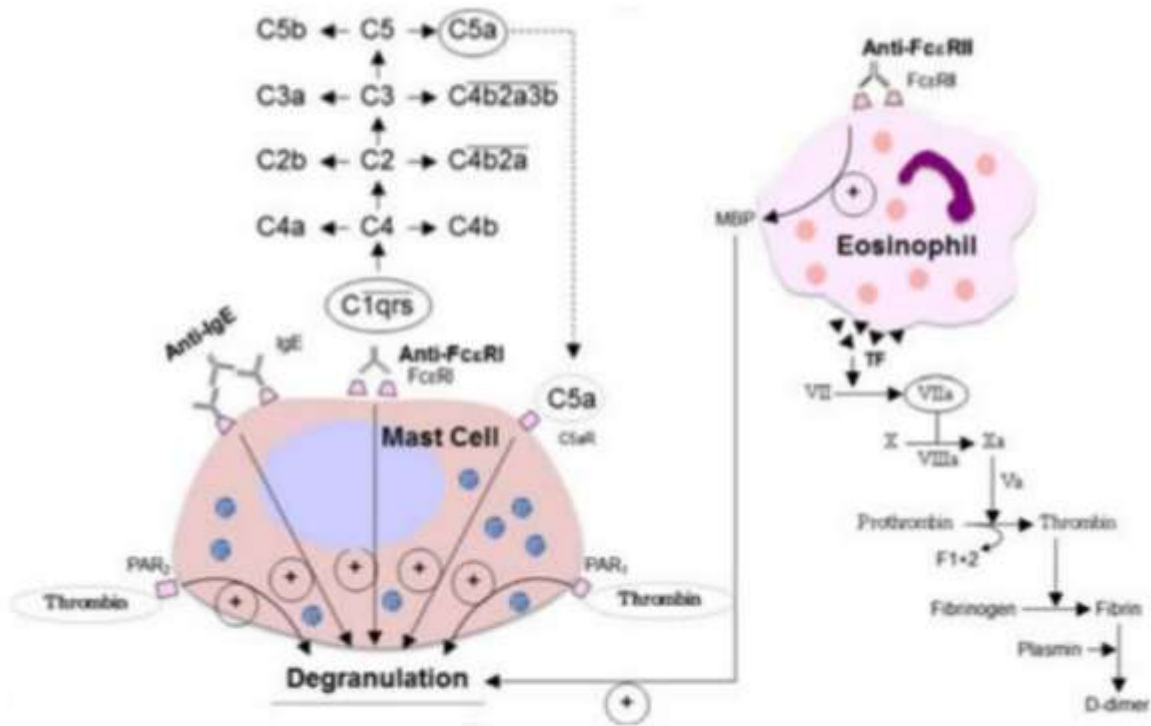


Spontaneous Urticaria

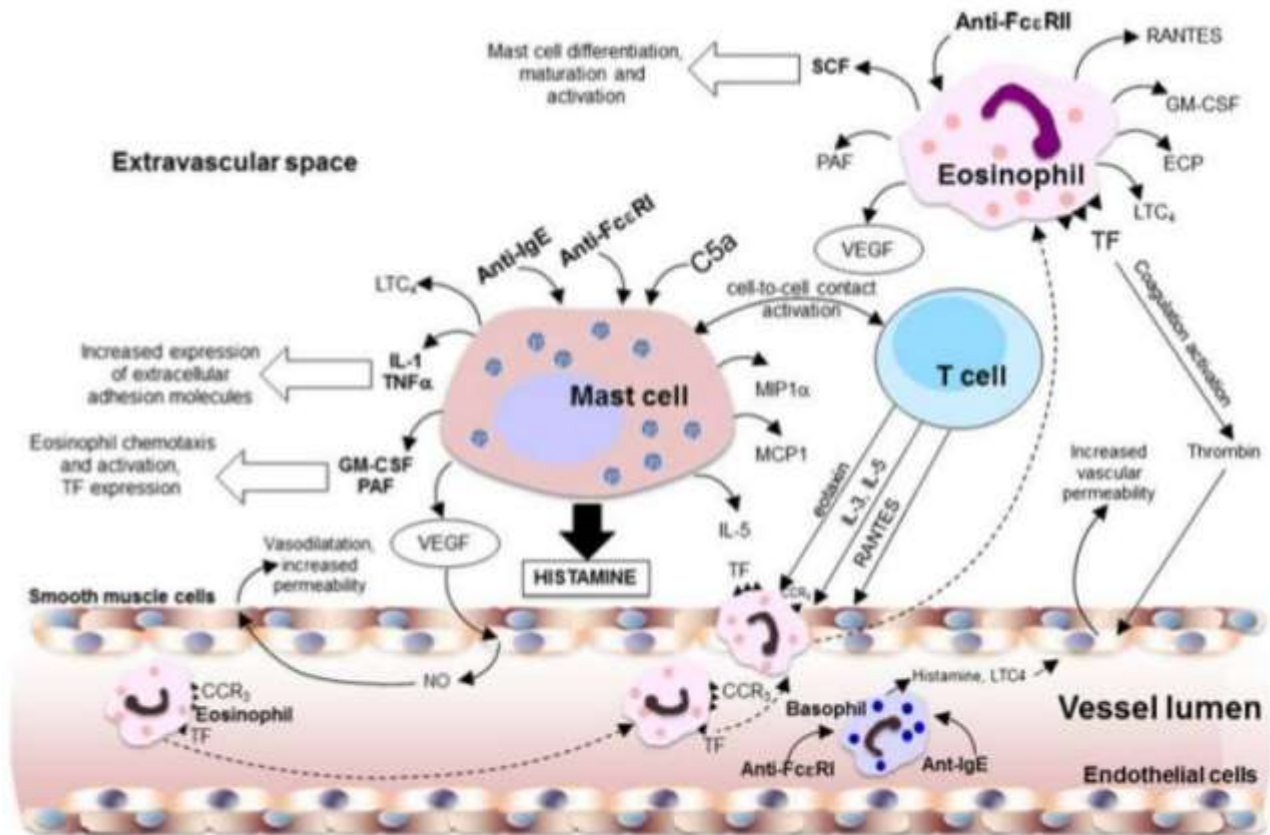
- 
- *H. pylori* infection rate in the population at large is far
 - greater than the incidence of chronic urticaria and in
 - the opinion of this author, the association is spurious

Activation of cutaneous mast cells by IgG antireceptor





Chronic urticaria and coagulation: pathophysiological and clinical aspects; Allergy (2014) 683–691

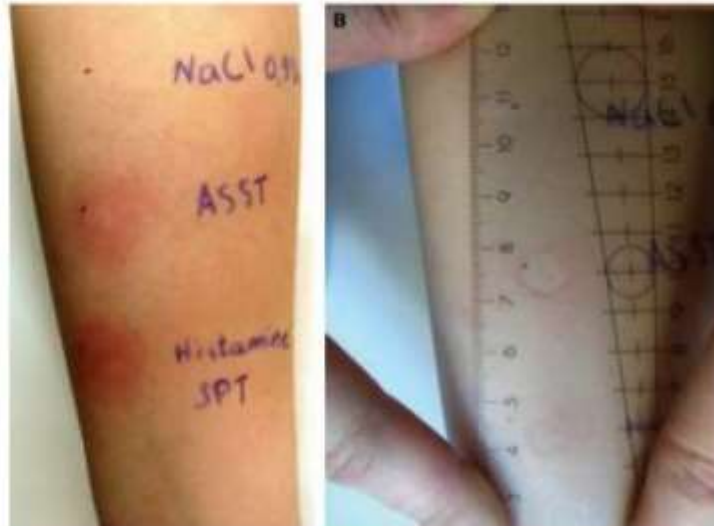
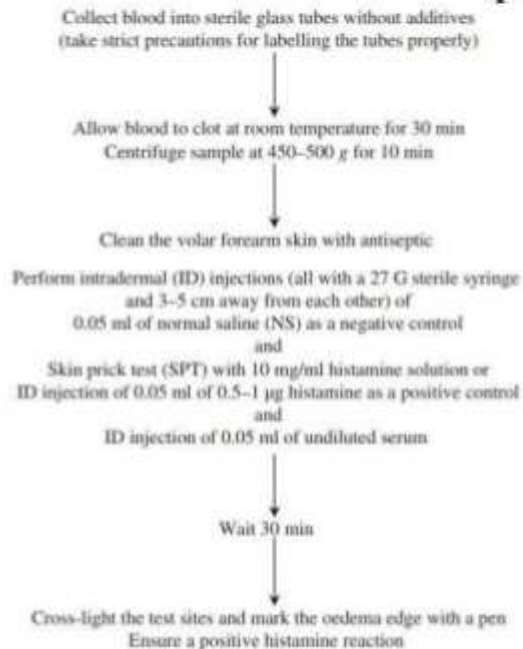


Chronic urticaria and coagulation: pathophysiological and clinical aspects; Allergy (2014) 683–691

Coagulation Cascade

- Presence of D-dimer and prothrombin 1 and 2 fragments (activation of prothrombin to thrombin, digestion of fibrinogen by thrombin)
- Tissue factor rather than factor XII : extrinsic coagulation pathway
 - Eosinophils : prominent source of TF
- Thrombin activation of mast cells
- Propose basophil activation by these eosinophil cationic proteins
 - May have additional mechanism

ASST : Autologous Serum Skin Test



Calculate the mean of the maximum perpendicular diameters
of any red wheal reactions to the ASST and the NS control skin test
ASST is positive if $ASST_{\text{mean wheal}} - NS_{\text{mean wheal}} \geq 1.5 \text{ mm}$

EAACI/GA2 LEN task force consensus report: the autologous serum skin test in urticaria; Allergy 2009

ASST : Autologous Serum Skin Test

- PPV : **55.1%** for a positive BHRA if use criteria ≥ 1.5 mm
- \uparrow NPV : 59% to 100% for different positivity criteria
 - **92.8%** (range 81.4–100%) if use criteria ≥ 1.5 mm
- Negative ASST : surrogate marker of the absence of circulating functional AutoAb

ASST : Autologous Serum Skin Test

- Indication of mast cell activating autoAb in ASST+ CU pa
- “assessing autoreactivity” but not define autoimmune urticaria
- Staubach et al. showed no difference between ASST+ and ASST- CU patients in QoL scores
- If available,
 - Functional autoAb need to be confirmed by the basophil histamine release assay
 - Specificity confirmed by immunoassay (Western blot or ELISA)

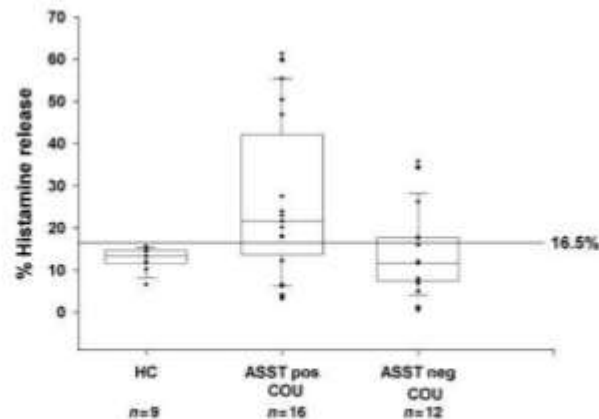
Basophil Histamine Release Assay

- (donor) Basophil incubate with serum for 60 min at 37C with 40 mcL
 - Basophil induced by anti-IgE and sera from urticaria patients
 - Absence and presence of 0.0125 M EDTA (compensate for nonspecific HR)
 - Serum diluted 1 : 4 or 1 : 8 (final concentration)
- Serum and released histamine was removed
- Cells lysis → PIPES were added → centrifuge samples at 2000 g for 10 min → measure histamine content in the filtrate
- %Histamine compared to total histamine content

Validation of basophil histamine release against the autologous serum skin test and outcome of serum-induced basophil histamine release studies in a large population of chronic urticaria patients; Allergy 2005

Basophil Histamine Release Assay

- > 16.5% is a positive test result in both children and adult patients
- Sensitivity and specificity of 75%



Validation of basophil histamine release against the autologous serum skin test and outcome of serum-induced basophil histamine release studies in a large population of chronic urticaria patients; Allergy 2005

Angioedema

Patients with acute or chronic urticaria can also experience angioedema

Angioedema typically affects areas of loose connective tissue, such as the periorbital region, lips, extremities, and genitals (e.g., scrotum)

Occasionally, the tongue and pharynx are involved

Swelling can take up to 72 hours to resolve



Diagnosis

Detailed history and physical examination

Characteristics of the lesions

Immunoglobulin E: cutaneous testing or serum radioallergosorbent testing (RAST)

Diagnosis

Most frequently implicated foods eliciting generalized urticaria in children include milk, soy, wheat, eggs, peanuts, tree nuts, shellfish, and fish

Peanuts, tree nuts, shellfish, and fish are common causes in adults

Occasionally, foods cause hives through a non-IgE-mediated reaction: scombroidosis

Treatment

Antihistamines

Patients should be instructed to take antihistamines on a regular basis, not simply as needed

Corticosteroids

Efficacious for treating urticaria, but use should be limited because of potential side effects

In chronic urticaria, corticosteroids should be used only in highly selective situations, such as during a significant exacerbation of symptoms or in severe cases refractory to other treatments

Epinephrine

Lifesaving for patients who experience laryngeal edema or anaphylaxis

The proper dose for adults is 0.3 mL to 0.5 mL of intramuscular epinephrine in 1 : 1000 concentration

Pediatric dosing is 0.01 mL/kg of intramuscular epinephrine in 1 : 1000 concentration, up to 0.3 mL

The lateral thigh is the preferred injection site

Patients with a history of : laryngeal edema or anaphylaxis, food allergy, stinging insect hypersensitivity, or latex allergy should have self-injectable epinephrine

Other Medications

Antileukotriene drugs

Montelukast (Singulair)

Zafirlukast (Accolate)

Mast cell-stabilizing agents

Oral sympathomimetic agents

Targeted Treatment

Anti-TNF therapies

Anti-CD20 – Rituximab

Anti-IgE therapies

- Omalizumab
- Ligelizumab
- Quilizumab

Summary

Urticaria is a common skin disorder that causes significant morbidity

Most cases of urticaria are self-limited

When there is an identifiable cause such as an immediate hypersensitivity reaction, avoidance is effective in preventing a recurrence

After a thorough evaluation, a significant portion of these patients have no identifiable cause

Hereditary Angioedema

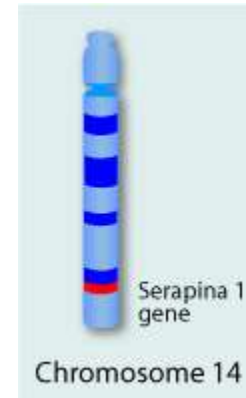
Hereditary angioedema (HAE) is an inherited disease that causes repeated episodes of swelling

C1-inhibitor (C1-INH) deficiency leads to recurrent attacks of mucocutaneous edema and may be inherited or acquired (AAE), which have the same clinical picture characterized by angioedema involving the skin, gastrointestinal tract, and larynx

Types of HAE

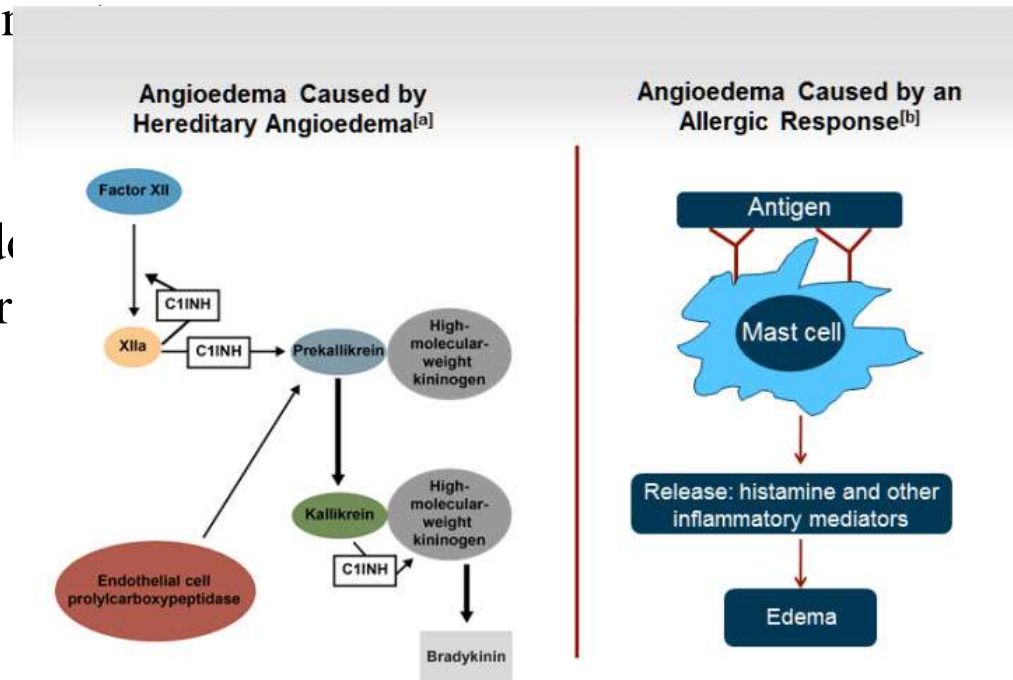
Type I

Mutations in the SERPING1 gene



This gene makes the protein C1 inhibitor-a part of complement system

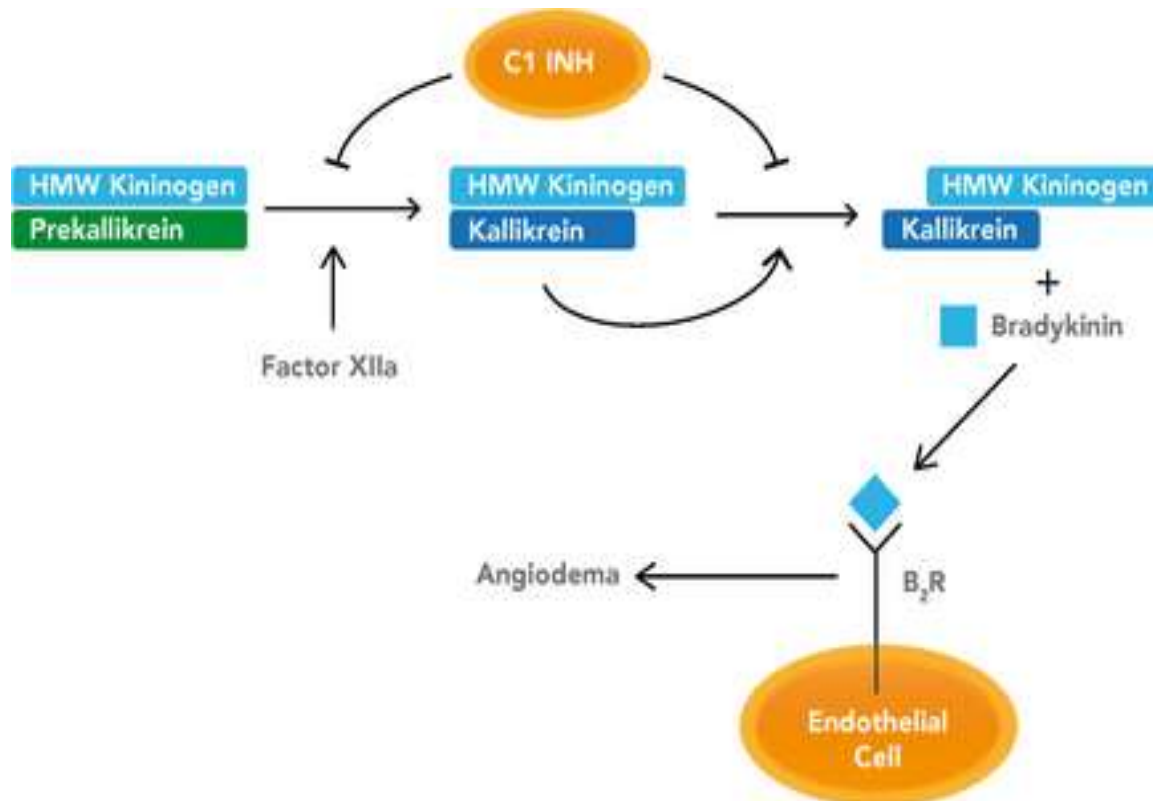
People with type I HAE do not make enough C1 inhibitor



^[a]Bowen T, et al. *Allergy Asthma Clin Immunol.* 2010;6:24.

^[b]Jutel M, et al. *Clin Exp Allergy.* 2009;39:1786-1800.

Pathophysiology





Type II HAE

People with type II HAE also have a mutation in the SERPING1 gene

They make enough C1, but the C1 doesn't work properly
Dysfunction of C1 inhibitor

Type III HAE

There is no abnormality with C1 inhibitor

It is associated with a mutation in the Factor XII gene and too much coagulation factor XII is produced



Triggering Factors

Physical exertion

Mental stress

Mechanical trauma

Pregnancy

Infection

Medical procedures

Weather changes

Fatigue/exhaustion

Menstruation

Dental procedures

Signs and Symptoms

HAE and AAE have the same symptoms of recurrent cutaneous edema attacks affecting the face, extremities, trunk, and genitals

Involvement of the gastrointestinal tract leads to bowel sub-occlusion with severe pain, vomiting, and diarrhea

laryngeal edema can be life-threatening



Signs and Symptoms

Rarely, attacks may involve other sites including the esophagus, brain, kidney, and pancreas

Attacks typically develop and resolve slowly, lasting 2–5 days

Diagnosis

C1-INH level

Type I- low levels of C1-INH protein

Type II - low C1-INH protein function

C4 - low

Treatment

Prevention of attacks- avoid contact sports

Emergency plan- patients need to seek emergency medical care for upper airway attacks

Medication

Plasma-purified C1-INH

Recombinant C1-INH

Food Allergy


An adverse reaction to food mediated by an immunologic mechanism, involving:

specific IgE (IgE-mediated), cell-mediated mechanisms (non-IgE-mediated) or both IgE- and cell-mediated mechanisms (mixed IgE- and non-IgE-mediated)

The prevalence of food allergy is generally higher in children than in adults

Prevalence of primary food allergy appeared is stable over time

Secondary food allergy caused by cross-reactions of food allergens with inhalant allergens is increasing



IgE-mediated food allergies are more common among infants and young children than among adults

Infants and young children are more likely to develop IgE-mediated food allergies than are older children and adults.

Food allergy is an adverse reactions to food in which immunologic mechanisms have been demonstrated

The true prevalence of food allergy is unknown. The frequency of FA is higher among children than among adults

The point prevalence of food challenge-confirmed FA is under 1% in Europe

Food Allergens

Peanuts

Fish shellfish

Tree nuts

Fresh fruits

Vegetables

Milk

Eggs





Pathophysiology

One of the first manifestations of the atopic syndrome and affects young children in the developing gut-associated lymphoid tissue

IgE-mediated and cellular hypersensitivity responses to ingested foods

Recent evidence suggest the presence of localized IgE-mediated responses: duodenal presence of IgE-bearing cells, activated eosinophils, and T cells

Pathophysiology

FA in adulthood seems to be commonly associated with sensitization to other allergens, particularly inhalants

OAS (oral allergic syndrome)

A number of studies have shown that between 50 and 93% of birch pollen-allergic patients have immunological reactivity to plant-derived foods

Signs and Symptoms

An adverse food reaction is any untoward response to the ingestion of a food

Adverse food reactions can be divided into food allergies, which are immunologically mediated, and all other reactions, which are non-immunologic

Besides, adverse reactions to food develop by different gastrointestinal tract pathologies. The algorithm of diagnostics, treatment and prevention of food allergy and food intolerance require different methodical approaches

Intolerance

“Intolerance” is a term loaded with different meanings and interpretations

Intolerance, or hypersensitivity, relates to all reactions to foods

Allergy is an immune mechanism and atopy is the terminology for immunoglobulin E (IgE) mediated reactions

Intolerance is also used when the symptoms are related to carbohydrates, when the sugar is malabsorbed because of a deficiency of one of the disaccharidases (actase, maltase, sucrase)

Gluten intolerance is used as a synonym for celiac disease

Signs and Symptoms

Mild, self-limiting reactions

Severe, life-threatening reactions

The most common food allergy signs and symptoms include:

itching in the mouth hives, itching or eczema

swelling of the lips, face, tongue and throat

wheezing, repetitive cough

abdominal pain, diarrhea, nausea or vomiting

dizziness, lightheadedness or fainting

Signs and Symptoms

Anaphylaxis

Exercise-induced food
allergy

Pollen-food allergy
syndrome (OAS)-swelling
of the throat or even
anaphylaxis



Diagnosis

Patient's clinical history and examination

Determination of sensitization to food - standardized tests and procedures

Elimination diets for diagnostic purposes

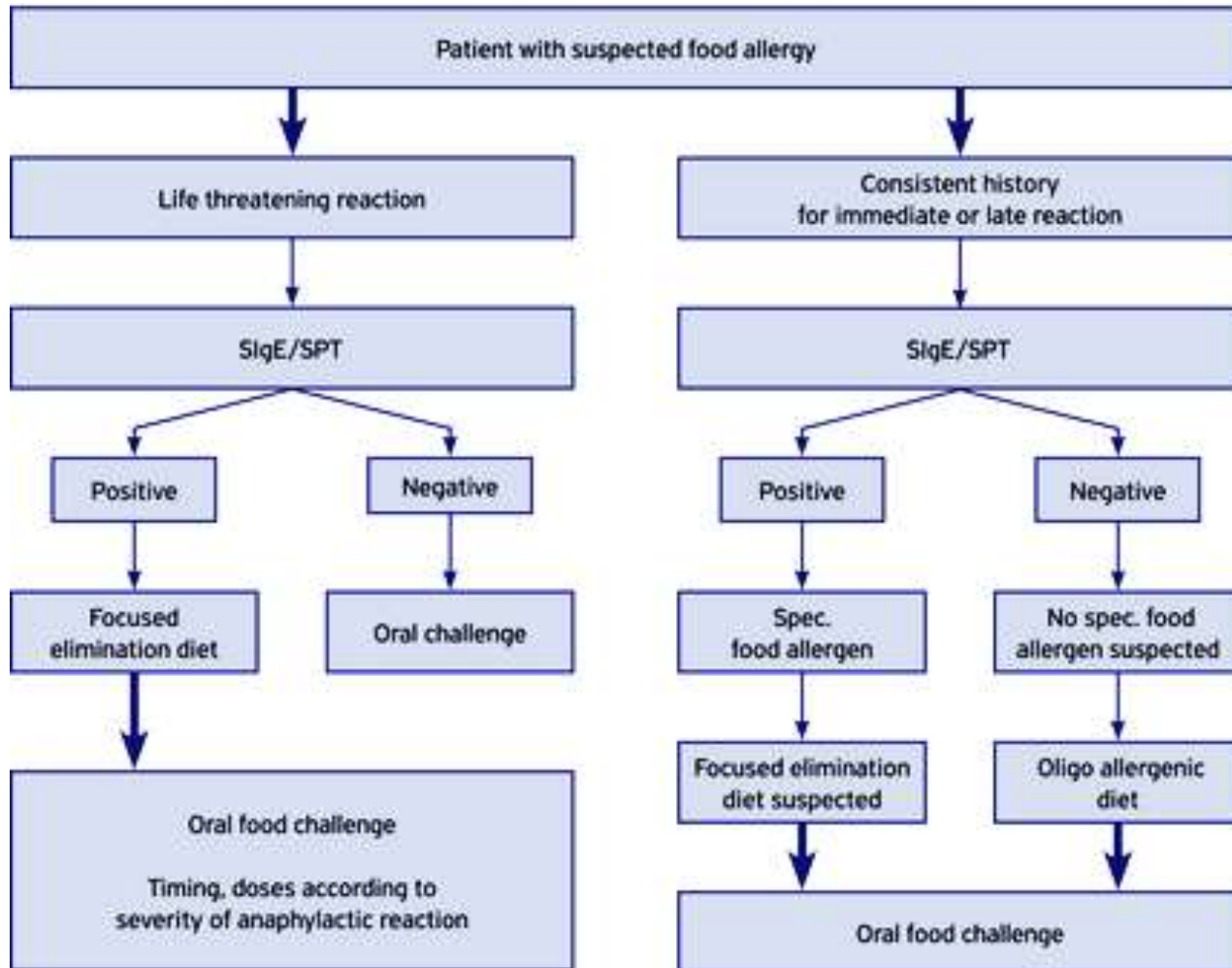
Oral food challenge (OFC) – DBPCFC is the gold standard

Diagnosis of EoE

Unconventional tests, including specific IgG testing

EAACI Food Allergy Guidelines

Algorithm for the diagnosis of food allergy

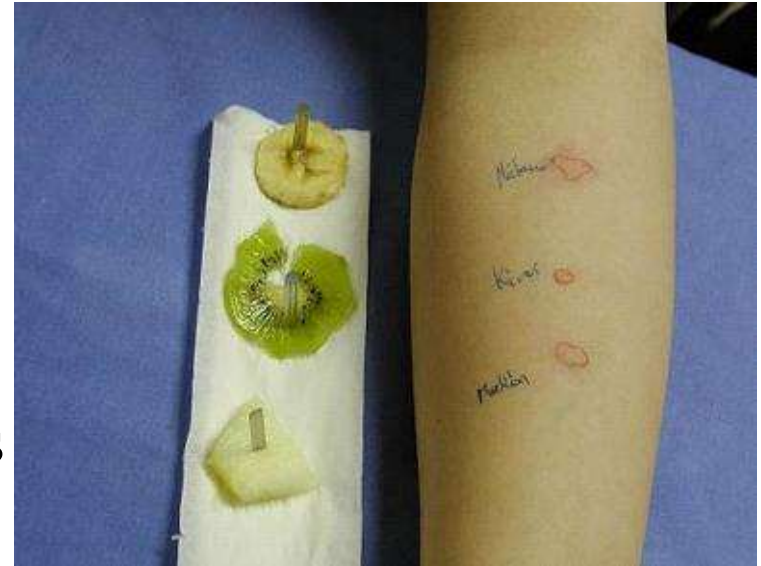


Diagnosis

Medical history

Skin prick tests

Blood tests for specific IgEs





Management and Treatment

Avoid consuming the food

Antihistamines-mild to moderate allergic reaction

Adrenaline-severe allergic reactions



**THANK YOU
FOR
YOUR
ATTENTION!
ANY QUESTIONS?**