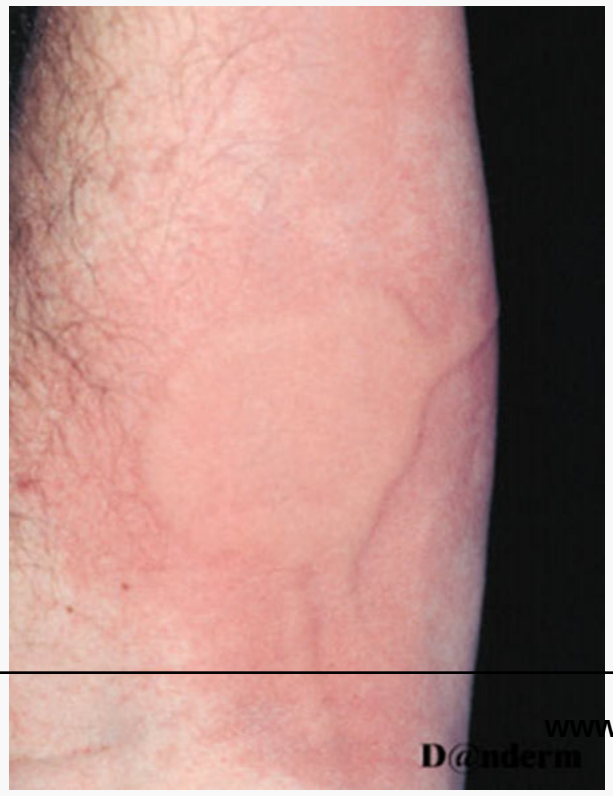
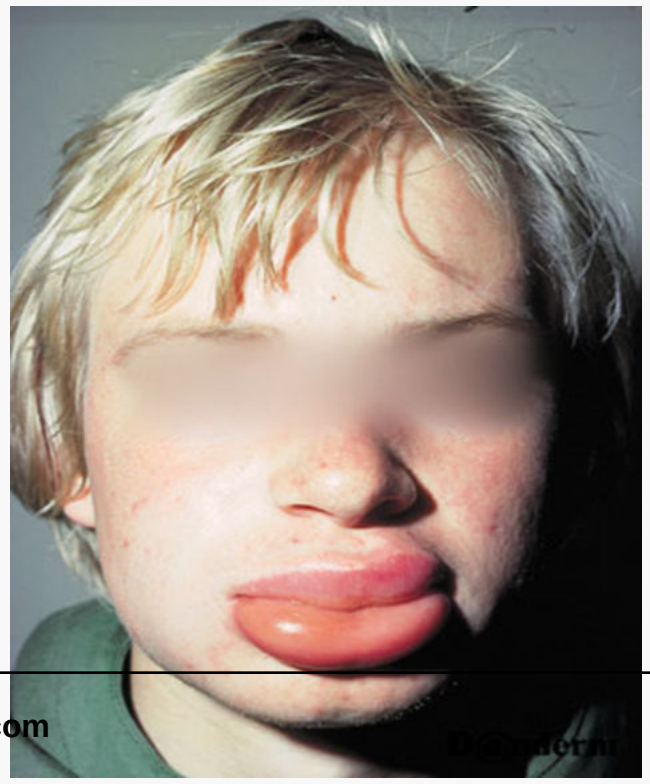
# URTICARIA & ANGIOEDEMA

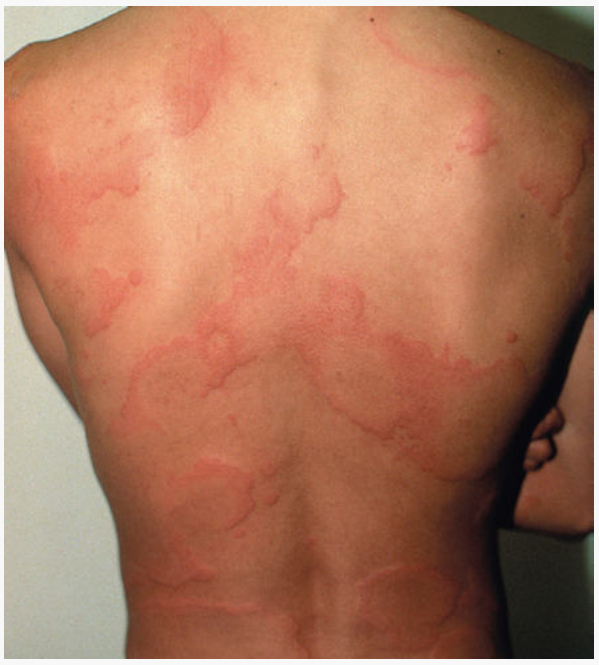
- Urticaria is characterized by transient skin or mucosal swellings due to plasma leakage.
- Superficial dermal swellings are wheals
- Deep swellings of the skin or mucosa are angioedema



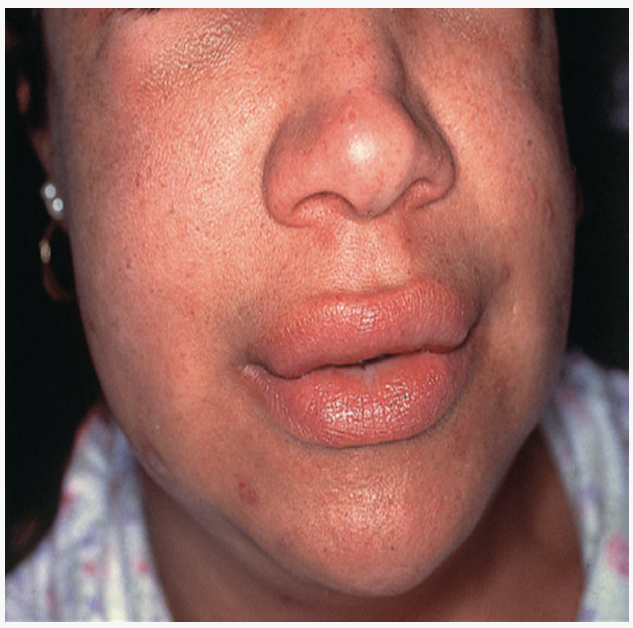
# WHEALS

- Pruritic, pink/ red/pale swellings of the superficial dermis
- ± Initial flare
- Few millimeters to several centimeters
- Number: few to numerous.
- Hallmark : individual lesions come and go rapidly, by definition, in general within 24 hours.



# ANGIOEDEMA

- Swellings occur deeper in the dermis/subcutaneous/submucosal tissue.
- May affect the mouth rarely, the bowel.
- Involved areas : normal or faint pink in color, rather than red
- Painful rather than itchy,
- Larger and less well defined than wheals
- Often last for 2 to 3 days



| ETIOLOGIES AND PATHOMECHANISMS OF URTICARIAL LESIONS |
|---|
| IDIOPATHIC |
| IMMUNOLOGIC |
| • Autoimmune (autoantibodies against FcεRI or IgE)<br>• IgE-dependent (allergic)<br>• Immune complex (vasculitic)<br>• Kinin- and complement-dependent (C1 esterase inhibitor deficiency) |
| NON-IMMUNOLOGIC |
| • Direct mast cell-releasing agents (e.g. opiates)<br>• Vasoactive stimuli (e.g. nettle stings)<br>• Aspirin, other nonsteroidal anti-inflammatory drugs, dietary pseudoallergens<br>• Angiotensin-converting enzyme inhibitors |

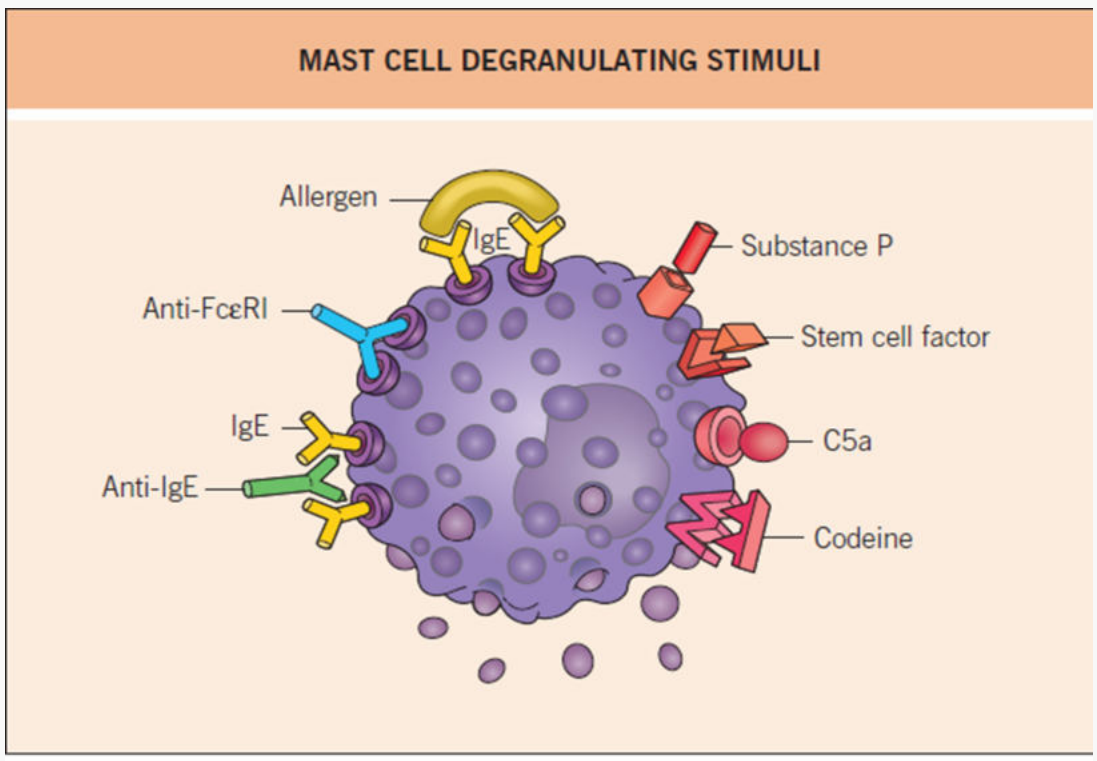



**Fig. 18.3 Mast cell degranulating stimuli.** Both immunologic and non-immunologic stimuli can lead to release of mediators. Stem cell factor is also known as KIT ligand.

1. **Classic immediate hypersensitivity** binding of receptor-bound specific IgE by allergen.

- Others: stimuli that act through the IgE receptor

2. anti-IgE and

3. anti-FcεRI antibodies

4. **Non-immunologic stimuli**:

opiates, C5a anaphylatoxin, stem cell factor,some neuropeptides(e.g. substance P)

- cause mast cell degranulation by binding specific receptors, independent of the FcεRI

# PATHOGENESIS

- The **mast cell** is the primary effector cell of urticaria.
- **Degranulation**:

1. Cross-linking of two or more adjacent FcεRI on the mast cell membrane
2. initiate a chain of calcium- and energy-dependent steps
3. fusion of storage granules with the cell membrane and externalization of their contents.

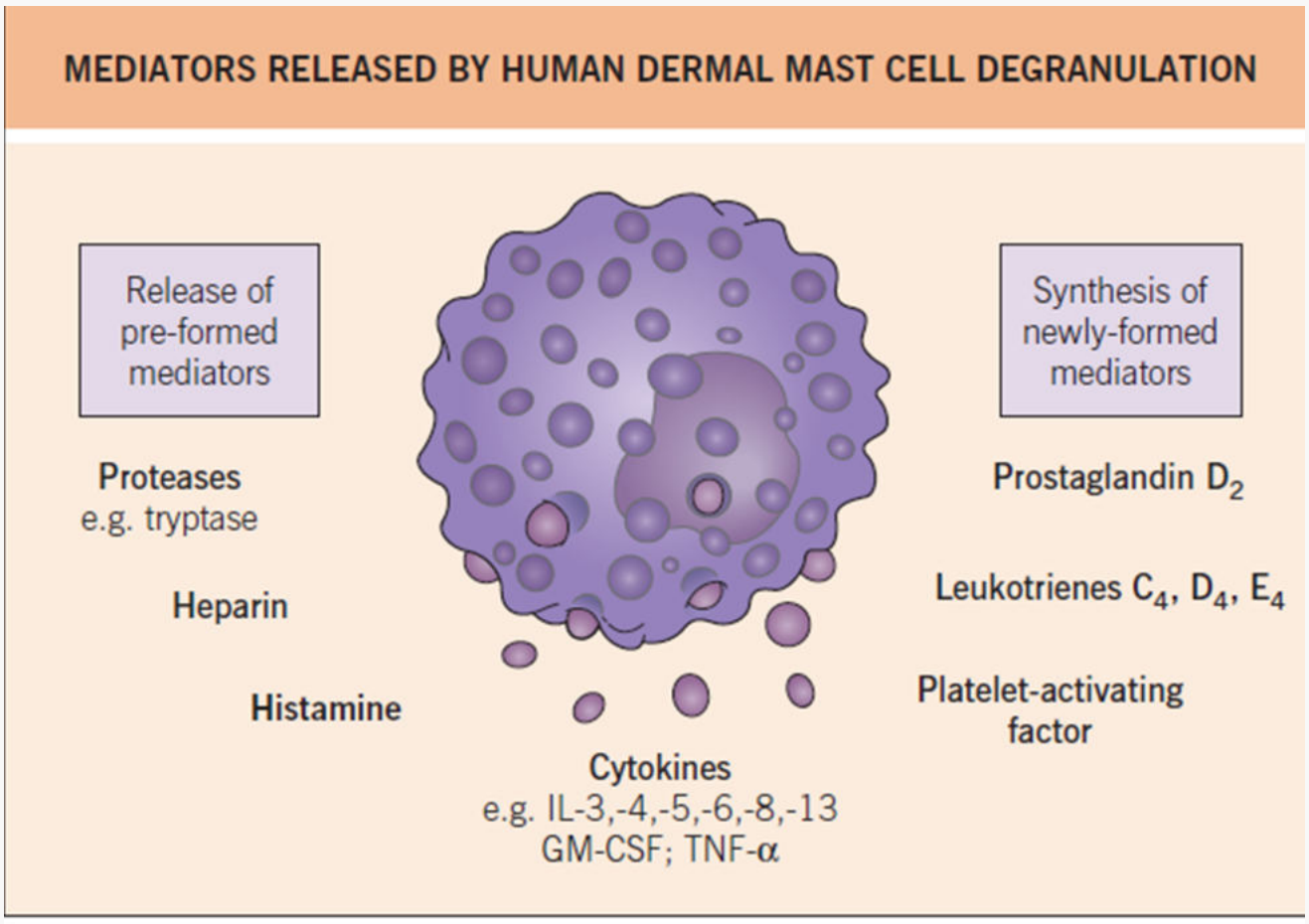



**Fig. 18.4** Mediators released by human dermal mast cell degranulation. Both preformed and newly synthesized proinflammatory mediators are released from mast cells.

# PATHOGENESIS

- **Basic pathology - ↑ capillary permeability,** allowing proteins and fluids to extravasate to the dermis.

1. Histamine and other proinflammatory mediators released on degranulation »

Bind receptors on postcapillary venules in the skin »

Vasodilation and increased permeability to large plasma proteins (albumin and immunoglobulins).

2. Histamine, TNF-α and IL-8 upregulate adhesion molecules on endothelial cells, promoting the migration of inflammatory cells into the urticarial lesion.

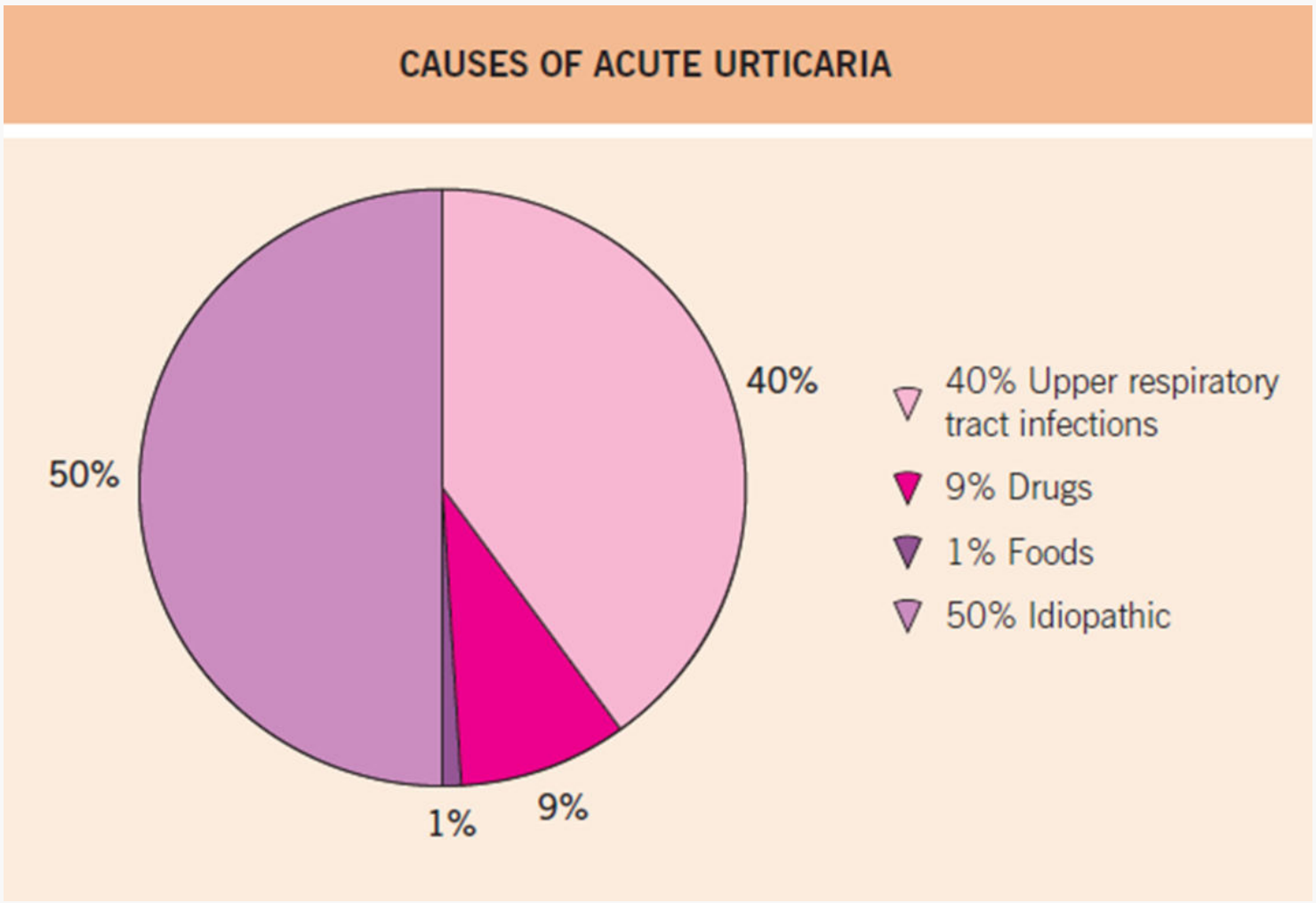
# CLINICAL CLASSIFICATION OF URTICARIA AND ANGIOEDEMA

1. "Ordinary" (spontaneous) urticaria
2. Physical (inducible) urticarias
3. Urticarial vasculitis (vasculitis on skin biopsy)
4. Contact urticaria (induced by percutaneous or mucosal penetration)
5. Angioedema without wheals
6. Distinctive urticarial syndromes

# ACUTE vs CHRONIC URTICARIA

- All urticarias are acute initially
- "Chronic urticaria": usually defined as 6 weeks or more.

  Applied to continuous urticaria occurring at least twice a week off treatment for ≥ 6 weeks
- Urticaria occurring ≤ 6 weeks is called episodic / recurrent



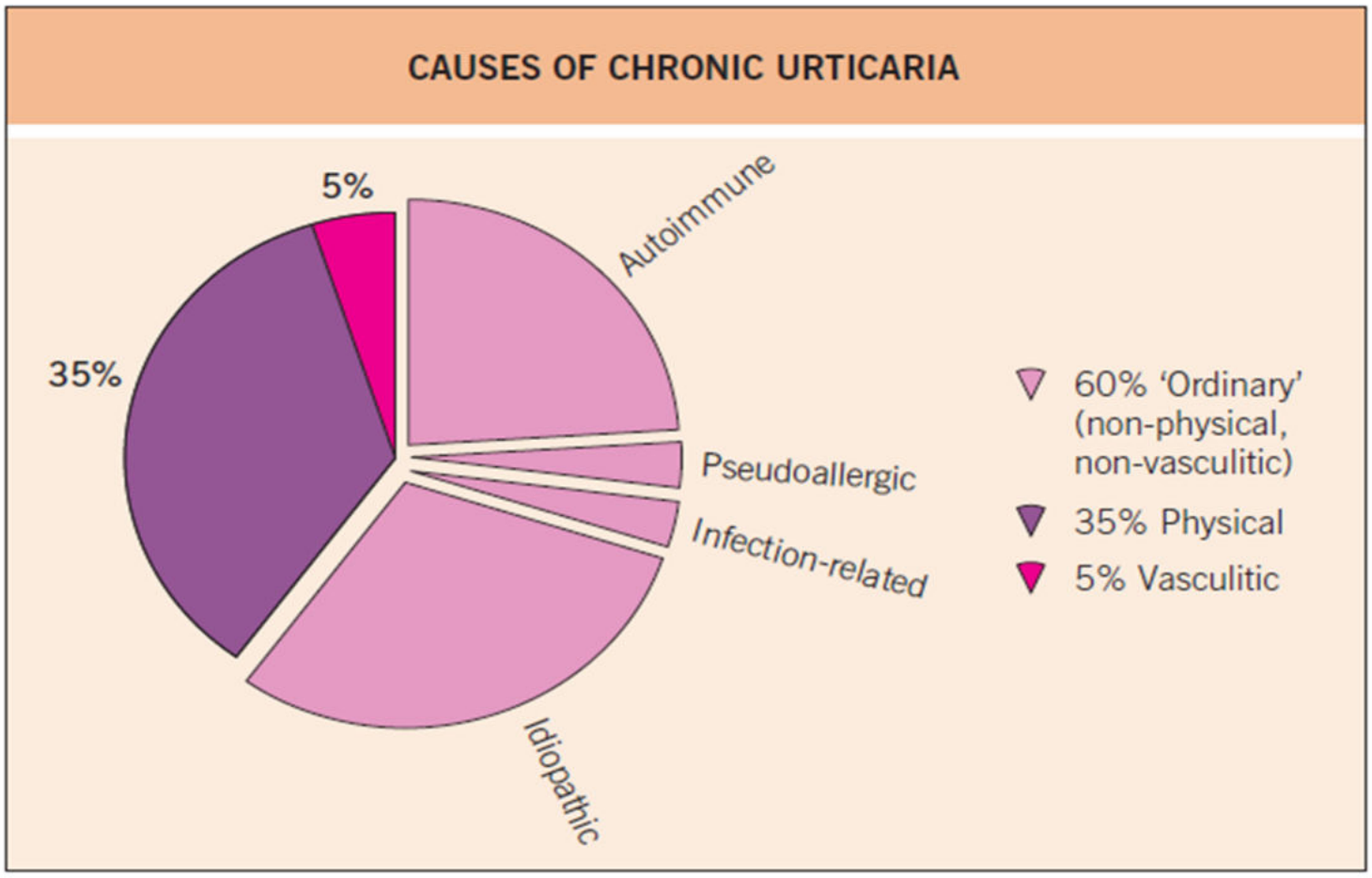



**Fig. 18.8** Causes of chronic urticaria. Autoimmune represents those patients with functional autoantibodies against FcεRI or the Fc portion of IgE.

# ASSOCIATIONS OF CHRONIC URTICARIA

- Autoimmune thyroid disorders
- Vitiligo
- Insulin dependent diabetes
- Rheumatoid arthritis
- Pernicious anemia
- Helicobacter pylori gastritis
- Intestinal strongyloidiasis(endemic countries)
- ???Dental infections or gastrointestinal candidiasis

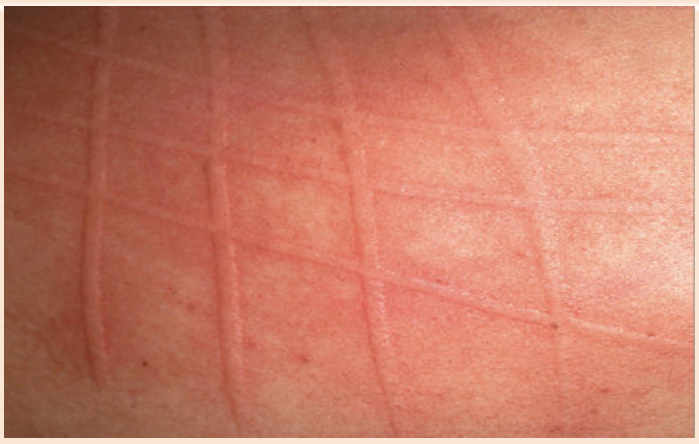
# CLASSIFICATION OF PHYSICAL URTICARIA

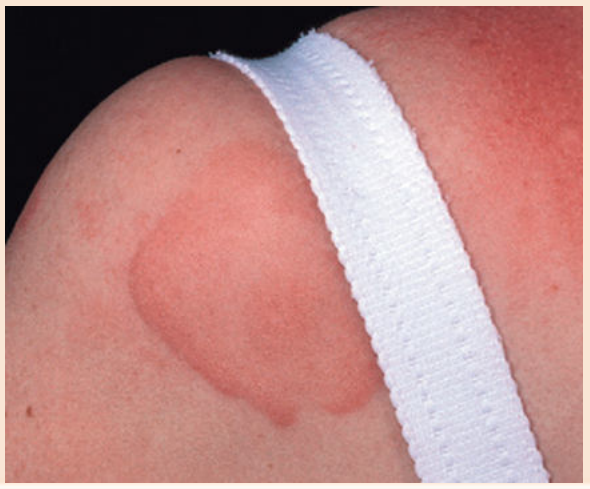
## URTICARIA DUE TO MECHANICAL STIMULI

Dermographism
- Immediate
  - Simple
  - Symptomatic
- Delayed

Delayed pressure urticaria

Vibratory angioedema
- Inherited
- Acquired





# CLASSIFICATION OF PHYSICAL URTICARIA

## URTICARIA DUE TO TEMPERATURE CHANGES

Heat
- Heat contact urticaria

Cold
- Cold contact urticaria
  - Primary
  - Secondary (cryoglobulins, cryofibrinogen)

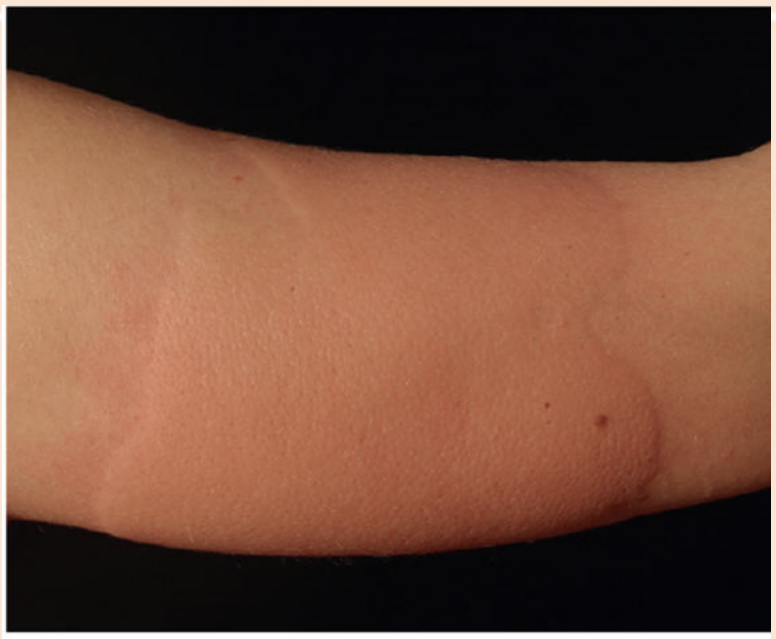
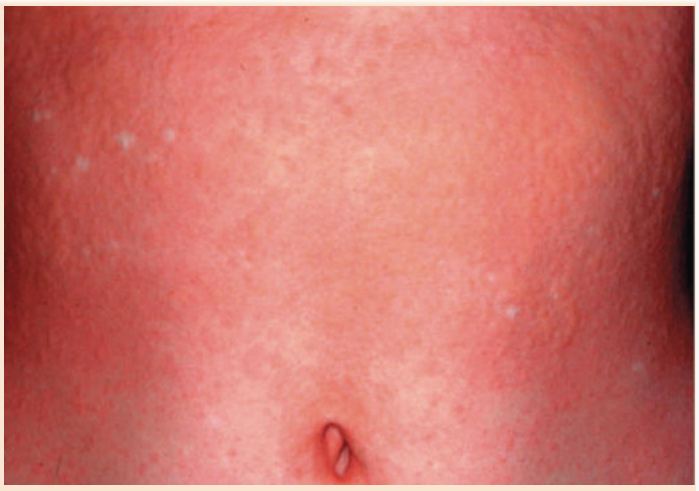


**Fig. 18.11** Cold urticaria. Wheals developed on the forearm after placement of an ice cube for 10 minutes, followed by rewarming. *Courtesy, Thomas Schwarz, MD.*

# CLASSIFICATION OF PHYSICAL URTICARIA

## URTICARIA DUE TO SWEATING OR STRESS

Cholinergic urticaria
Adrenergic urticaria
Exercise-induced urticaria
- Exercise-induced anaphylaxis
- Food- and exercise-induced anaphylaxis

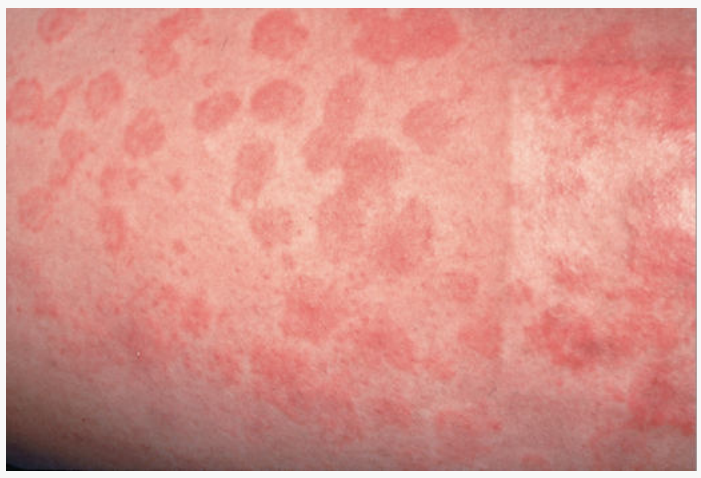


## SOLAR URTICARIA

## AQUAGENIC URTICARIA

# URTICARIAL VASCULITIS

1. Favors middle-aged women
2. Urticarial lesions >24 hours in duration; painful & burning sensation as well as pruritus;
3. Residual purpura as they resolve
4. Sites: often occur at pressure points
5. Concurrent angioedema :up to 40% of pts
6. Disease course: average of 3 years



# EXTRACUTANEOUS MANIFESTATIONS OF URTICARIAL VASCULITIS

1. Arthralgias (50%) – transient, migratory
2. GI (20%) – abdominal pain, nausea, vomiting, diarrhea
3. Pulmonary obstructive disease (20%)
4. Renal (5–10%) – proteinuria, hematuria
5. Ocular (unusual) – conjunctivitis, episcleritis, uveitis
6. Others - Raynaud's phenomenon, livedo reticularis, splenomegaly, lymphadenopathy, idiopathic intracranial HTN, pericardial or muscle involvement

# ASSOCIATED DISORDERS OF URTICARIAL VASCULITIS

- Systemic lupus erythematosus
- Sjögren's syndrome
- Serum sickness
- Cryoglobulinemia
- Infections – hepatitis B or C virus, Epstein-Barr virus
- Rarely, solar or cold urticaria, drugs, hypergammaglobulinemia

# CONTACT URTICARIA

- Development of urticaria at the site(s) of contact of urticant with skin or mucosa
- Percutaneous or mucosal penetration of the urticant may have distant effects, including acute urticaria or even anaphylaxis
- Immunologic and non-immunologic forms are recognized

# CONTACT URTICARIA

- Immunologic: sensitized to environmental allergens (grass, animals and foods) or in glove-wearers (latex).
- Non immunologic:
  - Percutaneous microinjection of vasomediators (histamine,acetylcholine, serotonin) via nettle stings
  - contact with histamine liberators that degranulate mast cells (dimethylsulfoxide,cobalt chloride)

# FOOD CONTACT HYPERSENSITIVITY SYNDROME

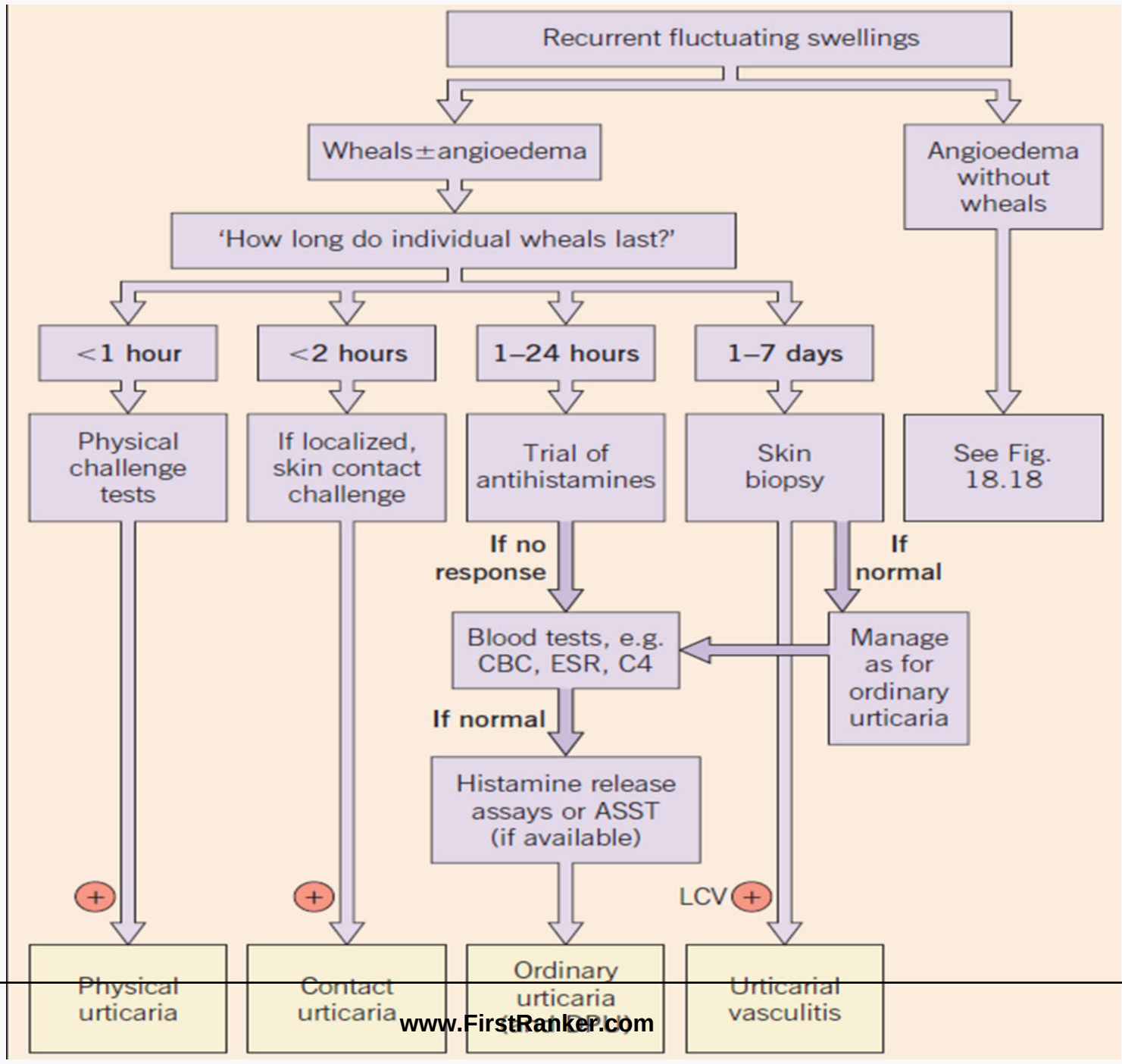
- Itching and mild swelling of the mouth, tongue and soft palate within minutes of eating fresh fruits but not cooked fruit
- apples, pears, peaches and cherries,

# DIAGNOSIS

- Comprehensive history
- Duration of individual lesions, presence of purpura
- Weals lasting more than 24–48 h, particularly if painful or tender, suggest urticarial vasculitis
- Frequency of attacks, duration of disease, previous treatment, known triggers
- Past and family history,
- Occupation and leisure activities,

# DIAGNOSIS

- Assessment of the impact of the disease on the patient's quality of life.
- Asso. angio-oedema (eg. Oropharynx result in difficulty in swallowing or breathing)
- Systemic symptoms
- Recent acute infection, drugs, non-prescription and prescription medicines, food



# INVESTIGATIONS

- Rule out Infections
- Complete blood count
- Stool for ova, cysts and parasites
- Thyroid autoab, Thyroid function tests
- C4 complement (angio-oedema without weals)
- Non-organ specific autoantibodies (eg ANA)
- Basophil histamine release assay / basophil activation tests
- Helicobacter pylori (stool antigen or urea breath test)
- Chest X-ray
- 25-hydroxycholecalciferol (vitamin D)

# TREATMENT

- Detection and avoidance of the cause.
- First line therapies (H1 antihistamines)

  minimal dosing which control episodes.

  H1 – non sedating day time, sedating at night.

  A combination of an H1 antihistamine with

  an H2 antagonist may be more effective than H1 antihistamines alone in some patients

## ANTIHISTAMINES FOR URTICARIA

| Class | Examples | Plasma half-life (hours) | Daily adult dose* |
|---|---|---|---|
| Classic (sedating) $H_1$ antihistamines | Chlorpheniramine (1) | 12–15 | 4 mg three times daily (up to 12 m night) |
| | Hydroxyzine (1) | 20 | 10–25 mg three times daily (up to 75 mg at night) |
| | Diphenhydramine (2) | 4 | 10–25 mg at night |
| | Doxepin† (1) | 17 | 10–50 mg at night |
| Second-generation $H_1$ antihistamines | Acrivastine‡ (1) | 2–4 | 8 mg three times daily |
| | Cetirizine§(1) | 7–11 | 10 mg once daily |
| | Loratadine (1) | 8–11 | 10 mg once daily |
| | Mizolastine‖ (1) | 13 | 10 mg once daily |
| Newer second-generation $H_1$ antihistamines | Desloratadine (1) | 19–35 | 5 mg once daily |
| | Fexofenadine (1) | 17 | 180 mg once daily |
| | Levocetirizine (1) | 7–10 | 5 mg once daily |
| | Rupatadine (1) | 6 | 10 mg once daily |
| $H_2$ antagonists¶ | Cimetidine (1) | 2 | 400 mg twice daily |
| | Ranitidine (2) | 2–3 | 150 mg twice daily |

# TREATMENT

Second line therapies (targeted therapy)

- Oral corticosteroids
- Leukotriene receptor antagonists
- Doxepin,
- Danazol
- Sulphasalazine and dapsone

| SECOND-LINE MEDICATIONS FOR CHRONIC OR PHYSICAL URTICARIA | | | |
|---|---|---|---|
| Generic name | Drug class | Route | Dose |
| Prednisone (2) | Corticosteroid | Oral | 0.5 mg/kg daily |
| Epinephrine (2) | Sympathomimetic | Subcutaneous, IM (self-administered) | 300–500 mcg |
| Montelukast (3) | Leukotriene receptor antagonist | Oral | 10 mg daily |
| Thyroxine (2) | Thyroid hormone | Oral | 50–150 mcg daily |
| Colchicine (3) | Neutrophil inhibitor | Oral | 0.5/0.6–1.5/1.8 mg* daily |
| Sulfasalazine (3) | Aminosalicylates | Oral | 2–4 g daily |

# THANK YOU