URTICARIA, ANGIOEDEMA, AND ANAPHYLAXIS

By:-

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ETIOLOGY

Definitions:-

1. **Urticaria**, commonly referred to as **hives**, is swelling of the **dermis**.
2. **Angioedema** results from a process similar to urticaria, but the reaction **extends below the dermis**.
3. **Anaphylaxis** and **anaphylactoid reactions:-** Both reactions are acute, severe, and can be life threatening due to massive release of inflammatory mediators.
   - **Anaphylaxis** is mediated by IgE
   - **Anaphylactoid reactions** result from mechanisms that are due to nonimmunologic mechanisms.

- **Urticaria**, **angioedema**, and **anaphylaxis** are best considered as symptoms because they have a variety of causes.

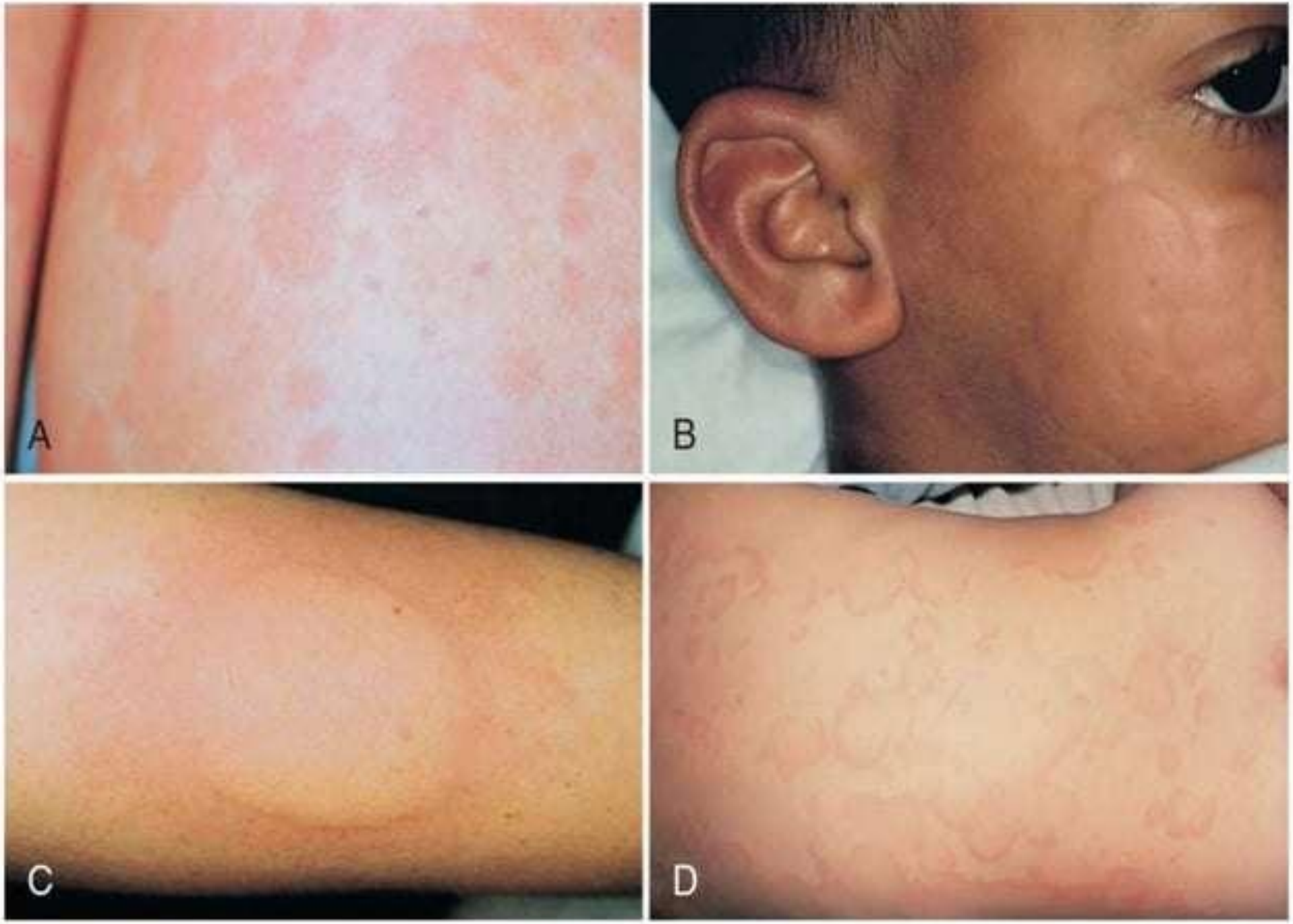
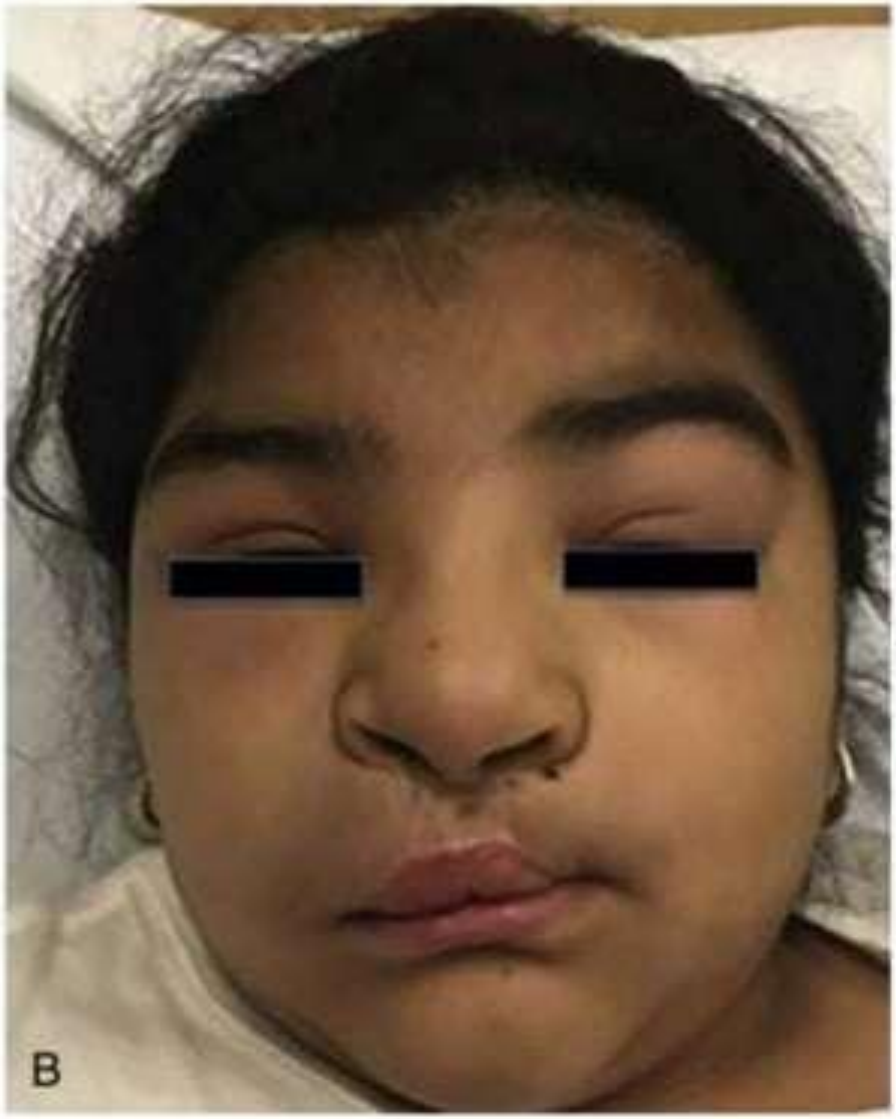
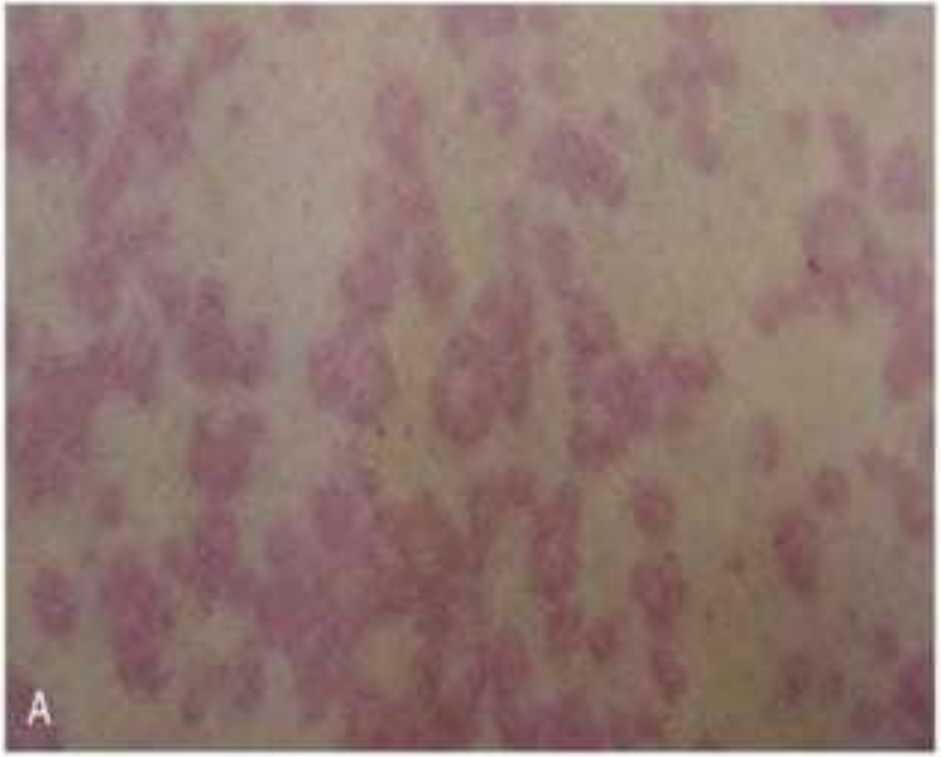


FIGURE 81.1 Examples of urticaria. (From Zitelli BJ, Davis HW, eds. *Pediatric Physical Diagnosis*

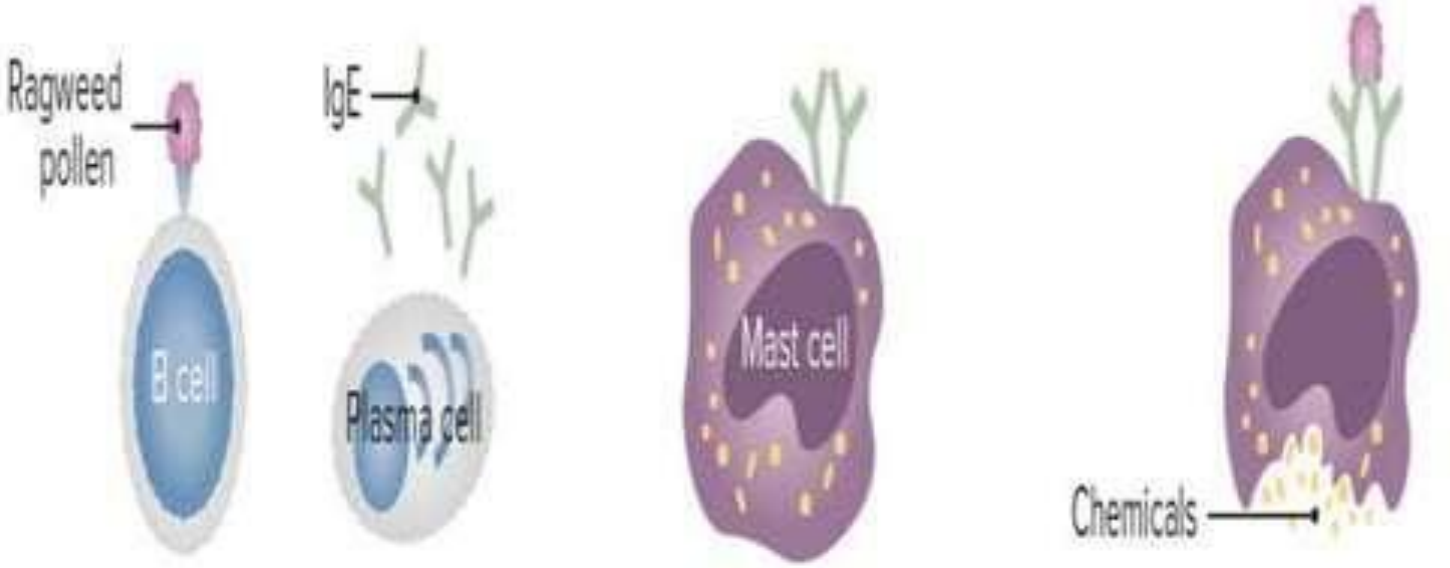




• **Fig. 39.1** Typical examples of urticaria and angioedema. (A) Urticarial lesions with areas of central pallor and confluence. (B) Angioedema of the eyelids, nose, and lips.

Pathophysiology:-

- Variety of stimuli → antigen cross links mast cell surface immunoglobulin (Ig)E → trigger mast cells residing in the skin → **mast cells degranulate** → mast cells release their chemical mediators – including histamine, leukotrienes, platelet-activating factor, prostaglandins, and cytokines – → vasodilation, increased vascular leak, and pruritus → Urticaria and angioedema
- Basophils from the peripheral blood can localize to tissue and release mediators.
- Patients with urticaria have elevated histamine content in the skin that is more easily released.



The first time an allergy-prone person runs across an allergen such as ragweed

The person makes large amounts of ragweed IgE antibody.

IgE attach to mast cells the second time the person comes into contact with ragweed.

The IgE-primed mast cells release granules and powerful chemical mediators, such as histamine and cytokines, into the environment.

These chemical mediators cause the characteristic symptoms of allergy.

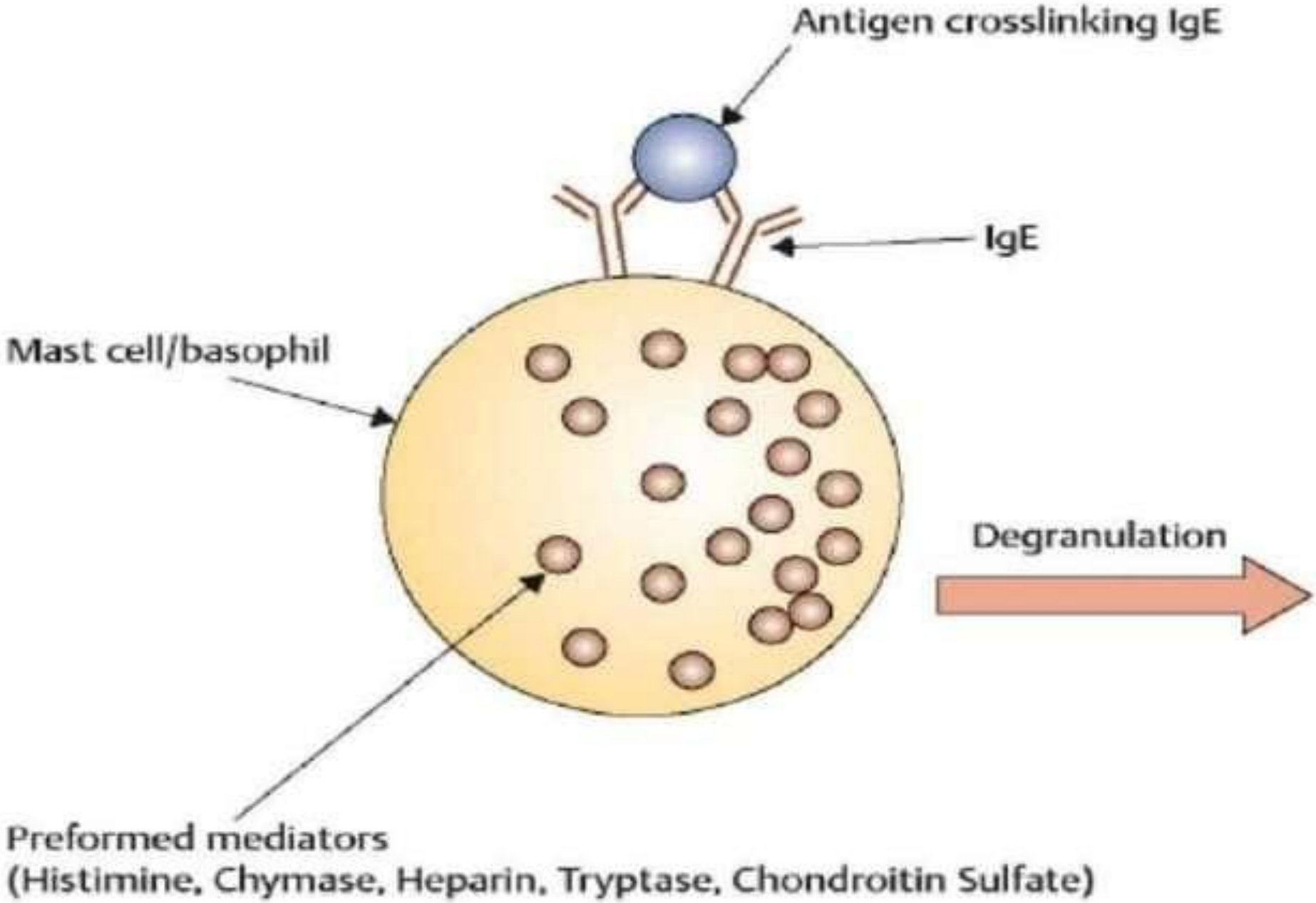


Fig. 9.1 Antigen crosslinking with immunoglobulin E (IgE).

Pathophysiology

Immunologic **Urticaria: antigen binds to IgE on the mast cell surface causing degranulation, which results in release of histamine**

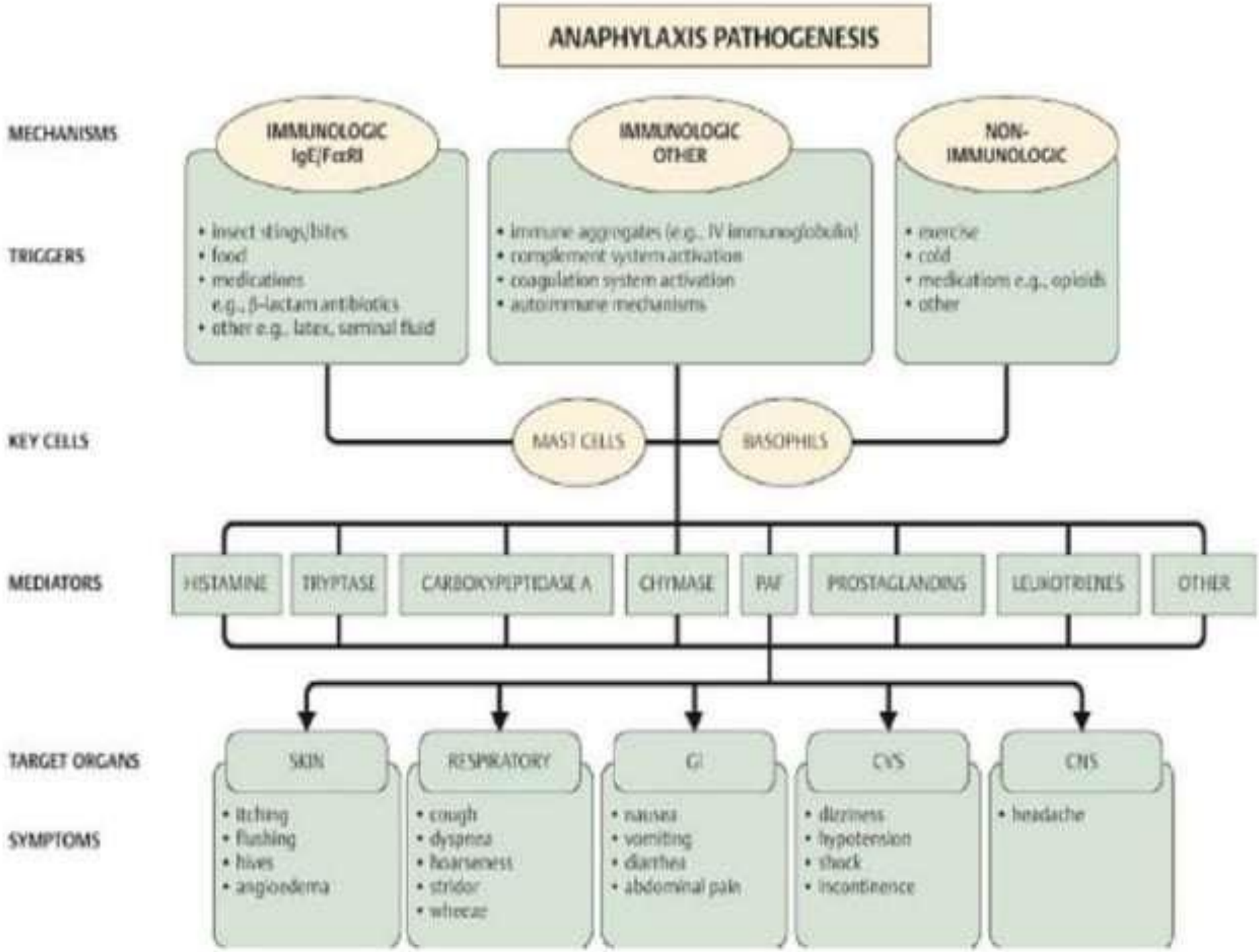
- **Histamine binds to H1 and H2 receptors to cause arteriolar dilatation, venous constriction and increased capillary permeability.**

Non-Immunologic **Urticaria: not dependent on the binding of IgE receptors**

- **For example, aspirin may induce histamine release through a pharmacologic mechanism where its effect on arachidonic acid metabolism causes a release of histamine from mast cells.**
- **Physical stimuli may induce histamine release through direct mast cell degranulation.**

Mast cell activation:-

- **Immunologic**
  - is IgE-mediated
- **Non-immunologic**
  1. Physical and chemical stimuli. E.g. dermatographism.
  2. Anaphylatoxins, C3a and C5a – are generated in serum sickness and in infectious, neoplastic, and rheumatic diseases.
  3. Direct pharmacologic effect e.g. urticaria after exposure to opiate medications


ANAPHYLAXIS PATHOGENESIS
MECHANISMS
TRIGGERS
KEY CELLS
MEDIATORS
TARGET ORGANS
SYMPTOMS
IMMUNOLOGIC IgE/FcεRI
• insect stings/bites
• food
• medications e.g., β-lactam antibiotics
• other e.g., latex, seminal fluid
IMMUNOLOGIC OTHER
• immune aggregates (e.g., IV immunoglobulin)
• complement system activation
• coagulation system activation
• autoimmune mechanisms
NON-IMMUNOLOGIC
• exercise
• cold
• medications e.g., opioids
• other
MAST CELLS
BASOPHILS
HISTAMINE
TRYPTASE
CARBOXYPEPTIDASE A
CHYMASE
PAF
PROSTAGLANDINS
LEUKOTRIENES
OTHER
SKIN
• itching
• flushing
• hives
• angioedema
RESPIRATORY
• cough
• dyspnea
• hoarseness
• stridor
• wheeze
GI
• nausea
• vomiting
• diarrhea
• abdominal pain
CVS
• dizziness
• hypotension
• shock
• incontinence
CNS
• headache

Classification:-

Urticaria and angioedema can be classified into three sub- categories:

- **Acute**
- **Chronic**
- **Physical**

Acute urticaria and angioedema:-

- By definition acute urticaria and angioedema are hives and diffuse swelling that **last less than 6 weeks**.
- Often the history is quite helpful in eliciting the cause of the acute reaction.
- An **IgE mechanism** is more commonly found in acute urticaria than in chronic urticaria.
- In the pediatric population, **viral illnesses** **are responsible for the majority of acute urticaria**.

ACUTE URTICARIA
Food
Medication
Insect sting or bite
Infection
Contact allergy
Transfusion reaction
Idiopathic

• BOX 39.2 Common Causes for Acute Urticaria and Angioedema in Children

Infections

- Viral, bacterial, fungal, parasitic

Mast Cell–Mediated

- Drugs
  - Nonsteroidal antiinflammatory drugs, antibiotics
- Foods
  - Cow's milk, egg, wheat, soy, peanut, tree nuts, fish, shellfish
- Insect bites/stings
  - Mosquitos, spiders, chiggers, hymenoptera, (fire) ants, bed bugs, fleas, mites

Contact allergens

- Poison ivy, foods, animals, latex

Chronic urticaria and angioedema:-

- Are characterized by persistence of symptoms **beyond 6 weeks.**
- Some have **daily symptoms** of hives and swelling
- Others have **intermittent or recurrent episodes**.
- **Has 3 subtypes:-**
  1. Chronic spontaneous (formerly idiopathic)
  2. Chronic autoimmune urticaria (Autoantibody associated)
  3. Physical or Inducible
     - are characterized by known eliciting external factors that may include pressure, cold, heat, exercise, vibration, Cholinergic or exposure to sun.

Chronic autoimmune urticaria:-

- Accounts for 35% to 40% of chronic urticaria
- Is an autoimmune process due to IgG autoantibodies binding directly to IgE or the high-affinity IgE receptor.

Dermatographism:-

- Is The most common physical urticaria
- Affecting 2-5% of persons.
- Dermatographism means "***writing on the skin***" .
- It is characterized by an **urticarial reaction localized to the site of skin trauma**.
- Is easily diagnosed by firmly scratching the skin with a blunt point, such as the wooden tip of a cotton swab or tongue depressor.
- It has been suggested that trauma induces an IgE-mediated reaction causing histamine to be released from the mast cells.

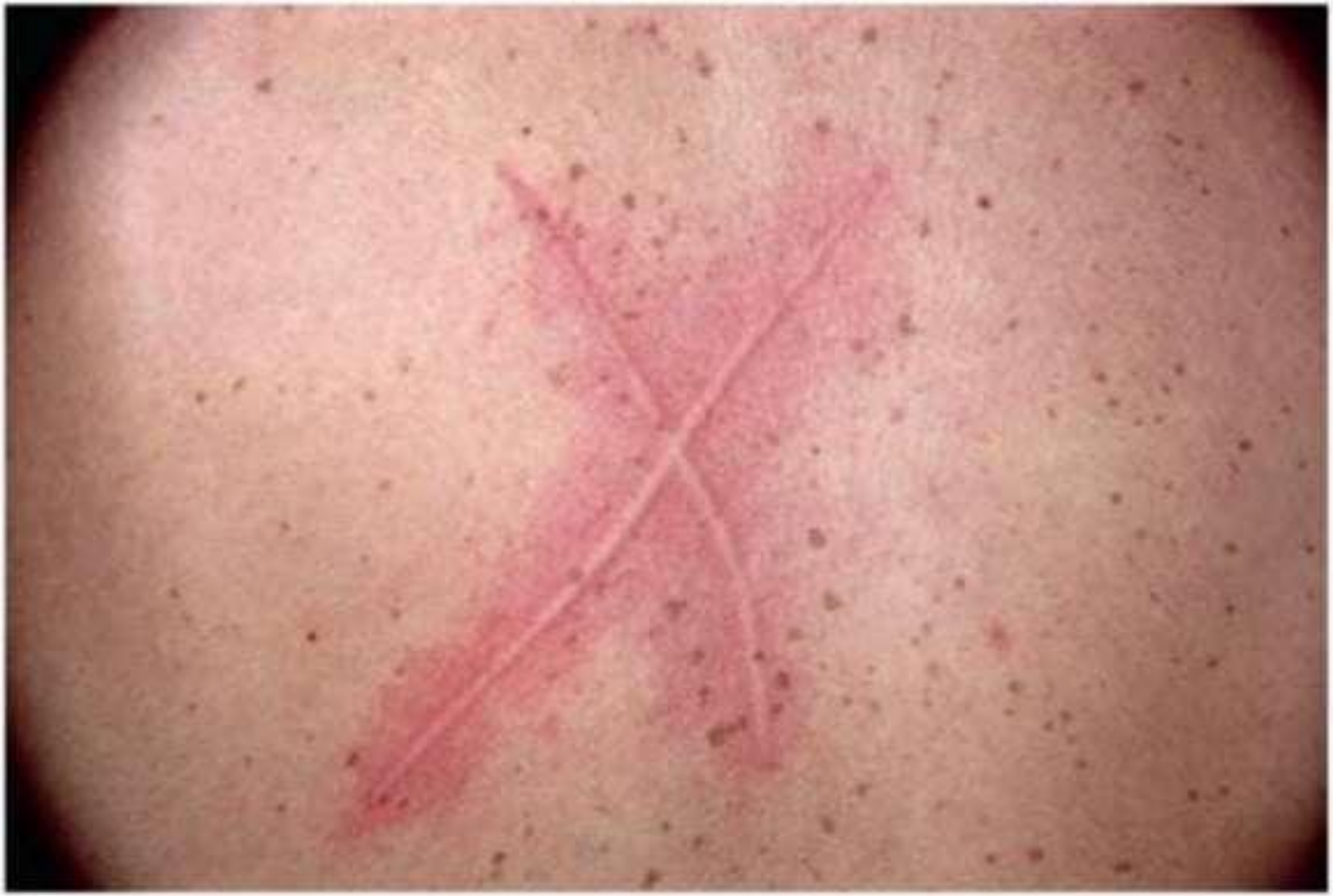


Fig. 7-16 Dermatographism.

Cholinergic urticarial:-

- Is produced by the action of acetylcholine on mast cells.
- Characterized by the appearance of minute, punctate, 1-3 mm wheals or papules surrounded by large erythematous flares after an increase in core body temperature.
- Occurs commonly in young adults.
- Lesions may develop
  - during strenuous exercise,
  - after a hot bath
  - with emotional stress.
- The lack of airway symptoms differentiates it from exercise-induced anaphylaxis.

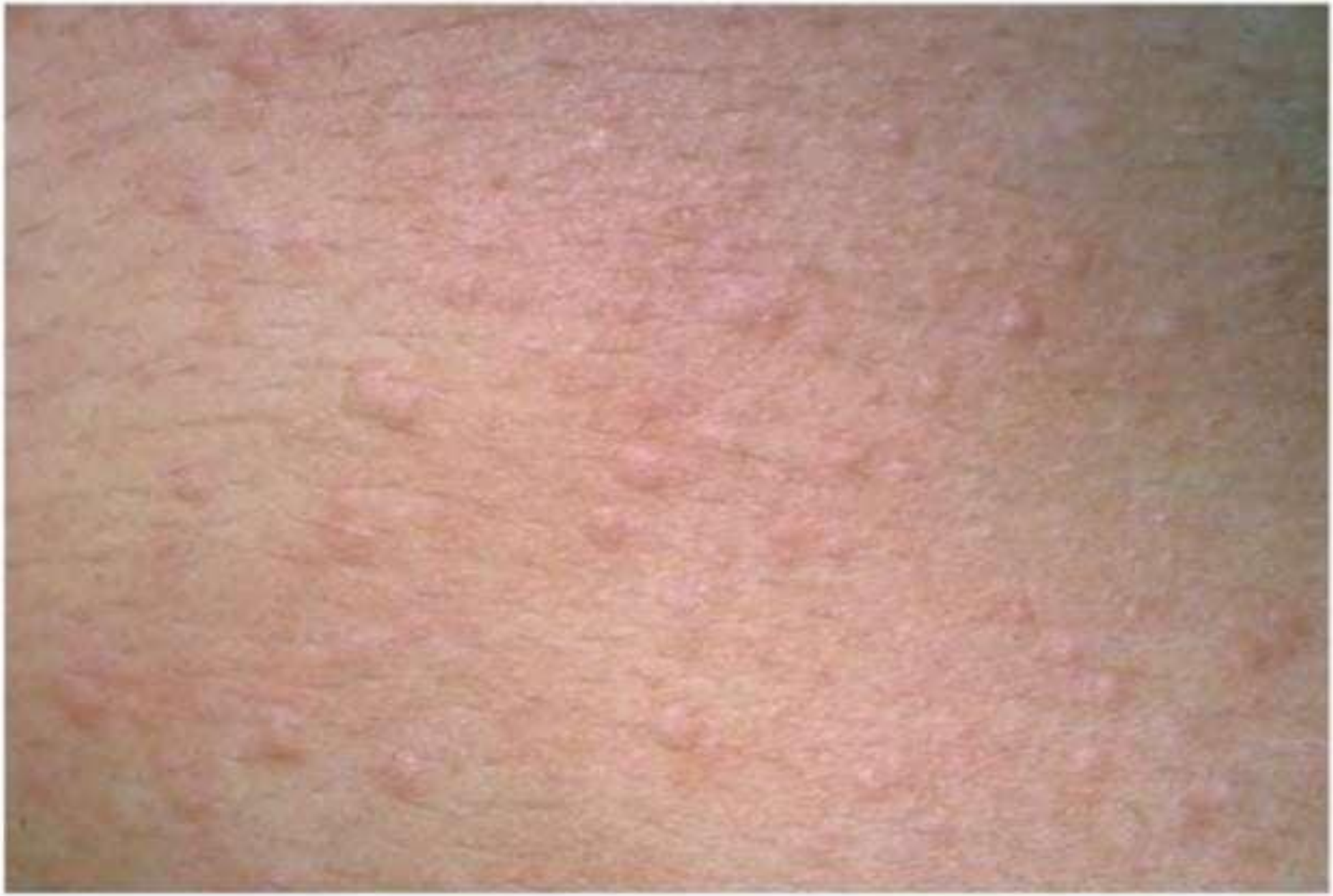
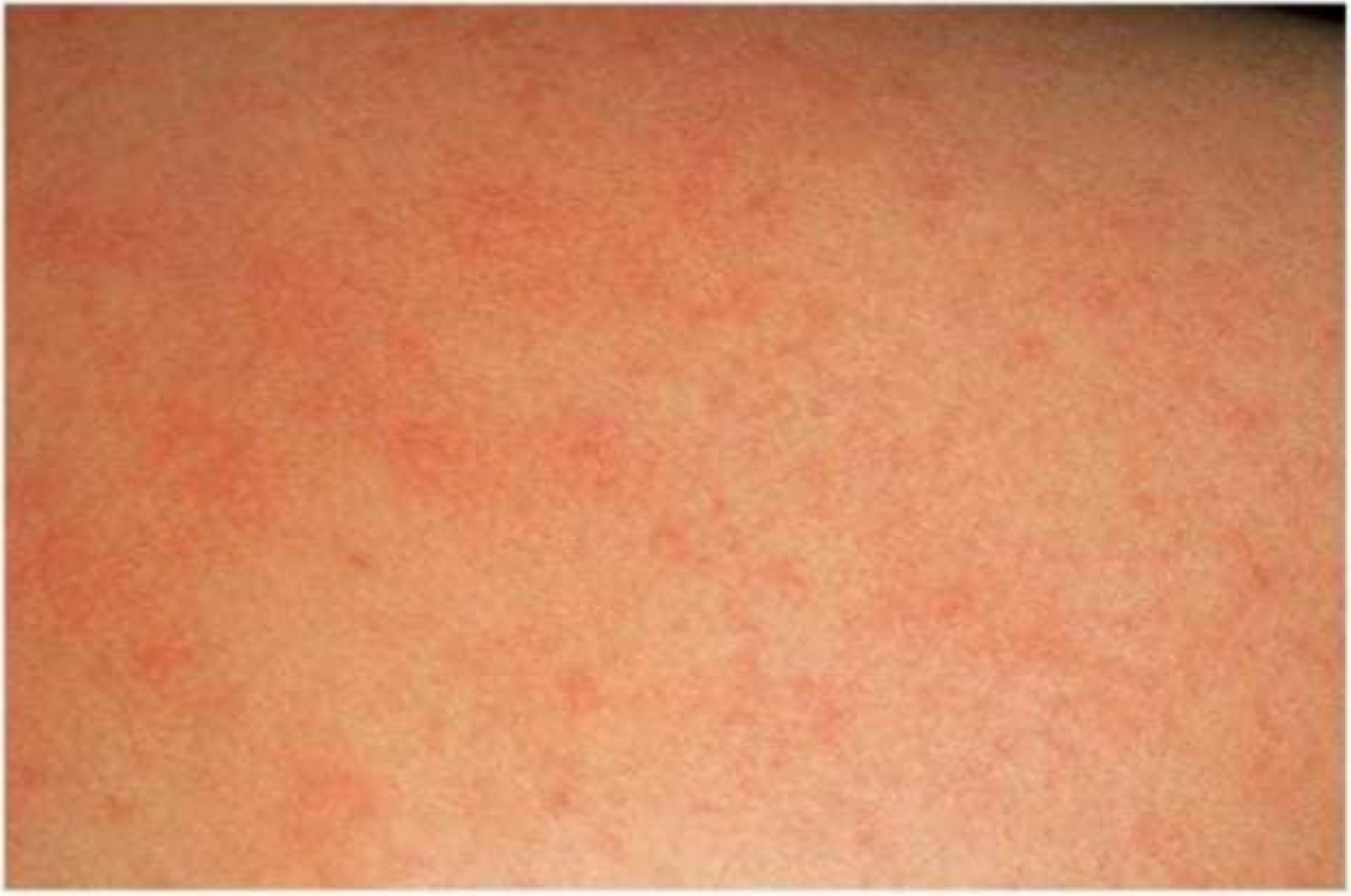


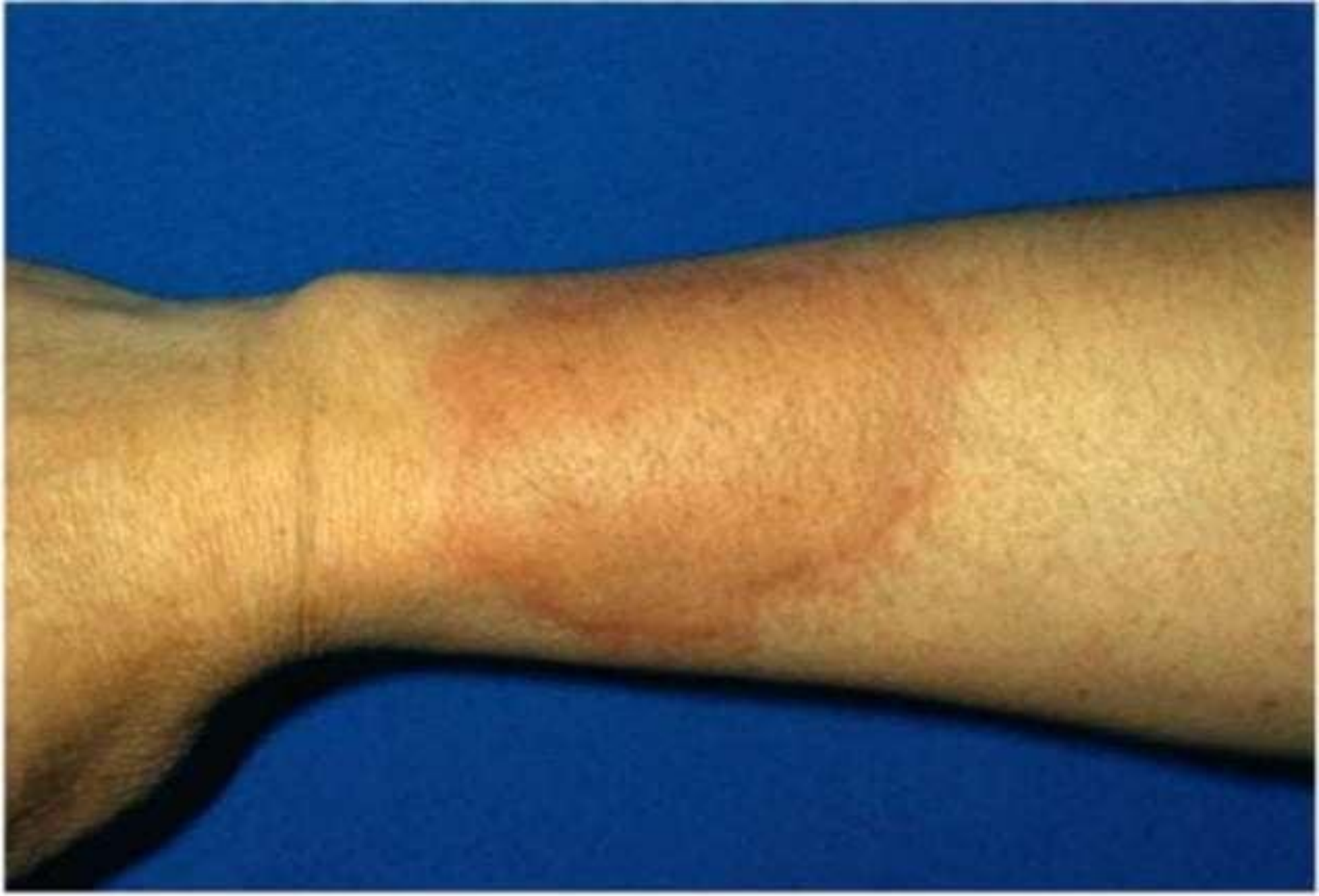
Fig. 7-17 Cholinergic urticaria, small papules with surrounding large, erythematous flare.



eFig. 7-12 Cholinergic urticaria, small papules with surrounding large, erythematous flare.

Cold urticarial:-

- Occurs with exposure to cold
- may develop within minutes on areas directly exposed to cold or on rewarming of the affected areas.
- Ingestion of cold drinks may precipitate lip swelling.
- Severe reactions resulting in death can occur with swimming or diving into cold water.
- Cold urticaria syndromes can be categorized into acquired and familial disorders.
- Patients must never swim alone, should avoid total body exposure to cold, and should have auto-injectable epinephrine available.



eFig. 7-13 Cold urticaria after ice cube applied to site for 3 min.

Hereditary angioedema (HAE):-

- Is an **autosomal dominant** disease due to a deficiency of **C1-esterase inhibitor**.
- 25% of cases occur in patients without any family history – spontaneous mutation.
- It is characterized by unpredictable, recurrent attacks of episodic swelling that involves the face, peripheral extremities, genitalia, abdomen, oropharynx, and pharynx.
- Episodes are often triggered by trauma.
- Asphyxiation from laryngeal attacks is a significant cause of mortality. Laryngeal edema, especially with abdominal pain, suggests HAE
- Features:-
  - Rarely associated urticaria
  - Not itching
  - the swelling is not relieved with antihistamines or oral corticosteroids.

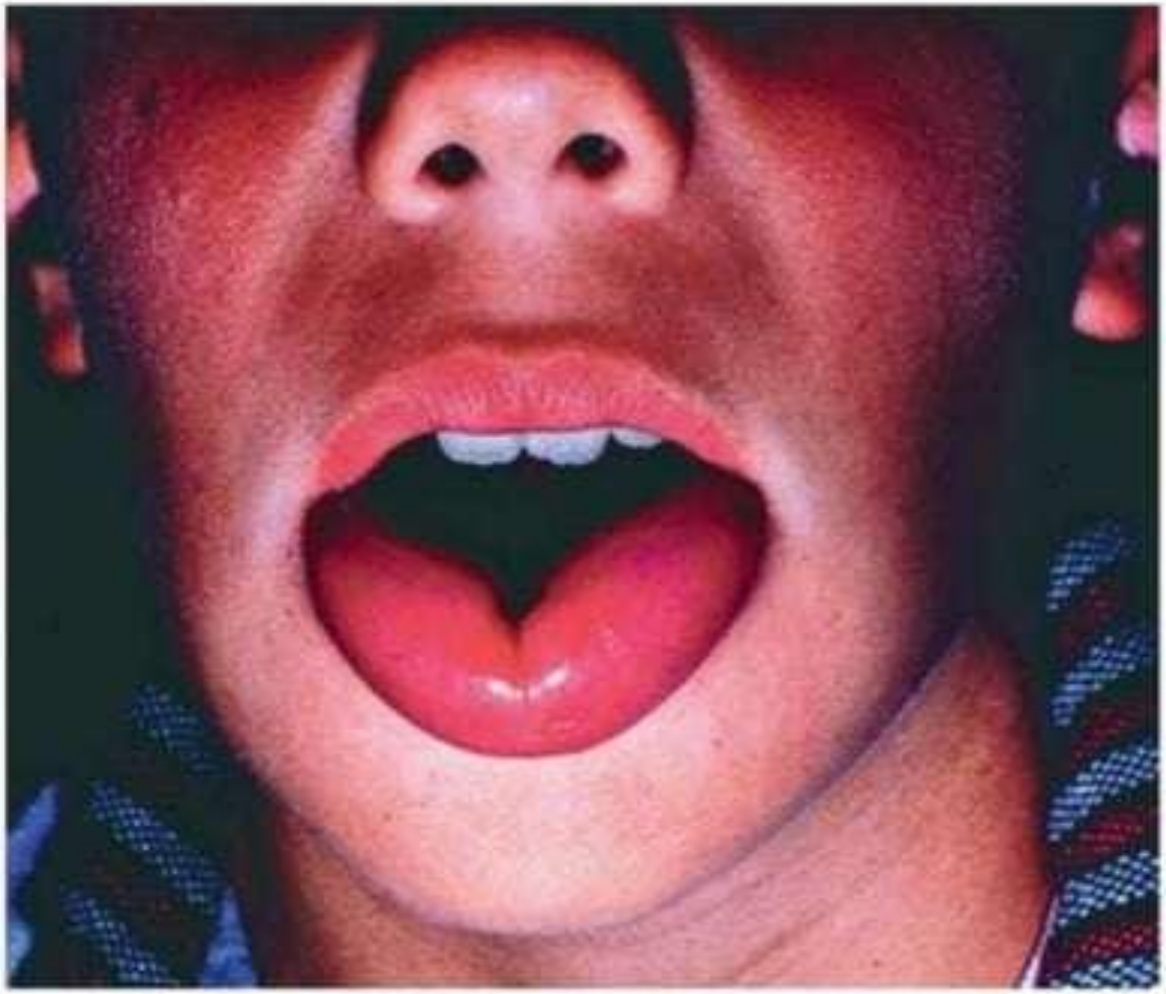


Fig. 7-19 Angioedema of the lips.

Hereditary angioedema (HAE):-

Type I disease	Type II disease	HAE with normal C1 inhibitor (formerly known as type III HAE)
• Seen in the majority of patients (85%) • Is due to decreased production of C1-esterase inhibitor	• Seen in minority of patients (15%) • Is due to production of dysfunctional C1-esterase inhibitor.	• Patients have normal laboratory evaluation of C1-esterase inhibitor. • These patients are more typically females.

Lab test	HAE Type 1	HAE Type 2	HAE with normal C1-INH
C4 concentration	Low	Low	Normal
C1-INH concentration	Low	Normal/high	Normal
C1-INH function	Low	Low	Normal

Hereditary angioedema (HAE):-

- Treatment for HAE is divided into
  1. on-demand treatment for acute attacks
  2. prophylaxis.
- **Prophylactic C1INH** concentrate has advantage over other prophylactic therapies in terms of availability, effectiveness, and side effects.

TABLE 81.2 Hereditary Angioedema Treatment

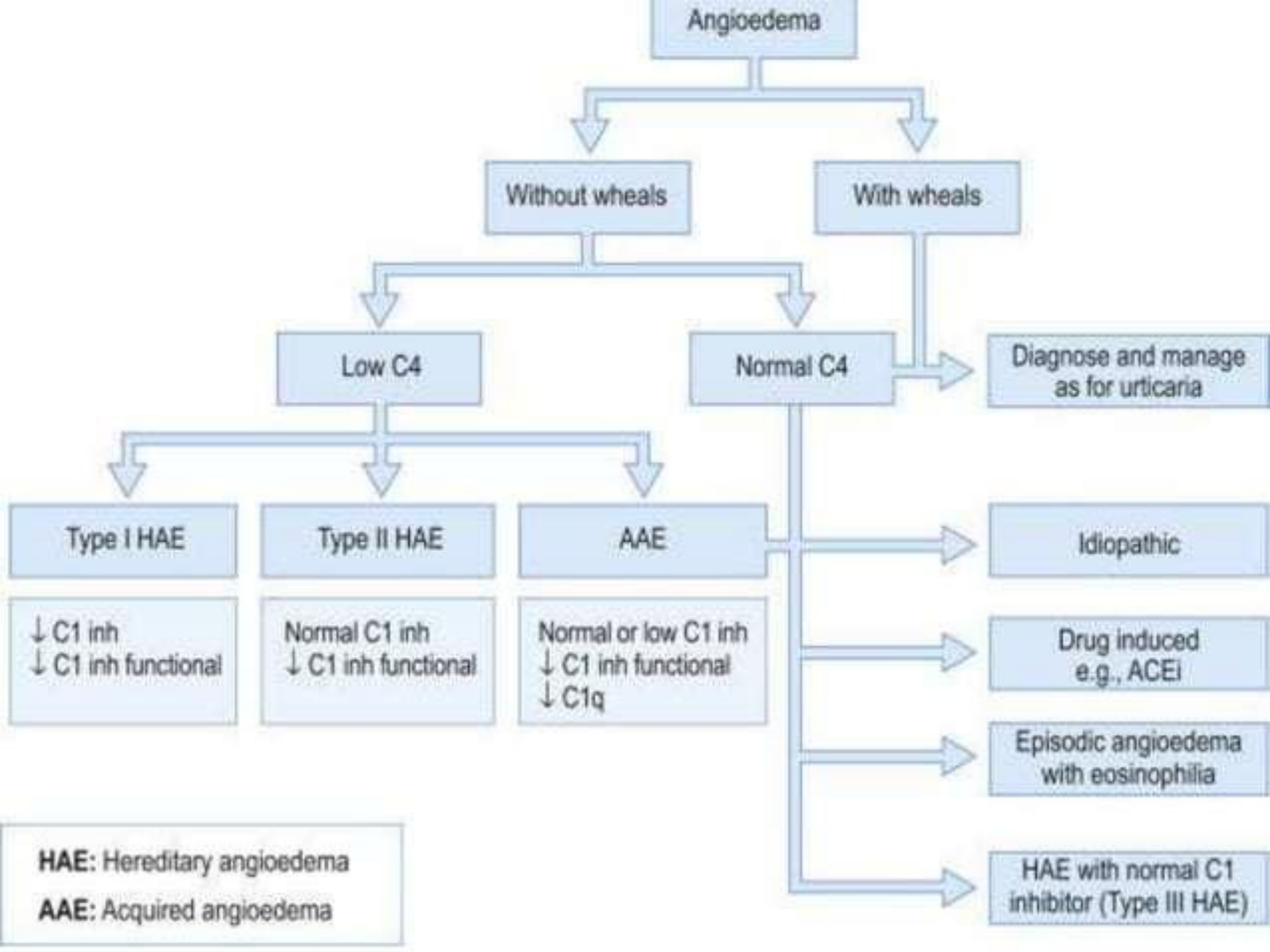
DRUG CLASS AND NAME	INDICATION	APPROVED AGE
C1INH concentrate	Acute attacks	
Berinert		Children and adults
Ruconest		≥12 yr of age
Plasma kallikrein inhibitor	Acute attacks	
Ecallantide		≥16 yr of age
Bradykinin B_2 receptor antagonist	Acute attacks	
Icatibant		≥18 yr of age
17α-Alkylated androgens	Long-term prophylaxis	
Danazol		Adults
Stanozolol		Children and adults
C1INH concentrate	Long-term prophylaxis	
Cinryze		≥12 yr of age

BOTTOM LINE/CLINICAL PEARLS

- A history of one or more of the following may suggest HAE:
  - Recurrent swelling (without urticaria) of the extremities (hands, feet), abdomen, face, oropharynx, genitourinary;
  - Angioedema not improving with antihistamines and corticosteroids;
  - Unexplained recurrent abdominal pain;
  - A history of laryngeal edema.
- The diagnosis of HAE I or II is confirmed with at least two sets of complement testing with similar results, ideally carried out without recent use of HAE medications and separated by 1 month.
- Results of laboratory testing for complement studies takes >24 hours; an immediate diagnosis of HAE with initial presentation may be difficult.

TABLE 81.4 Complement Evaluation of Patients With Recurrent Angioedema

ASSAY	IDIOPATHIC ANGIOEDEMA	TYPE I HEREDITARY ANGIOEDEMA	TYPE II HEREDITARY ANGIOEDEMA	HEREDITARY ANGIOEDEMA WITH NORMAL C1 INHIBITOR	ACQUIRED C1-ESTERASE INHIBITOR DEFICIENCY	VASCULITIS
C4	Normal	Low	Low	Normal	Low	Low or normal
C1-esterase inhibitor level	Normal	Low	Normal	Normal	Low	Normal
C1-esterase inhibitor function	Normal	Low	Low	Normal	Low	Normal
C1q	Normal	Normal	Normal	Normal	Low	Low or normal


Angioedema
Without wheals
With wheals
Low C4
Normal C4
Diagnose and manage as for urticaria
Type I HAE
Type II HAE
AAE
Idiopathic
↓ C1 inh
↓ C1 inh functional
Normal C1 inh
↓ C1 inh functional
Normal or low C1 inh
↓ C1 inh functional
↓ C1q
Drug induced
e.g., ACEi
Episodic angioedema with eosinophilia
HAE with normal C1 inhibitor (Type III HAE)
HAE: Hereditary angioedema
AAE: Acquired angioedema

EPIDEMIOLOGY

- Urticaria and angioedema are common skin conditions affecting 15-25% of individuals at some point in their lives.
- Most cases of urticaria are self-limited, but for some patients, they are chronic.
- In approximately 50% of patients, urticaria and angioedema occur together.
- In the remaining 50%,
  - 40% have urticaria alone
  - 10% have angioedema alone.
- The incidence of anaphylaxis in children is unknown.

CLINICAL MANIFESTATIONS

Urticaria	Angioedema
Raised, erythematous lesions with pale centers	Swelling is the principal symptom
Intensely pruritic	not pruritic may be mildly painful
Involves the dermis only	Involves the deeper dermis or subcutaneous tissue
Typically, urticaria arises suddenly and may resolve within 1-2 hours or may persist for up to 24 hours.	Persists for longer than 24 hours
	In rare cases it may become life threatening if swelling affects the upper airway.

The clinical manifestations of anaphylaxis and anaphylactoid reactions:-

1. **90% of patients present with cutaneous symptoms**, including urticaria, angioedema, flushing, and warmth, but the **absence of dermal symptoms does not exclude the diagnosis of anaphylaxis**.
2. Respiratory tract (rhinorrhea, oropharyngeal edema, laryngeal edema, hoarseness, stridor, wheezing, dyspnea, and asphyxiation),
3. Cardiovascular system (tachycardia, hypotension, shock, syncope, and arrhythmias),
4. Gastrointestinal tract (nausea, abdominal pain, diarrhea, and vomiting)
5. Neurological system (syncope, seizure, dizziness, and a sense of impending doom).

Diagnostic Criteria for Anaphylaxis:-

Anaphylaxis is likely when any one of the three criteria is fulfilled:

1

Acute onset of an illness (minutes to several hours) with involvement of:

Skin and/or mucosa

Pruritus
Flushing
Hives
Angioedema

And either

Respiratory compromise

Dyspnea
Wheeze-bronchospasm
↓Peak expiratory flow
Stridor
Hypoxemia

Or

↓BP or end-organ dysfunction

Collapse
Syncope
Incontinence

2

2 or more of the following that occur rapidly after exposure to a likely allergen for that patient:

Skin and/or mucosa

Pruritus
Flushing
Hives
Angioedema

Respiratory compromise

Dyspnea
Wheeze-bronchospasm
↓Peak expiratory flow
Stridor
Hypoxemia

↓BP or end-organ dysfunction

Collapse
Syncope
Incontinence

Persistent GI symptoms

Vomiting
Crampy Abdominal Pain
Diarrhea

3

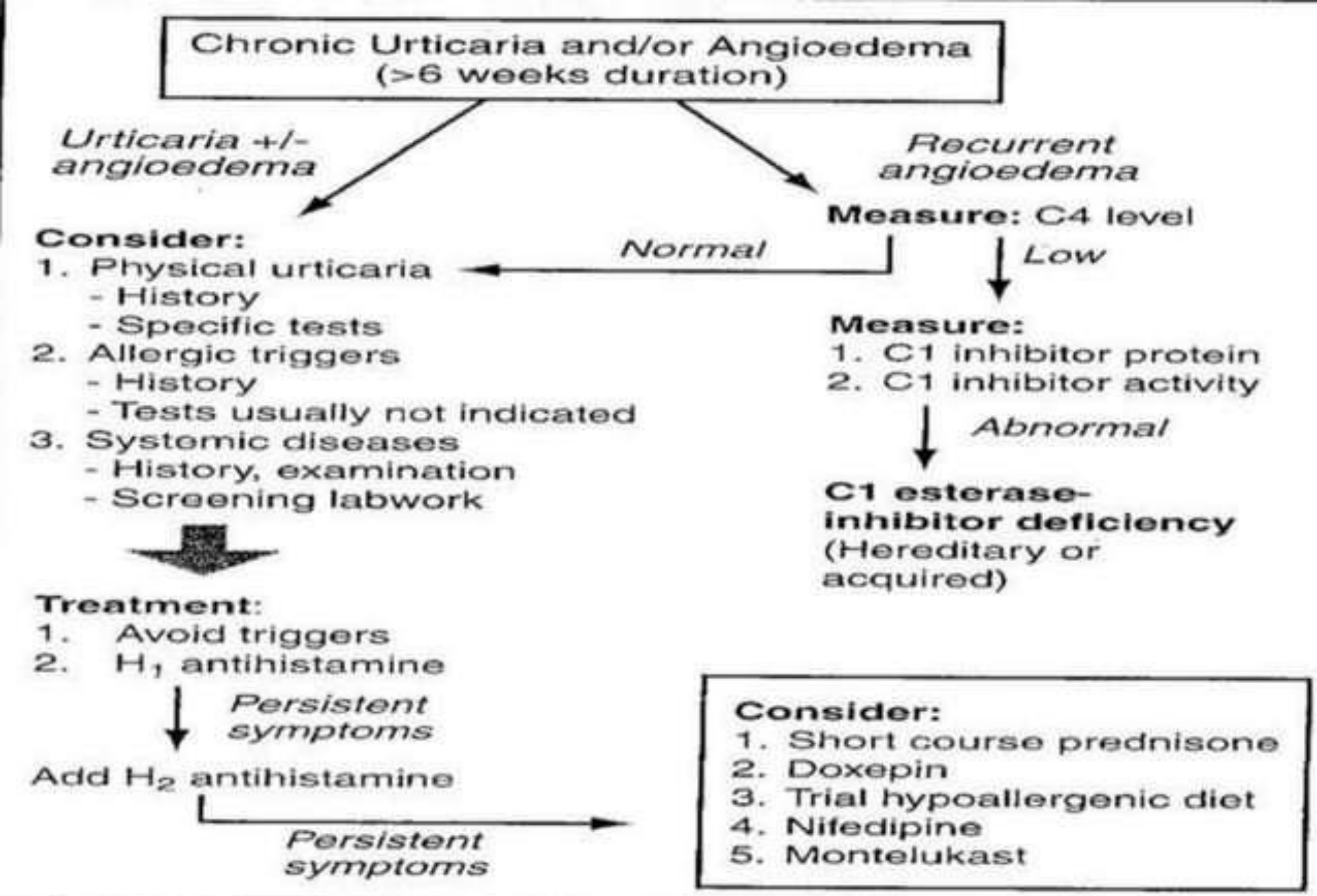
After exposure to known allergen for that patient (minutes to several hours):

↓BP

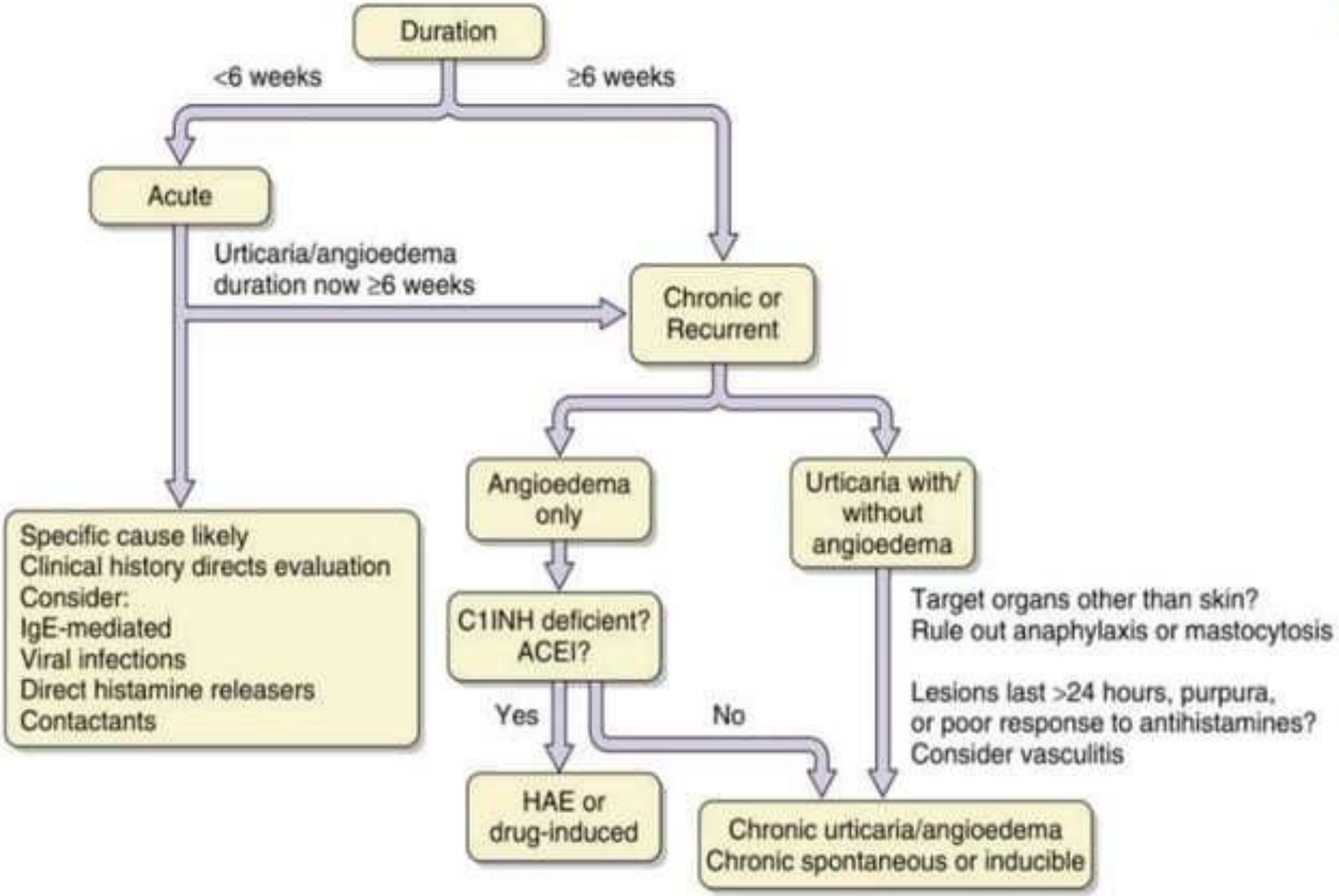
LABORATORY AND IMAGING STUDIES

Urticaria and angioedema:-

- According to the clinical situation
- **Acute urticaria and angioedema:-**
  - do not require specific laboratory evaluation
  - document the suspected cause.
- **For patients with chronic urticaria and angioedema**:-
  - current recommendations advise against routine lab testing
  - Accordingly if the history suggests a potential etiology.
- **Patients with recurrent angioedema without urticarial, should be evaluated for HAE**:-
  - A low C4 level serves as an initial screening test.
  - Patients with reduced C4 should have quantitative and functional levels of C1-esterase inhibitor measured.
  - C2 levels are low during an acute attack of HAE.



igure 10-1: Management of chronic urticaria and angio
dema.



• **Fig. 39.2** Diagnostic algorithm for urticaria and angioedema. *ACEI*, Angiotensin-converting enzyme inhibitor; *AE*, angioedema; *C1INH*, C1 inhibitor; *HAE*, hereditary angioedema; *IgE*, immunoglobulin E.

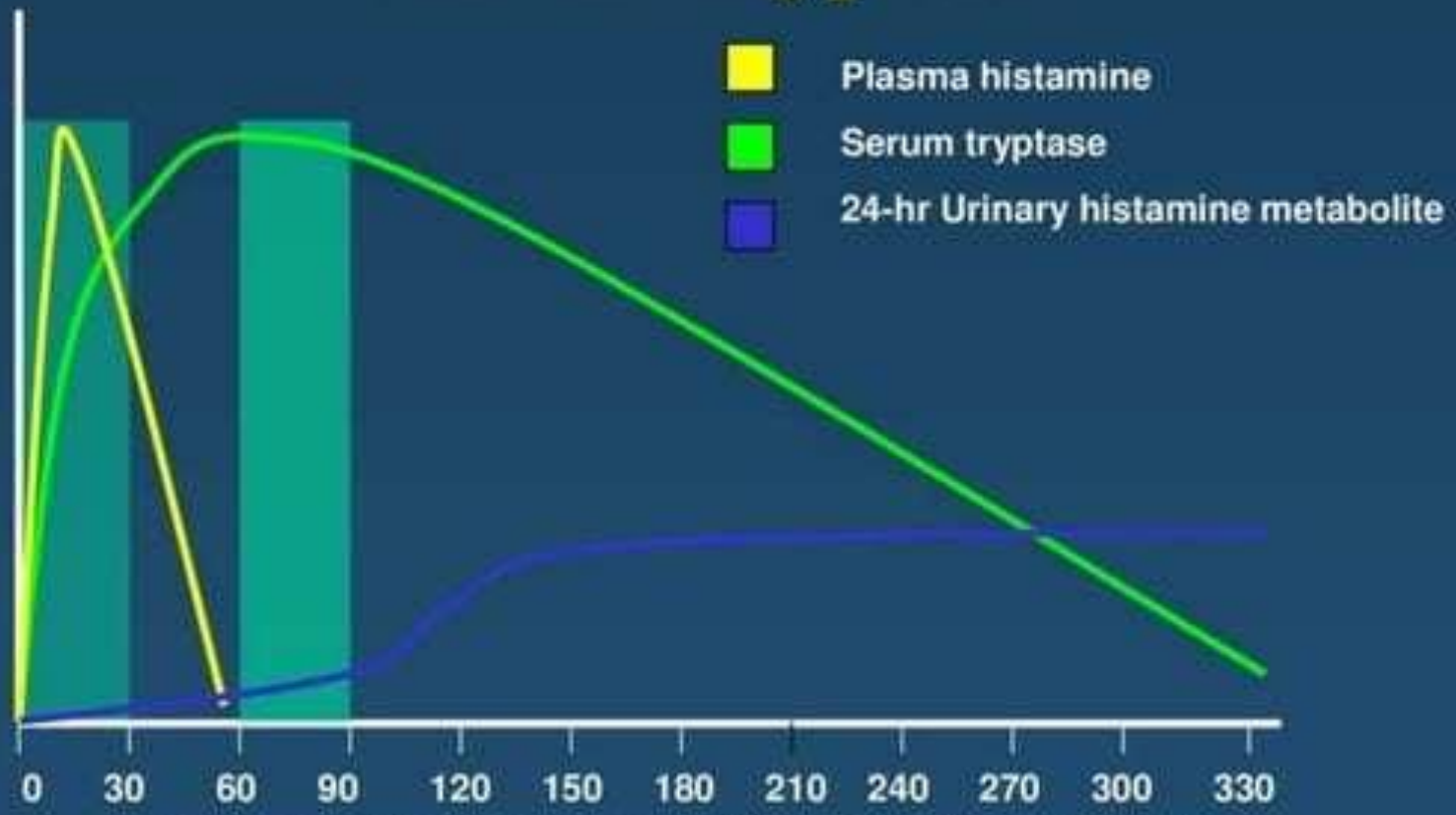
Anaphylaxis:-

- Investigations are ordered when the diagnosis of anaphylaxis is in question:- Measurement of the mast cell mediators,

1. **Histamine**
   - histamine is released quickly,
   - has a very short half-life
   - is often difficult to detect in the serum.
2. **Tryptase**
   - A tryptase level is a more useful test
   - Levels peak 1-1.5 hours after anaphylaxis.
   - Elevated levels may be helpful in establishing the diagnosis
   - normal tryptase levels do not rule out the diagnosis.
   - It is best to measure a serum tryptase level 1-2 hours after the onset of symptoms

Immediate reactions

Serum tryptase



An elevated level supports a diagnosis of anaphylaxis.
Normal levels do not exclude anaphylaxis.

DIFFERENTIAL DIAGNOSIS

DDx of Urticaria:-

1. **Erythema multiforme**
   - has target-shaped,
   - erythematous,
   - macular, or papular lesions
   - the lesions are fixed and last for several days.
2. **Dermatitis herpetiformis**
3. **Bullous pemphigoid**
4. **Mastocytosis**
   - Is characterized by mast cell infiltration of various organs, including the skin.
   - Classically associated with urticaria pigmentosa:-
     - Appears as hyperpigmented, red-brown macules that may coalesce.
     - When these lesions are stroked, they urticate, which is called the Darier sign.

DDx of Urticaria:-

1. **Urticarial vasculitis**
   - Is a small vessel vasculitis with histological features of a leukocytoclastic response. Skin biopsy is required for definitive diagnosis.
   - The main distinguishing feature is that
     1. the lesions last longer than 24 hours and are fixed rather than migratory.
     2. Lesions are tender rather than pruritic
     3. Leave behind skin pigmentation.
2. **Muckle- Wells syndrome**.
   - It is an autosomal dominant autoinflammatory disorder characterized by
   - episodic urticaria presenting in infancy
   - sensorineural deafness,
   - amyloidosis,
   - Arthralgias
   - skeletal abnormalities.
3. **Schnitzler syndrome**
   - is characterized by
   - chronic urticaria,
   - macroglobulinemia,
   - bone pain,
   - anemia, f
   - ever,
   - Fatigue
   - weight loss.

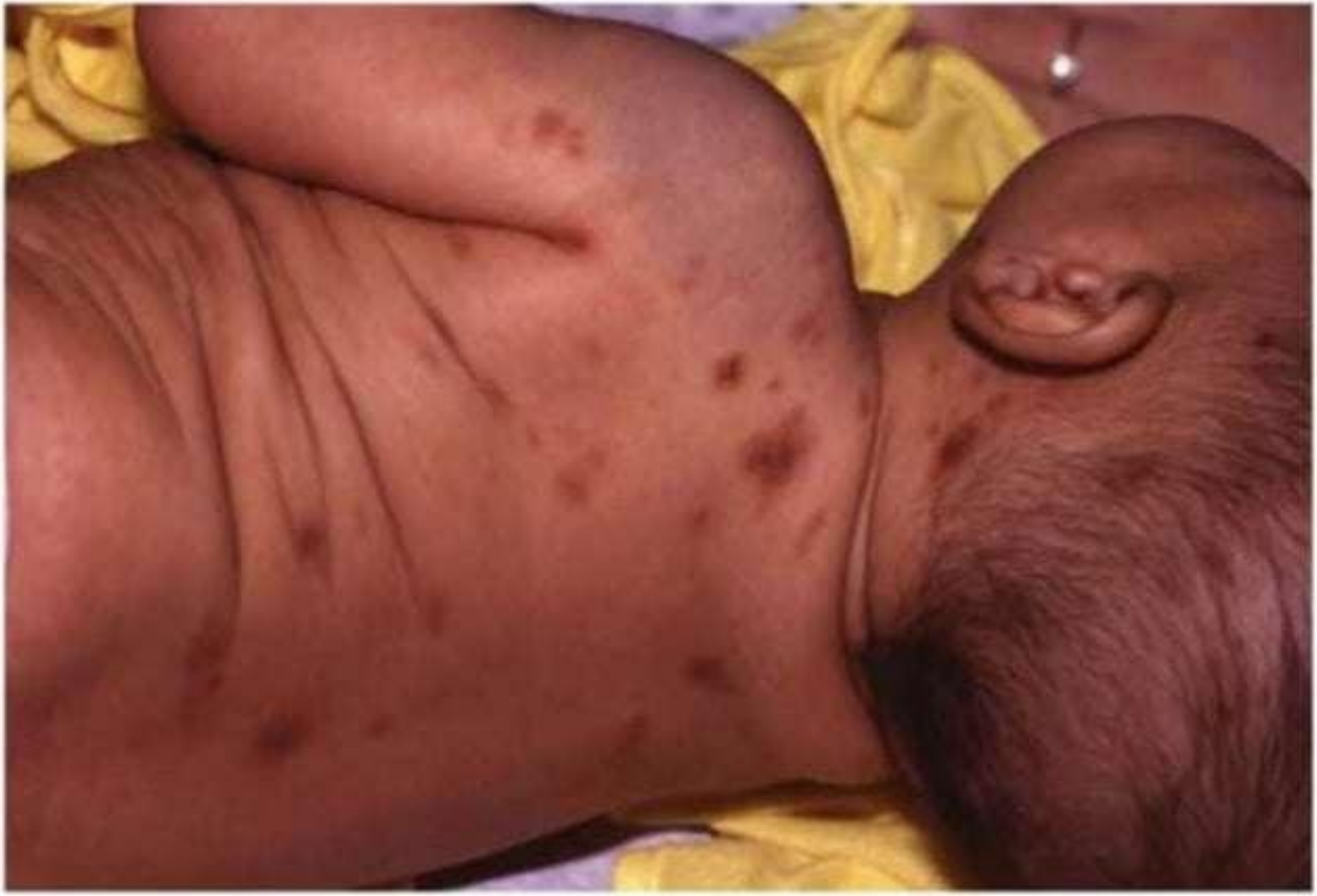


Figure 658-13. Hyperpigmented papular lesions of urticaria pigmentosa.

Table 21.1 Differences between erythema multiforme and urticaria.

DIFFERENCES BETWEEN ERYTHEMA MULTIFORME AND URTICARIA	
Urticaria	**Erythema multiforme**
Central zone is normal skin	Central zone is damaged skin (dusky, bullous or crusted)
Lesions are transient, lasting several hours	Lesions 'fixed' for at least 7 days
New lesions appear daily	All lesions appear within first 72 hours
Associated with swelling of hands and feet (angioedema)	No edema

TREATMENT

Acute urticaria and angioedema:-

- Most cases resolve spontaneously.
- Avoidance of triggering agents.
- Use of pharmacologic agents will provide symptom relief and include H1 antihistamines.
- If acute urticarial and angioedema do not respond to this therapy, a short course of oral steroids may be considered.

Stepwise therapy for chronic Urticaria:-

Step 5
Immunosuppressant (cyclosporine, tacrolimus, sirolimus)
Ultraviolet light therapy

Step 4
Antiinflammatory alternative agent (dapsone, sulfasalazine, or hydroxychloroquine)

Step 3
Omalizumab 300 mg every 4 weeks (titrate dose and/or frequency to effect)

Step 2
Add leukotriene receptor antagonist (montelukast)
Increase dose of second-generation H1 antihistamine up to 4 times daily recommended dose
Add first-generation H1 antihistamine (hydroxyzine or doxepin) at bedtime

Step 1
Second-generation H1 antihistamines (cetirizine, fexofenadine, levocetirizine, or loratadine)
Avoid NSAIDs, alcohol, or opiates
Avoidance of physical triggers

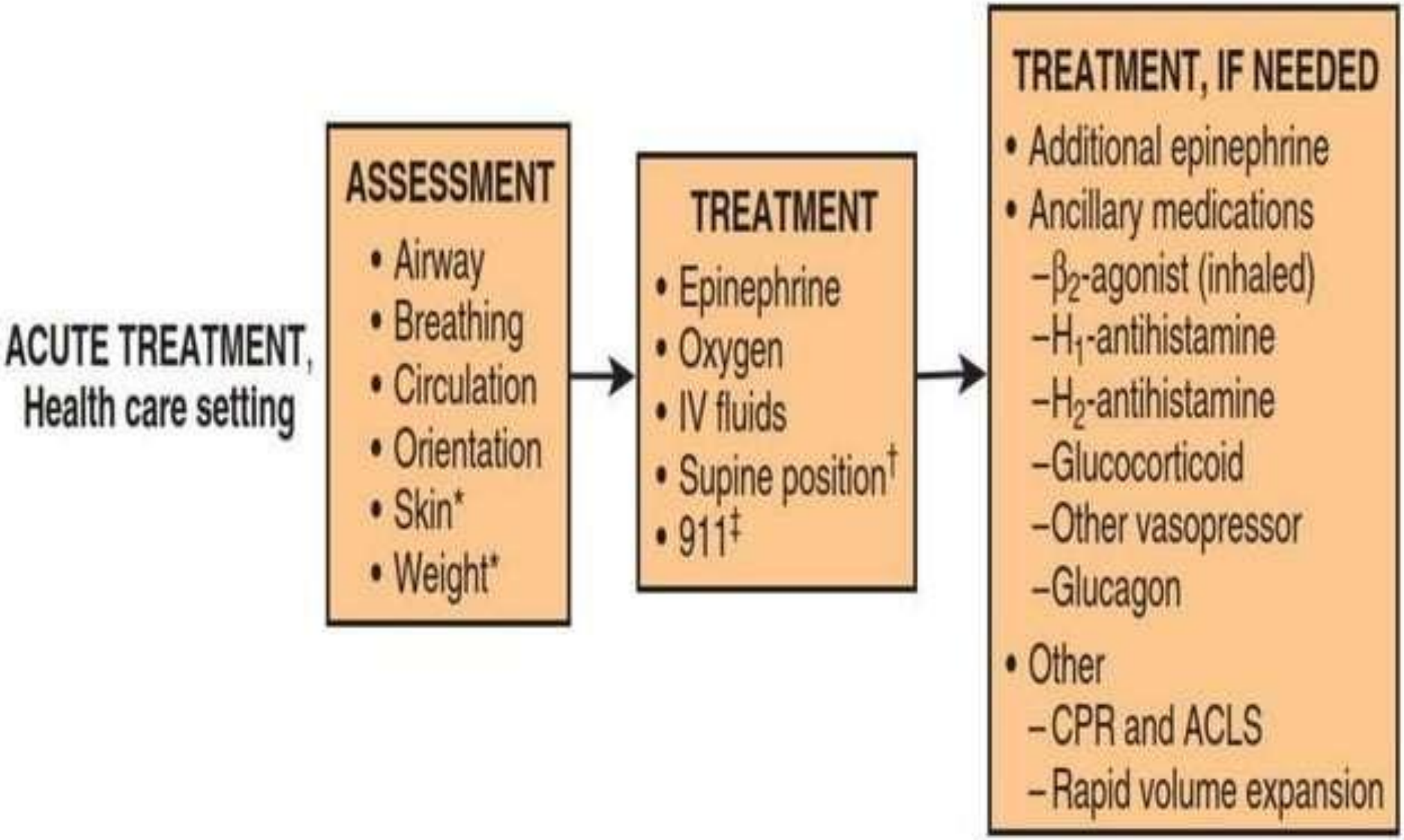
• BOX 39.3 Therapeutic Principles and Treatment of Urticaria and Angioedema

- Avoidance of known provoking stimuli can greatly improve treatment outcomes.
- Histamine 1 (H1) antihistamines are the mainstay of treatment, and second-generation H1 antihistamines are preferred because they have fewer side effects.
- Difficult cases may require treatment with various combinations of second-generation H1 antihistamines, first-generation H1 antihistamines, H2 antihistamines, and leukotriene receptor antagonists.
- Omalizumab is effective for antihistamine-resistant chronic urticaria.
- Delayed-pressure urticaria does not generally respond well to antihistamines.
- Corticosteroids should be avoided for long-term therapy.
- The angioedema of hereditary angioedema does not respond to antihistamines, corticosteroids, or epinephrine; oropharyngeal attacks of hereditary angioedema must be treated as a medical emergency.

Anaphylaxis:-

- Is a medical emergency.
- Early administration of **intramuscular epinephrine** is the mainstay of therapy and should be given at the same time that basic measures of cardiopulmonary resuscitation are being performed.
- Supplemental **oxygen** and **intravenous fluid** should be administered
- The child should be lying in **Trendelenburg** – Supine position, as tolerated, to prevent empty ventricle syndrome.
- An **airway must be secured** as intubation or tracheotomy may be required.
- Additional pharmacologic therapies, such as corticosteroids, antihistamines, H2-receptor antagonists, and bronchodilators, may be given to improve symptoms.

Summary of anaphylaxis management



Epinephrine	0.01 mg/kg IM Repeat every 5–10 min Peds EpiPen (0.15 mg)
Diphenhydramine	1 mg/kg IV/IM up to 50 mg
Ranitidine	1 mg/kg IV/IM
Cimetidine	4 mg/kg IV/IM up to 150 mg
Albuterol	2 puffs
Prednisone	1 mg/kg
Hydrocortisone	10–100 mg IV/IM
Methylprednisolone	1–2 mg/kg IV up to 125 mg
Glucagon	5–15 µg/min
Dopamine	

The first and most important therapy in anaphylaxis is epinephrine. There are **NO absolute contraindications to epinephrine** in the setting of anaphylaxis.

Airway: Immediate intubation if evidence of impending airway obstruction from angioedema. Delay may lead to complete obstruction. Intubation can be difficult and should be performed by the most experienced clinician available. Cricothyrotomy may be necessary.

IM epinephrine (1 mg/mL preparation): Epinephrine 0.01 mg/kg should be injected intramuscularly in the mid-outer thigh. For large children (>50 kg), the maximum is 0.5 mg per dose. If there is no response or the response is inadequate, the injection can be repeated in 5 to 15 minutes (or more frequently). If epinephrine is injected promptly IM, patients respond to one, two, or at most, three injections. If signs of poor perfusion are present or symptoms are not responding to epinephrine injections, prepare IV epinephrine for infusion (refer to below).

Place patient in recumbent position, if tolerated, and elevate lower extremities.

Oxygen: Give 8 to 10 L/minute via facemask or up to 100% oxygen, as needed.

Normal saline rapid bolus: Treat poor perfusion with rapid infusion of 20 mL/kg. Re-evaluate and repeat fluid boluses (20 mL/kg), as needed. Massive fluid shifts with severe loss of intravascular volume can occur. Monitor urine output.

Albuterol: For bronchospasm resistant to IM epinephrine, give albuterol 0.15 mg/kg (minimum dose: 2.5 mg) inhaled via nebulizer. Dilute in saline if using a concentrated albuterol solution (≥0.5%). Repeat, as needed.

H1 antihistamine: Consider giving diphenhydramine 1 mg/kg (max 50 mg IV, over 5 minutes) or cetirizine (children aged 6 months to 5 years can receive 2.5 mg IV, those 6 to 11 years of age can receive 5 or 10 mg IV, over 2 minutes).

H2 antihistamine: Consider giving famotidine 0.25 mg/kg (max 20 mg) IV, over at least 2 minutes.

Glucocorticoid: Consider giving methylprednisolone 1 mg/kg (max 125 mg) IV.

Monitoring: Continuous noninvasive hemodynamic monitoring and pulse oximetry monitoring should be performed. Urine output should be monitored in patients receiving IV fluid resuscitation for severe hypotension or shock.

- Up to 30% of people with anaphylaxis have **biphasic** or **protracted** anaphylaxis.
- A person with **biphasic anaphylaxis** has both early- and late-phase reactions. The biphasic reaction is a recurrence of anaphylactic symptoms after an initial remission, occurring within 8-72 hours after the initial reaction.
- A person with **protracted anaphylaxis** has signs and symptoms that persist for hours or even days despite treatment, although this is rare.

PREVENTION

- Recommendations for avoidance is suggested for patients following severe reactions or anaphylaxis.
- Skin testing and serum IgE-specific testing are available for foods, inhalants, insect venoms, drugs (penicillin), vaccines, and latex.
- Educating the patient and family members about the signs and symptoms of anaphylaxis and using auto-injectable epinephrine early result in better outcomes.

- **Fatal anaphylaxis has occurred despite timely and appropriate treatment.**
- Medical informational jewelry with appropriate information should be worn.
- Medications such as **β-blockers**, **angiotensin-converting enzyme inhibitors**, and **monoamine oxidase inhibitors** should be discontinued because they may exacerbate anaphylaxis or interfere with its treatment.

Thanks