# Mechanisms underlying urticaria

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***Urticaria, a clinically distressing disorder, is dermal oedema resulting from vascular dilatation and leakage of fluid into surrounding tissue, often in response to histamine (and other mediators) released from mast cells. A clear history of events surrounding the onset, together with laboratory investigations, in some cases allows us to find a cause and eliminate it.***

Urticaria is a common disorder in childhood, and may be very alarming. Short-lived swellings or 'weals' (also called 'nettle rash' or 'hives') appear anywhere on the body. Although these usually last less than 24 hours, new lesions appear in different sites, so the symptoms continue, either continuously or intermittently. 'Acute' urticaria lasts less than 6 weeks, whereas if it persists it is termed 'chronic' urticaria (Kobza-Black and Champion, 1997). In urticaria there is dermal oedema. If the deeper subcutaneous tissues are affected, angio-oedema results. This often affects the mucous membranes (lips, tongue, larynx, eyes and genitalia) but may affect any region. Fifty per cent of patients with angio-oedema also have urticarial weals. Rarely, the reaction becomes systemic and anaphylaxis may occur.

## MECHANISMS UNDERLYING URTICARIA

Mast cells play a major role in the development of urticaria. When stimulated, mast cells release histamine and other vasoactive mediators from granules in their cytoplasm. This leads to vasodilatation and increased vessel permeability, causing the weals seen in urticaria. The immediate response lasts only half an hour, but 'chemoattractant' substances (e.g. cytokines and platelet-activating factor) are released at the same time. These prolong the response by inducing expression of endothelial adhesion molecules and attracting white blood cells including eosinophils into the dermis.

Mast cell stimulation occurs for a variety of reasons and maybe immunological (acute immunoglobulin E (IgE)-mediated type I hypersensitivity; autoantibody formation directed against mast cell receptors), or non-immunological (direct action on mast cells). In many cases, however, the underlying cause for the release of the mediators remains unknown, and the urticaria is known as 'ordinary' or 'idiopathic'. Kozel et al (1988) confirmed the history to be the most useful tool in finding the underlying cause of the urticaria and investigations should be guided by the history. In children, reports of success in identifying a cause for the urticaria varies from 21% (Volonakis et al, 1992) to 83% (Ghosh et al, 1993).

Pathways involved in producing urticaria are diverse, and it is easiest to consider a clinical or aetiological classification as seen in *Table 1*.

### Acute idiopathic urticaria

Neither the underlying cause nor the exact incidence of this is known, but it resolves within 6 weeks. Mortureux et al's (1998) findings suggest that in many cases in children it is presumed to follow a benign viral illness, and that 20–30% of children with acute urticaria are at risk of chronic urticaria.

### Acute type I hypersensitivity or allergic urticaria

This is an IgE-mediated response to a foreign 'allergen'. IgE is produced by plasma cells (Ishizaka, 1970) and it attaches to mast cells via its Fc or 'combining end', leaving its Fab or 'antigen binding end' dangling free. When the specific antigen (or allergen) combines with the IgE free end, the mast cell is altered and liberates its mediators into the surrounding tissue. The presence of specific IgE (i.e. previous exposure and sensitization to the antigen) is essential.

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The allergens may reach the mast cell via the blood stream from a number of routes:

- Ingestion of food, food additives and drugs, especially antibiotics and antipyretics
- Inhalation of pollen, dust, animal dander or perfumes
- Injection of drugs, vaccines or venom
- Insertion of allergens including natural rubber latex gloves for internal examinations
- Insect bites and stings (may also cause a papular urticaria)
- Infestation — parasitic, e.g. giardia lamblia, toxocara canis
- Infection — viral, bacterial and rarely fungi.

Allergies to foods may cause urticaria, angio-oedema and rarely anaphylaxis. The specific antigen is absorbed from the gut and reaches the skin mast cell via the circulation where it binds to the specific IgE. Typical foods include shellfish, nuts, beans, celery, eggs, exotic fruits (which may cross react with latex). Cows milk is the commonest food involved in children under 6 months. Food additives such as azo-dyes and preservatives are also known to cause problems in some children. Relevant allergens are demonstrated by a positive prick test, a specific radioallergosorbent test (RAST) and in some cases a challenge test may be indicated (in a paediatric department with resuscitation facilities available).

Urticaria in response to a drug usually occurs between the 6th and 10th days of therapy.

If a patient has specific IgE to bee venom, as well as the usual cutaneous response there will be urticarial swelling at the site of the sting.

**Contact urticaria:** This is a wealing reaction at sites of penetration of chemical substances throughout the epidermis or mucous membranes, which may become generalized urticaria (Krogh and Maibach, 1982).

**Allergic contact urticaria:** This results when allergens (and the list of them is long) cause IgE-mediated mast cell degranulation. It occurs preferentially in atopic individuals (70% of individuals with latex allergy are atopic). Foods are frequent eliciting agents, as are animal and plant allergens, and low molecular weight substances in the fields of medicine and industry, e.g. natural rubber latex.

Atopic individuals with sensitization to pollen suffer from cross reaction to carrots, celery, apples, hazelnuts, pitted fruits, herbs and spices. These can induce mucous membrane symptoms and anaphylaxis in addition to local urticaria, particularly when eaten raw.

**Non-allergic contact urticaria:** This condition occurs when elicitors penetrate the skin or mucous membranes to cause wealing through non-immunological mechanisms.

Elicitors of non-allergic contact urticaria include direct histamine liberators, peptides and amines and others with unknown mechanisms of action. They may cause their effect at the first exposure.

**TABLE 1.**
**Types and potential causes of urticaria**

| Type of urticaria | Diagnosis/course (history is essential) | Cause (with examples) |
|---|---|---|
| Acute idiopathic (less than 6 weeks) | If patient is well reassure/treat. No investigations necessary | Unknown |
| Chronic idiopathic (longer than 6 weeks) | Skin tests not helpful. Check eosinophilia (full blood count) and thyroid function | Unknown. 30% autoimmune *vs* mast cell high affinity IgE receptors |
| Type I hypersensitivity IgE-mediated 'allergy' | May be emergency. Consider RAST test, prick test and/or oral challenge | Allergens: foods, drugs, foreign material, all by various routes |
| Direct drug action 'Pseudo-allergic' | Consult list of known culprits | Aspirin, non-steroidal anti-inflammatory drugs |
| Direct drug action 'Non-allergic' | Consult list of known culprits | Morphine, radiocontrast media |
| Contact immunological | Skin testing with suspected antigen | Foods, drugs, animal saliva, plants, caterpillars, metals |
| Contact non-immunological | Problem substance usually obvious — avoid (and/or test) | De-novo handling ammonia, persulphate etc. |
| Physical and dermographism | Challenge with physical agent | Pressure, cold, water, sunlight, heat, cholinergic |
| Hereditary (recurrent angio-oedema) | C1 esterase inhibitor levels. C2 and C4 to screen | Autosomal dominant deficiency C1esterase inhibitor |
| Acquired C1 esterase inhibitor deficiency | C1 esterase inhibitor levels. C1 and C4 to screen | Associated with lymphoproliferative or autoimmune disease, e.g. systemic lupus erythematosis |
| Urticarial vasculitis | Affected skin histology. May be underlying systemic cause | Unknown response to vasculitis (of many different causes). Immune complex deposition |
| (Associated with internal disease) | Identify underlying illness and treat symptoms | Infections, e.g. hepatitis B. Autoimmune disease, e.g. Still's disease, thyroid, diabetes |
| Urticaria pigmentosa | Typical appearance of skin lesions, with positive Darier's sign (urticate on rubbing) | Abnormal accumulations of mast cells |

IgE = immunoglobulin E; RAST = radioallergosorbent test

Cobalt chloride, nettles, jellyfish, chicken proteins, strawberries and a topical antibiotic bacitracin have all been reported to liberate histamine directly from mast cells (Janssens et al, 1995).

Some plants and animals 'sting' with a mixture of vasoactive substances which act directly on the vessels independently of the mast cells, e.g. the plant family *Euphorbiaceae*, marine animals such as Portugese man-o'war jellyfish, caterpillars, mites, fleas and ants.

**Chronic idiopathic urticaria**

Although, by definition, no underlying cause is found for the urticaria in these patients, it is interesting that in 30%, histamine-releasing autoantibodies have been found (Grattan, 1986). The autoantibodies bind to the high-affinity IgE receptor on mast cells thus causing degranulation and urticaria.

Thyroid autoimmunity is more prevalent in patients with chronic urticaria (14%) than in population controls (6%) (Heymann, 1999). Administration of thyroid hormone may alleviate the urticaria in selected patients.

Many studies have looked for associations between chronic 'idiopathic' urticaria and chronic or occult infections. Dental infection and abscesses (Resch and Evans, 1958), candidal carriage (subclinical infection) (James and Warin, 1971) and more recently *Helicobacter pylori* (Tebbe et al, 1996) have all been proposed, but not substantiated in later studies.

**Drug-induced 'pseudo-allergic' and 'non-allergic' urticaria**

The term 'pseudo-allergic reaction' has been used to describe non-immunologically induced urticaria where the clinical manifestations mimic type I allergic reactions, but they are not IgE mediated (Schlumberger, 1983). Symptoms may occur on first exposure to the elicitor (no previous sensitization is necessary), but may also occur with substances that have been tolerated in the past. The reaction is dose dependent, and skin tests are not helpful.

Most frequently encountered elicitors are aspirin and non-steroidal anti-inflammatory drugs, including natural salicylates in food, food additives, radiocontrast media, colloidal plasma expanders, local and intravenous anaesthetics.

In addition, some substances can act directly on mast cells to cause histamine release, a 'non-allergic' urticaria. Some commonly used drugs may do this, e.g. morphine, codeine and chlorpromazine. It remains uncertain why only some people react to these histamine liberators.

**Physical urticaria**

Physical urticarias occur when a specific physical stimulus causes the reproducible wealing of urticaria, within minutes of the exposure, and persists for several hours. If the stimulus is sufficiently great, or the patient is very sensitive, angio-oedema and systemic reactions may occur. Mast cell degranulation occurs, and sometimes associated diseases or a genetic predisposition can be found. In the latter (e.g. familial cold urticaria) onset in early childhood is usual, but in other types onset is in late childhood or young adults, and persists for several years or even decades.

There are five main groups of physical urticaria:

1. Physical: dermographic, delayed pressure and vibratory
2. Thermal: cold and heat
3. Electromagnetic: solar, laser and X-ray
4. Cholinergic: sweating
5. Aquagenic: water.

**Dermographism**: This is an exaggerated version of the normal 'triple response' of skin to firm stroking. Local erythema as a result of capillary vasodilatation is followed by oedema and then a flare caused by axon reflex-induced dilation of arterioles. It occurs in 5% of people at any age, and is symptomatic with itching in some patients. It has been transferred when IgE from patients' sera has been injected into normal recipients (Breathnach et al, 1983). Mast cells sensitized with IgE react to an antigen released by mechanical stimulation of the skin.

**Delayed pressure urticaria:** To find this alone is uncommon but it occurs in a minor form in over a quarter of patients with idiopathic urticaria. Wealing occurs at sites of sustained pressure after a delay of 4–8 hours and lasts up to 3 days. The underlying mechanism is unclear, but histology of an affected area shows reduced numbers of stainable mast cells, implying that they have released their granules (Barlow et al, 1995).

**Vibratory angio-oedema:** This condition is very rare, and usually familial. Sufferers learn to avoid the precipitating cause (jogging, using vibratory tools or toys).

**Cold urticaria:** This is an urticarial reaction elicited by cold, whether solid, fluid or gaseous. Although most cases are idiopathic, some occur secondarily with infectious, immunological or neoplastic diseases. In these cases, abnormal body proteins altered by cold probably act as antigens. Certain drug therapy may elicit it (e.g. griseofulvin, penicillin), and it may be secondary to cryoglobulinaemia. There are also rare

familial cases of cold urticaria when onset may be in childhood, otherwise onset is rare before the late teens. Diagnosis is most readily established using the ice cube test (ice cubes in water in a plastic bag are held against the lower arm for 3–10 minutes).

**Heat urticaria:** Heat urticaria is very rare, only 20 cases are reported in the literature since the first case in 1924. Most cases prove to be solar or cholinergic urticaria (see below). It may persist for many years; one patient's symptoms started in childhood and persisted into her 40s.

**Solar urticaria:** This is also is rare, and occurs within minutes on skin exposed to sunlight (wavelengths 280–760 nm) in predisposed individuals. It usually clears within an hour. There is no recorded familial incidence, and it is not usually seen before the age of 20 years. However, it may occur as a secondary phenomenon in porphyria, systemic lupus erythematosus (SLE) and drug reactions.

Urticaria to other types of radiation are more rare, but there have been case reports of urticarial response to both X-ray treatment and to laser.

**Cholinergic urticaria:** Characteristic urticarial weals develop in association with sweating, whether induced by exercise or stress. The onset is often in adolescence, symptoms are usually mild, and improvement is usual within 5 years. It is possibly related to stimulation of the cholinergic postganglionic sympathetic nerve supply to the sweat glands. There may be a specific autoantibody, perhaps even an allergy to sweat (Adachi et al, 1994).

**Aquagenic urticaria:** In patients with aquagenic urticaria, contact with water at any temperature causes urticaria. It is postulated that water dissolves a water-soluble antigen in the epidermis for presentation to the sensitized mast cell (Czarnetzki et al, 1986).

### Angio-oedema

Angio-oedema occurs when the effects are in the deeper subcutaneous tissues, but is not merely a more severe form of urticaria. Angio-oedema may occur with or without urticaria (see below), suggesting the underlying mechanisms are somewhat different.

**Hereditary angio-oedema:** This is transmitted as an autosomal dominant trait on chromosome 11. Several mutations have been identified. The onset is usually in childhood.

Patients are deficient in C1 esterase inhibitor, either amount or activity, which normally acts to inhibit the activated first component of complement. C2 and C4 are usually low, and measurement provides a good screen. Attacks are probably triggered by events that normally activate complement.

**Acquired C1 esterase deficiency angio-oedema:** A similar acquired problem may arise in B cell lymphoma in which abnormal cells expressing monoclonal antibody allow complement activation and consumption of C1q and of the inhibitor. Antibodies directed against the inhibitor may rarely occur in other conditions, e.g. SLE.

**Drug-induced angio-oedema:** Angiotensin-converting enzyme inhibitors (ACEIs) may cause angioedema by prolonging bradykinin survival and increasing its effect. Such reactions may be intermittent, but all ACEIs are contraindicated.

### Urticarial vasculitis

Sometimes typical urticarial weals occur, but histologically vasculitis is seen. This may occur acutely as in serum sickness, when substances are given intravascularly, or with drugs, and a type III hypersensitivity immune reaction occurs with immune complex deposition in small vessels. It may also occur chronically or intermittently. It is possible to show circulating immune complexes, deposition of complement and immunoglobulin in vessel walls, and consumption of complement (with or without anti-C1q antibodies) (Mehregan et al, 1992).

The main underlying causes of the vasculitis are infections, e.g. hepatitis B and C, collagen vascular diseases, e.g. SLE or hypergammaglobulinaemia, and drugs, e.g. cimetidine.

### Urticaria pigmentosa

Urticaria pigmentosa, or 'mastocytosis', usually presents in the first 6 months of life and is caused by local proliferation of mast cells in the dermis underlying brown skin patches that urticate when rubbed (Darier's sign). In most patients mast cell proliferation subsides and the lesions regress by puberty. In generalized mastocytosis, systemic symptoms are common as a result of histamine release, but malignant transformation is very rare in children.

## CONCLUSIONS

The underlying mechanisms in urticaria and angio-oedema are multiple, but fall into three main groups:

1. Idiopathic
2. Immunological
   a. Type I hypersensitivity, IgE mediated e.g. nuts, bee stings, latex

b. Autoimmune — autoantibodies directed against high affinity IgE receptors
c. Immune complex (urticarial vasculitis)

3. Non-immunological
   a. Direct mast cell-releasing agents, e.g. codeine, morphine, plants, jellyfish
   b. Pseudo-allergic agents, e.g. aspirin
   c. Hereditary or aquired C1 esterase inhibitor deficiency
   d. Angiotensin-converting enzyme induced
   e. Proliferation of mast cells.
   f. Physical stimuli.

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*Conflict of interest: none.*


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## KEY POINTS

- The multiple mechanisms underlying urticaria show it to be a very complex group of disorders.
- The history surrounding the onset and persistence of the weals is the most helpful in identifying an underlying cause.
- The cutaneous mast cell is central to most forms of urticaria by releasing its granule contents, including histamine and other pre-inflammatory mediators including cytokines and proteases.
- This stimulation of mast cells may occur by immunological causes, non-immunological causes or as yet uncertain causes (idiopathic).