



The diagnosis and treatment of

URTICARIA

Urticaria is a common condition, in which the majority of cases are non-allergenic. A focused clinical history and physical examination are the most useful tools when diagnosing and treating urticaria. Specific triggers are often not found, therefore extensive diagnostic testing is not recommended, unless there is strong evidence to suspect a specific trigger. In some cases, urticaria may be a symptom of an underlying systemic disease and it is important to be aware of this possibility and to refer for further investigation when necessary.

Classification and aetiology of urticaria

Urticaria is the term used to describe a group of skin conditions, characterised by the presence of wheals. Approximately one in five people experience urticaria (commonly referred to as hives) at some stage in their life.^{1,2} In many cases, a specific trigger for the urticaria is not found. In rare cases, urticaria may be a sign of systemic disease, such as an autoimmune condition.

The two main classifications of urticaria are:

- Ordinary (spontaneous) urticaria – which can be acute or chronic
- Physical urticaria

Acute urticaria describes “one-off” outbreaks and recurrent episodes occurring over a period of less than six weeks. It is the most common type of urticaria, and is more frequently seen in children and young adults.^{1,3} It is estimated that 20 – 30% of cases of acute urticaria in infants and young children develop into chronic urticaria.⁴ Approximately 50% of cases of acute urticaria are idiopathic, i.e. a specific trigger is not identified.³

Chronic urticaria describes episodes of urticaria which occur over a period longer than six weeks. In rare cases urticaria may persist for a lifetime, but this is more common in cases of physical urticaria.⁵ Approximately 30% of patients presenting

in primary care with urticaria will have chronic urticaria.⁶ Chronic urticaria occurs more frequently in adults, and in women (approximately 60% of cases).¹ It is estimated that in 40% of people with chronic urticaria, there is evidence of an autoimmune process, and in 20% there is evidence of a physical stimulus,¹ although a specific cause is often not found.

Physical urticaria occurs in a localised area after contact with a physical stimulus. Individual episodes usually resolve within a two hour period, but physical urticaria often persists as a chronic, recurring condition.³ Dermatographism (skin writing) is the most common form of physical urticaria, triggered by firm stroking or scratching of the skin, or contact with clothes or other objects (Figure 1).³

Other types of physical urticaria include;

- Contact urticaria – absorption of substances through the skin or mucous membranes
- Cholinergic urticaria – sweating, e.g. after exercise or exposure to heat
- Delayed pressure urticaria – sustained pressure to a site on the body, e.g. on the buttocks after sitting
- Cold urticaria – most frequently caused by swimming in cold water or exposure to cold wind (Figure 2)
- Solar urticaria
- Vibratory urticaria



Figure 1: Dermatographism

Images provided by DermnetNZ



Figure 2: Cold urticaria

Most cases of urticaria are non-allergenic

Most cases of urticaria are **not** caused by allergy but are the result of histamine being released by direct mast cell degranulation (i.e non-IgE mediated).

Examples of causes of non-allergenic urticaria include:²

- Infection – bacterial (e.g. *Helicobacter pylori*, *Mycoplasma pneumoniae*), viral (e.g. infectious mononucleosis, viral hepatitis), parasitic (e.g. Giardia) or fungal (e.g. Candida)
- Medicines – especially opiates, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)
- Non-allergenic contact with topical compounds, food preservatives, raw meat or vegetables
- Non-allergenic food reactions to compounds such as alcohol, salicylates in fruit or from bacterial decomposition (food poisoning)
- Hypersensitivity to physical stimuli such as scratching, friction from clothing or other objects, light, heat, cold, water or vibration
- Autoimmune conditions such as systemic lupus erythematosus and autoimmune thyroid disease

Allergy-induced urticaria

Allergy induced urticaria is most common in people with a history of atopy.

Examples of causes of allergenic urticaria include:²

- Medicines, e.g. antibiotics
- Food allergy, e.g. fish, eggs or nuts
- Insect stings, e.g. wasp, bee
- Contact allergens, e.g. latex or cosmetics

Clinical history and examination

Clinical history and physical examination are usually sufficient to diagnose urticaria. A specific cause is identified in approximately one-half of patients with acute urticaria and one-quarter of patients with chronic urticaria.^{3,7}

Clinical history

The clinical history should cover:

- Frequency, size, distribution and duration of the lesions – to determine type of urticaria
- Recent consumption of new or unusual food or medicines, recent infections, or participation in or

exposure to new activities, locations or products or chemicals – to determine potential triggers

- Occupational exposure to chemicals or inhalants – to determine potential long-term triggers
- History of similar episodes and response to treatment
- Personal and family history of atopy – more likely to be allergy-induced urticaria

Physical examination: clinical features of urticaria

An episode of urticaria is identified by highly pruritic, well-defined, pink-to-red wheals, often with a pale centre (Figure 3), which usually last no more than 48 hours and leave no remaining marks. The lesions may occur anywhere on the skin and can range in size, from a few millimetres to centimetres, and vary in shape, forming round, oval, annular (ring) (Figure 4), serpiginous (wavy), gyrate (circular, coiled) or targetoid (target pattern) plaques. The lesions may also merge to form large geographic or giant patches (Figure 5). The surface skin remains smooth. The presentation of urticaria is similar in both children and adults.

Approximately 40% of people with urticaria also have signs of angioedema.¹ Angioedema involves the deeper epidermis and subcutaneous tissues and most frequently affects the eyes, mouth, throat, tongue, hands and feet. Angioedema without urticaria is rare and can be life-threatening if the larynx is involved. Further discussion of this condition is outside the scope of this article.

Further examination should be guided by the clinical history. Dermatographism can be tested for by stroking the skin firmly and looking for linear wheals occurring within a five minute period. The application for several minutes of an ice cube, heat, pressure or water may rule out other forms of physical urticaria.

In some cases, examination may be necessary for underlying conditions that may precipitate urticaria, such as:

- Bacterial or fungal infections of the skin
- Autoimmune thyroid disease – may be indicated by an enlarged thyroid
- Connective tissue diseases – may be indicated by joint swelling or tenderness or oral ulceration, e.g. rheumatoid arthritis, systemic lupus erythematosus
- Liver disease/dysfunction – may be indicated by tenderness on palpation of the liver or jaundice, e.g. cholestasis can cause pruritus and acute urticaria can be an early sign of hepatitis A, B and rarely C⁸

Differential diagnosis

There are a large number of conditions (some of them rare) which may cause symptoms similar to urticaria. The transient and pruritic nature of lesions is one of the most distinctive aspects of urticaria, but pruritus is sometimes absent. Angioedema is also more likely to be associated with urticaria than other skin conditions.

If the signs and symptoms are not typical of urticaria, other diagnoses that may be considered include:

- **Atopic dermatitis** – usually highly pruritic, but can be distinguished from urticaria by the lack of transitory wheals, excessively dry skin and other skin surface abnormalities, strongly associated with personal or family history of atopy
- **Contact dermatitis** – can be distinguished from urticaria by a lack of transitory wheals and the presence of skin surface changes such as blisters, dryness and peeling
- **Fixed drug eruptions** – tender, well defined, round or oval patches, often with central blistering that generally occur in the same place on the body each time a specific medicine is taken
- **Erythema multiforme** – an acute, and at times recurring, hypersensitivity to a variety of causes including infections and medicines. Lesions are usually present on the face and distal limbs and can last for up to seven days.
- **Bullous pemphigoid** – a chronic, autoimmune condition, which usually affects elderly people. Characterised by erosions and tense bullae filled with clear, cloudy or blood-stained fluid, most frequently occurring in body folds.
- **Urticarial vasculitis** – characterised by wheals that resemble urticaria, but last longer than 48 hours and often leave bruising and areas of increased pigmentation as they resolve
- **Papular urticaria** – urticated pruritic papules at the site of insect bites, common in young children and in people who have travelled.

Laboratory investigation of urticaria

Laboratory testing is not indicated for patients with acute urticaria as the diagnosis is usually clinical.

In patients with chronic urticaria, testing does not usually help to establish a cause, direct management or improve patient outcomes.⁹ In a study of 356 patients with urticaria referred for allergy and immunology evaluation, only one patient benefited from a change in management due to testing



Figure 3: Classical whealing



Figure 4: Annular pattern



Figure 5: Giant urticaria

Images provided by DermnetNZ

and only 319 (17%) of the 1872 tests ordered had abnormal findings.¹⁰

Laboratory testing may be useful in selected patients with chronic urticaria, e.g. if an underlying condition is suspected, they have failed to respond to treatment, or if the condition is severe.⁹ The choice of investigations should be guided by positive findings from the clinical history and physical examination. Discussion with a dermatologist may also be helpful.

The following investigations may be appropriate for specific clinical circumstances:

Skin prick testing may be considered when an allergic cause for the urticaria is suspected and confirmation would be useful for management, e.g. if avoidance measures are being considered. Skin prick testing should not be performed routinely. Skin prick testing may not be reliable in older adults and children aged under two years should be referred to an allergy clinic for testing as the results may be difficult to interpret. Skin prick testing in pregnant women should only be requested if the benefits outweigh the risks, as in rare cases it can cause uterine contractions.¹¹

Serum allergen-specific IgE testing is second-line to skin prick testing when skin prick testing is unsuitable or unavailable.

 For further information see: "Appropriate use of allergy testing in primary care", Best Tests (Dec, 2011)

Full blood count may indicate an allergy or an intestinal infection if the eosinophil count is elevated. Neutropenia may suggest an autoimmune or viral cause, while neutrophilia may be caused by a bacterial infection. Acute viral infections, e.g. Epstein-Barr virus, or autoimmune thyroiditis may cause a high lymphocyte count.

Thyroid antibody testing may be useful following discussion with an appropriate specialist, if a thyroid autoimmune disorder is suspected. Chronic autoimmune urticaria is associated with antithyroid antibodies in approximately one-quarter of cases.³

Skin biopsy (3 mm punch biopsy) is only rarely required, if urticarial vasculitis is suspected or when the diagnosis is uncertain. Atypical features of urticaria include pain or burning rather than pruritis, complete non-response to antihistamines, wheals persisting for longer than 48 hours, or not fully resolving, with remaining hyperpigmentation.

 **Best Practice tip:** Before contacting a dermatologist, take anatomic views and close-up digital images of the patient's skin lesions. Emailing good quality clinical images may assist the discussion, particularly if the patient's clinical signs are intermittent.

Treatment for urticaria

Acute urticaria generally resolves over a short period of time, however, chronic urticaria can persist for months or even years (particularly physical urticaria). This can be frustrating for both patient and doctor, especially when there is no known cause.

In a study of 220 patients with chronic idiopathic urticaria, it was found that after one year:⁶

- 47% were symptom-free
- 60% with ordinary urticaria and angioedema were symptom free
- 39% with ordinary urticaria only were symptom free
- 16% with physical urticaria were symptom free

Management is focused on avoiding triggers where known, and using medicines for symptom relief.

Avoidance strategies

When the clinical history does not reveal an obvious cause for the urticaria, an avoidance strategy for potential triggers may be considered.

Patients can be advised to stop any non-essential medicines, herbal supplements or topical preparations. In particular, aspirin, codeine and non-steroidal anti-inflammatory drugs (NSAIDs) may contribute to wheal formation, even when they are not the primary cause of the eruption. If symptoms resolve (or do not recur), medicines/products can be reintroduced sequentially, if necessary, and the patient should report any return of symptoms.

Dietary investigations rarely identify a specific trigger for chronic urticaria, and are not necessary in cases where symptoms can be easily controlled with oral antihistamines. However, if the patient wishes to, a food diary may be used to record and eliminate suspected triggers. Particularly motivated people may try a narrow diet of rice and a single source of protein for two weeks, while discontinuing all antihistamines. Foods can then be slowly reintroduced and reactions noted in the food diary.¹

Pharmacological treatment

Introduction of medicines for the treatment of urticaria should be considered in the following order:

1. Commence non-sedating oral antihistamines
2. Add conventional sedating oral antihistamines and/or H2 receptor antagonists
3. Add tricyclic antidepressants
4. Add oral corticosteroids - only for patients with severe acute urticaria

Non-sedating oral antihistamines are the first-line pharmacological treatment for both acute and chronic urticaria due to their effectiveness and relative lack of anticholinergic and central nervous system effects. Although referred to as “non-sedating”, these medicines may still cause sedation at usual doses in some patients. In New Zealand cetirizine and loratadine are fully-funded (see Table 1 for recommended doses). Individual response to antihistamines may be variable, however, cetirizine is thought to be the quickest acting, therefore may be trialed first.²

Oral antihistamines may be taken on an “as-required” basis, due to their rapid onset of action, but may be more effective when taken daily. The recommended maximum adult dose of cetirizine and loratadine is 10 mg per day, however, European guidelines recommend non-sedating antihistamines be prescribed at up to four times the standard dose (i.e. cetirizine or loratadine 40 mg daily) before second-line medicines are considered as adjunctive treatment.¹²

Sedating oral antihistamines are rarely used as a monotherapy for urticaria, but can be used in combination with non-sedating antihistamines. These medicines may be useful for patients with nocturnal symptoms that prevent sleep. Promethazine (fully funded) is a suitable choice and can be prescribed at the following doses:^{13,14}

- Adults; 25 – 75 mg, at night
- Children aged five to ten years; 10 – 25 mg, at night
- Children aged two to five years; 5 – 15 mg, at night

H2 receptor antagonists such as ranitidine or famotidine, when used in combination with antihistamines, may be of benefit to some people with chronic urticaria as 15% of histamine receptors in the skin are H2-type.³ These medicines are not recommended as monotherapy because their ability to reduce pruritus is limited and there is little clinical evidence of their effectiveness.

Tricyclic antidepressants have histamine receptor antagonist activity and may be especially useful in treating chronic urticaria, in combination with non-sedating antihistamines. Due to its sedating properties doxepin (30 – 50 mg) is an appropriate treatment for nocturnal symptoms. Amitriptyline (10 – 50 mg) may also be effective.

Oral corticosteroids may be added for people with severe acute urticaria. The recommended dose for adults is 20 – 40 mg daily, or for children 1 mg/kg daily, maximum 40 mg, tapering to the lowest effective dose over the course of two to five days.¹³ Corticosteroids are nearly always inappropriate in people with chronic urticaria as long-term use should be avoided.

Table 1: Recommended doses for fully-funded, non-sedating antihistamines available in New Zealand^{13,14,15}

Antihistamine	Adult dose	Child dose (6 – 12 years)	Child dose (2 – 6 years)
Cetirizine	10 mg, once or twice daily*	10 mg, once daily or in divided doses	5 mg, once daily or in divided doses
Loratadine	10 mg, once or twice daily*	> 30 kg: 10 mg, once daily < 30 kg: 5 mg, once daily	5 mg, once daily

* Although the maximum dose in the New Zealand medicine datasheet is 10 mg, this medicine is often used (and required) in higher doses, without any reports of adverse effects, in order to successfully manage urticaria^{12, 16}

Antihistamines during pregnancy

Ordinary urticaria is uncommon in pregnant women and little is known about the safety of antihistamines in women who are pregnant or breastfeeding. The majority of information that is available concerns the older, first-generation sedating antihistamines. Generally, all antihistamines should be avoided by women who are pregnant, especially during the first and third trimester.¹⁷ However, there have been no reports of major birth abnormalities in women who have used newer, non-sedating antihistamines during pregnancy.¹² Loratadine (pregnancy category B1)¹⁹ may be considered for the treatment of urticaria in women who are pregnant when the benefits of treatment are thought to outweigh the risks.¹² Sedating antihistamines may be considered in severe cases of urticaria occurring during pregnancy, if the patient has not responded to non-sedating antihistamines. However, these medicines should be avoided around the time of delivery to reduce the chance of causing sedation in the infant.

It is recommended that antihistamines are avoided during breastfeeding as most are present in breast milk, however, a similar consideration of risk vs. benefit may occur.



N.B. Topical corticosteroids are not useful in the treatment of urticaria and may cause adverse effects with longer-term or higher-potency use, e.g. skin atrophy. Topical antihistamines are also not effective for treating urticaria and are not recommended due to the risk of sensitisation and resulting contact dermatitis.¹⁷

Cooling preparations containing 0.5 – 1% menthol in a cream or lotion base, e.g. cetomacrogol cream, may provide symptom relief. The use of cool damp cloths, reduction of night-time heating and tepid showers may also be useful.

Referral for specialist treatment may be considered if the diagnosis is uncertain or where symptoms are severe and poorly controlled. A number of further treatment options are available including immunosuppressants, e.g. cyclosporin, and leukotriene receptor agonists, e.g. montelukast. If a complex drug or food trigger is suspected then consider referral to an immunologist. **Phototherapy** using ultraviolet B radiation reduces the number of mast cells in the upper dermis,¹² and may be effective in reducing symptoms in cases of physical urticaria that are resistant to antihistamines.¹⁸ Patients can be referred to a dermatologist for this treatment.

 **Best Practice tip:** A standard treatment regimen for urticaria – begin with cetirizine, if symptoms are not controlled, add promethazine 25 mg at night and ranitidine 300 mg during the day. This will settle symptoms for most people. If symptoms still persist, add in a tricyclic antidepressant.

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