Urticaria (Hives) — Definition and Treatment

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Urticaria is a very common dermatological condition, which is classified into acute urticaria and chronic urticaria based on duration of symptoms. Etiology is different for acute and chronic urticaria. Diagnosis requires thorough history taking and physical examination, laboratory evaluation may be helpful depending upon underlying etiology. In this article, etiology, pathophysiology, clinical features, diagnosis, differential diagnosis, and management of urticaria will be discussed.

Definition and Epidemiology of Urticaria

Wheals (hives or “nettle rash”) are the hallmark lesions in urticaria. Wheals are self-limiting, superficial, erythematous or pale, raised lesions due to edema of dermis and epidermis. Urticaria lasting up to six weeks is called acute urticaria, while that lasting for more than six weeks is called chronic urticaria.

Urticaria is the most common dermatologic disorder seen in emergency department. About 15 to 20 % of general population experiences acute urticaria during their life time, while life-time incidence of chronic urticaria is 2-3 %. Chronic urticaria is more common in females.
Etiology of Urticaria

Etiology of acute and chronic urticaria is different.

Acute urticaria

- **Allergy**
  - Foods: fish, shellfish, eggs, nuts, milk, soy
  - Drugs: penicillins, cephalosporins
  - Insect venom: bee stings, wasp stings
  - Inhalants: house dust mites, pollens, molds, animal danders
  - Miscellaneous: blood products, implants, contactants
  - As part of anaphylaxis

- **Infections**
  - Upper respiratory tract infections, pharyngitis, urinary tract infections, gastrointestinal infections
  - Viral infections (Epstein-Barr virus, hepatitis B virus, HIV, coxsackievirus)
  - Fungal infections
  - Bacterial infections (streptococcal infections, campylobacter jejuni, mycoplasma)
  - Parasitic infections (anisakiasis, ascariasis, strongyloidiasis)
  - Post-infectious (following non-specific viral infections)

- **Non-allergic**
  - Non-IgE-mediated histamine release: polymyxin, vancomycin, opioids, atracurium, radiocontrast media, dextrans
  - Pseudoallergic reactions: aspirin, other NSAIDs, alcohol, foods rich in vasoactive amines (cheese, fish, tomatoes, pineapples, etc.), food additives (tartrazine, other azo dyes, benzoates, sulphites, monosodium glutamate, aspartate, etc.)
  - Physical urticarias
  - Hormonal changes: pregnancy, menstrual or pre-menstrual period
  - Emotional stress
  - Idiopathic

Chronic urticaria

- **Autoimmune**
  - Autoantibodies against α-subunit of FcεRI (most common)
  - Anti-IgE antibodies

- **Infections**
  - Helicobacter pylori
  - Candida infections
  - Intestinal helminth, dental sepsis, sinusitis, urinary tract infections, cholecystitis, toxocara canis, urticarial vasculitis
  - Parenteral antisera, penicillins, radiocontrast media, hepatitis B
  - Associated with other medical disorders

- **Autoimmune disorders** (systemic lupus erythematosus, thyroiditis, rheumatoid arthritis, vitiligo, pernicious anemia, celiac disease, etc.)

- **Hypo- or hyperthyroidism
- Malignancies, lymphoma

**Amyloidosis**

- **Mastocytosis, urticaria pigmentosa** (cutaneous mastocytosis)
- Idiopathic – also called chronic spontaneous urticaria (CSU)

*Note:* In more than half of chronic urticaria, exact etiology cannot be identified.

**Pathology and Pathophysiology of Urticaria**

Basic pathophysiology for development of urticaria involves **extravasation of fluid in dermis and epidermis** due to release of vasoactive substances from cells, most commonly mast cells and basophils.

**Histamine** is the most important vasoactive substance; stimulation of $H_1$ receptors on endothelial and smooth muscle results in increased capillary permeability, while that of $H_2$ receptors dilatation of arterioles and venules. Other vasoactive substances include **bradykinin, leukotriene C4**, and **prostaglandin D2**.

Typical allergic urticarias involve **IgE-mediated histamine release** (type I hypersensitivity), while urticarial vasculitis involve **cytotoxic T cell-mediated responses** (type II hypersensitivity).

Urticarias associated with autoimmune conditions involve **immune complex-mediated reactions** (type III hypersensitivity), while urticarias associated with some infections and transfusion reactions involve complement system.

**Symptoms of Urticaria**

**Duration of urticarial lesion** (> 24 hours in urticarial vasculitis and delayed pressure urticaria), and **detailed history of triggers** (allergic, pseudoallergic, and physical urticaria) are most important characteristics that give clues towards etiology. Although cholinergic urticarias are typically **papular urticaria**, shape or size of lesions are not always suggestive of etiology.

Image: “Hives on back.” by DLdoubleE – Own work. License:
Urticarias occur as **erythematous macules** developing into edematous raised skin lesions, usually accompanied by **significant itching** and are self-limiting (usually < 24 hours).

The lesions classically have **central pallor** with surrounding **red flare**. Lesions can be **single or multiple**, can be of **variable size** (tiny to large lesions) and **shapes** (linear, annular, serpiginous, or irregular), and can occur **anywhere on body surface**. They are usually **transient**, may be **migratory or coalescent**, typically **blanch with pressure**, and leave normal skin after resolution.

**Angioedema** is simultaneously present in half of the patients with urticaria. Urticaria may be accompanied by systemic symptoms such as malaise, feelings of heat or cold, **headache**, pain in abdomen, vomiting, **diarrhea**, arthralgia, dizziness, etc.

**Acute allergic urticaria** develops within minutes (not more than one hour) after exposure to food, drug, insect sting, or other substance causing IgE-mediated allergic reaction. Acute urticaria due to inhalant allergy is rare.

Acute urticaria may occur as a **symptom of anaphylaxis** due to severe allergic reaction to an allergen. **Food-dependent exercise-induced anaphylaxis** (FDEIA) is a condition when allergic reaction occurs only if intake of a food allergen is followed by exercise.

Acute urticaria due to **pseudoallergic reaction** or **non-IgE-mediated histamine release** clinically resembles acute allergic urticaria, but the mechanism does not involve IgE antibodies.

Clinically, wheals in chronic urticaria are similar to those seen in acute urticaria. Features of underlying autoimmune or other medical disorder may be present. Physical urticarias are also simultaneously present in many patients with **idiopathic or autoimmune chronic urticaria**.

**Chronic urticaria** may be aggravated by non-specific viral infections, upper respiratory tract infections, drugs (aspirin, other NSAIDs, ACE inhibitors), alcohol, dietary pseudoallergens, physical factors, emotional stress, and hormonal changes.

**Physical urticarias** occur as both acute and chronic urticaria. In this group, wheals develop within minutes of exposure to physical factors such as cold temperature, heat, vibration (vibratory urticaria), pressure (pressure urticaria), water (aquagenic urticaria), or sunlight (solar urticaria).

Among cold urticarias, **idiopathic immediate cold contact urticaria** is most common, which is characterized by development of wheals immediately on exposure of skin to cold stimuli such as cold objects, cold winds, or cold rain. **Systemic symptoms** like flushing, palpitation, headache, wheezing, loss of consciousness may be present; edema of mouth or pharynx can develop after exposure to cold drinks/foods.

Other cold urticarias include **delayed cold contact urticaria** (development of wheals after a few hours after contact with cold), **familial cold urticaria, localized cold contact urticaria, acquired cold contact erythema** (painful erythema without whealing), and **generalized reflex cold urticaria** (widespread wheals in response to reduced core body temperature).

Cold urticaria may also be seen in some patients with **cryoglobulinemia, collagen vascular disease, chronic lymphatic leukemia, myeloma, infectious mononucleosis**.
Cholinergic urticaria is a physical urticaria characterized by development of typical small wheals in association with sweating or raised core body temperature. It is more common in adolescents, during winter months, and is aggravated by emotional stress and spicy foods. Heat contact urticaria develops in response to localized warming of skin.

Delayed pressure urticaria is characterized by development of wheals at sites of sustained pressure after 30 minutes to a few hours of delay. Unlike other types of urticarias, wheals last longer (up to 72 hours) and are painful or tender than itchy.

Immediate symptomatic dermographism, the most common form of dermographism, is characterized by development of exaggerated wheal-and-flare reaction along with itching in response to firm stroking of skin. It is more common in young adults.

Other forms of dermographism include red dermographism (development of punctate wheals in response to repeated rubbing), cholinergic dermographism (development of erythematous line containing punctate wheals after firm stroking of skin), and delayed dermographism (return of wheal after fading of normal wheal-and-flare response, persisting up to 48 hours).

Development of wheal following friction is called “Darier’s sign”, seen in urticaria pigmentosa (cutaneous mastocytosis).

Urticarial vasculitis is characterized by urticarial lesions that last for > 24 hours that may be painful, tender, or burning and may resolve with residual hyperpigmentation.

Systemic symptoms like migratory arthralgia, gastrointestinal symptoms (nausea, vomiting, abdominal pain), pulmonary involvement (cough, wheezing), renal involvement (proteinuria, hematuria, nephritis), fever, lymphadenopathy, splenomegaly, are usually present. The syndrome develops as serum sickness-like syndrome after 1-3 weeks of exposure to etiologic agent and lasts for 1-4 weeks.

**Diagnosis of Urticaria**

Due to variable etiology, a thorough history and complete physical examination are necessary for diagnosis of urticaria. In addition to details of urticaria and symptoms related to different systems, history must also include possible triggers, drug history, and family history.

Clinical history and examination is usually sufficient to diagnose acute urticaria and laboratory investigations may not be necessary.
Challenge tests for physical urticaria

Dermatographic urticaria (“skin writing”). Done by writing the “invisible” letters with an empty ball-point pen and waiting for a couple of minutes. by Mysid - Own hand, own photo. License: Public Domain

Dermographism: development of wheal within minutes in response to stroking of skin with a blunt object or with a calibrated dermographometer at \( \leq 36 \text{ g/mm}^2 \)

- **Cholinergic urticaria**: development of wheals within minutes in response to increasing core body temperature by 0.7-1.0°C by either exercising in warm environment or after taking a hot (42°C) bath for 15 minutes
- **Cold urticaria (contact)**: development of urticaria within minutes after application of an ice-containing plastic bag for up to 20 minutes
- **Cold urticaria (generalized reflex)**: development of urticaria within minutes in response to exposure to cold room (4°C) environment for 30 minutes
- **Heat contact urticaria**: Development of urticaria within minutes after application of an heated (39-45°C) object for 2-5 minutes
- **Solar urticaria**: development of urticaria within minutes in response to exposure to sunlight or solar simulator
- **Aquagenic urticaria**: development of urticaria within minutes in response to application of water or water-soaked towel at body temperature for 15-30 minutes
- **Vibratory urticaria**: development of urticaria within minutes in response to application of a laboratory vortex resting on forearm or finger for 1-5 minutes
- **Delayed pressure urticaria**: development of urticaria within 24 hours after application of sustained pressure over back, shoulder, or thigh using a hanging weight or calibrated dermographometer at 100 g/mm\(^2\)

In patients with chronic urticaria, after a thorough history and physical examination, basic laboratory evaluation includes **complete blood counts, erythrocyte sedimentation rate (ESR), thyroid function tests**, and **antinuclear antibodies (ANA)**. Other useful investigations are as follows, which are performed depending upon clinical features:

- Evaluation for **serum cryoglobulins** in patients with cold urticaria
- **Allergy evaluation** for patients with suspected allergies
- Appropriate pathological and microbiological evaluation for suspected...
infections
- Anti-IgE, anti-FcεRI antibodies and autologous serum skin test (ASST) for autoimmune urticaria
- **Punch biopsy** from urticarial lesion in suspected urticarial vasculitis, which would suggest leukocytoclastic vasculitis

Differential diagnoses
- Acute contact dermatitis
- Atopic dermatitis
- Urticarial drug reactions
- Drug eruptions/non-urticarial drug reactions
- Erythema multiforme
- **Henoch-Schonlein purpura** and other causes of purpura
- Pityriasis rosea

Therapy of Urticaria

**H₁-antagonists** are used as first line treatment of urticaria. **Non-sedating second generation antihistamines** (levocetirizine, fexofenadine, loratadine, desloratadine) are preferred over sedating first generation antihistamines (diphenhydramine, hydroxyzine). To achieve symptom control, dose of a non-sedating antihistamine is uptitrated to up to four-fold, after which a first generation antihistamine can be added to the treatment regimen.

If H₁-antagonists cannot control symptoms, second-line add-on drug options include **H₂-antagonists** (cimetidine, ranitidine, famotidine) and **leukotriene antagonists** (montelukast). Doxepin is an **antidepressant** with combined H₁- and H₂-antagonist effects, used in treatment of refractory urticarias.

**Drugs with immunomodulatory effects** like cyclosporin, mycophenolate mofetil, methotrexate, colchicine, dapsone, and hydroxychloroquine can be used in treatment of refractory urticaria. Omalizumab has been found to be effective in some patients with chronic urticaria. Other drugs/therapies that have can be tried are **ultraviolet B, PUVA, intravenous immunoglobulin** (IVIG), plasmapheresis, etc.

**Oral glucocorticosteroids** are effective, but should not be used in treatment of urticaria except as short courses in management of exacerbations.

**Topical cooling moisturizing applications** are helpful to reduce itching. Topical corticosteroids have no role.

H₁-antihistamines are usually effective in treatment of physical urticarias. **Ultraviolet B therapy** at suberythrogenic doses may additionally improve symptomatic dermographism. Danazol, stanozolol, **beta blockers**, and omalizumab have been used in treatment of cholinergic urticaria. A short course of prednisolone is effective in severe delayed pressure urticaria.

Tolerance can be induced by **repeated controlled exposure to physical factor** like cold, heat, or ultraviolet light (solar urticaria). **Intravenous immunoglobulin and cyclosporin** have been found useful in solar urticaria.

When urticaria occurs as a symptom of **anaphylaxis**, emergency management of anaphylaxis including **intramuscular epinephrine** is necessary. Etiological condition
underlying acute or chronic urticaria should be treated. Avoidance of allergens and avoidance of non-allergic triggers is important in patients when they are known or identified.

Prognosis of Urticaria

Prognosis depends upon the cause of urticaria. Idiopathic chronic urticarias and physical urticarias tend to undergo remission after a variable period ranging from a few months to 6-9 years.

Review Questions on Urticaria

The correct answers can be found below the references.

1. Which of the following physical urticarias are characterized by urticarial lesions that last longer than 24 hours?
   A. Idiopathic cold contact urticaria
   B. Cholinergic urticaria
   C. Delayed pressure urticaria
   D. Solar urticaria
   E. Vibratory urticaria

2. Which of the following infections is known to be associated with chronic urticaria?
   A. Epstein-Barr virus infection
   B. Streptococcal pharyngitis
   C. Campylobacter jejuni gastroenteritis
   D. Staphylococcal skin infection
   E. Helicobacter pylori gastritis

3. Urticarial lesions in which of the following conditions are most likely to resolve with residual hyperpigmentation?
   A. Acute drug allergy
   B. Urticarial vasculitis
   C. Chronic idiopathic urticaria
   D. Solar urticaria
   E. Chronic autoimmune urticaria

References


Urticaria via medscape.com

Correct answers: 1C, 2E, 3B

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