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Chronic urticaria

Assessment and treatment

Background
Chronic urticaria is a common condition encountered in general practice and a frequent source of referral to the clinical immunologist, allergist and dermatologist.

Objective
This article discusses the assessment and management of chronic urticaria in the general practice setting.

Discussion
Chronic urticaria is defined as the occurrence of transient wheals lasting more than 6 weeks in duration. In 80% of cases, a cause is not identified and this is classified as chronic idiopathic urticaria. A physical trigger, vasculitis or systemic disease account for a smaller proportion of cases. Allergic causes are rarely responsible. A detailed history provides the most useful information in determining the presence of chronic urticaria and a possible aetiology. Apart from thyroid function tests and thyroid autoantibodies, other investigations should only be performed if clinically indicated. Second generation antihistamines are the mainstay of treatment and usually twice daily regimens are required for adequate control. H2 antagonists, doxepin and immunomodulation may be necessary in some patients.

Keywords: allergy and immunology; skin diseases; urticaria

Urticaria is characterised by the rapid appearance of transient, pruritic skin swellings (wheals) of variable size surrounded by reflex erythema lasting less than 24 hours and leaving no residual skin changes (*Figure 1*). Urticaria is a common condition, affecting up to 20% of the population.[1] It is broadly classified into acute and chronic forms. Acute urticaria is defined as episodes of less than 6 weeks duration and accounts for over two-thirds of cases. An allergic or infectious trigger is sometimes identified (*Table 1*). Chronic urticaria (CU) is defined as episodes extending beyond 6 weeks and accounts for 30% of cases.

Episodes of CU typically occur daily or most days of the week. If urticaria lasts beyond 6 months, up to 40% of patients will still experience symptoms at 10 years.[2] In contrast to acute urticaria, in CU an external trigger is absent in the vast majority (80%) of patients (*Table 1*). Approximately 40% of patients with CU have associated angioedema, which typically affects the face, extremities, and genitals.[3] Involvement of the airways is rare.

Assessment

Careful history taking and physical examination are the cornerstone of assessment of CU. Careful questioning can help identify triggers if present. Investigations such as physical provocation, laboratory tests, and biopsy should only be performed if clinically indicated.

Physical urticaria

Physical urticaria is responsible for up to 20% of CU cases. If physical triggers are present, they can be identified on history in most cases. Dermographism is the most common form of physical CU and affects 2–5% of the general population.[4] Dermographism can occur in isolation

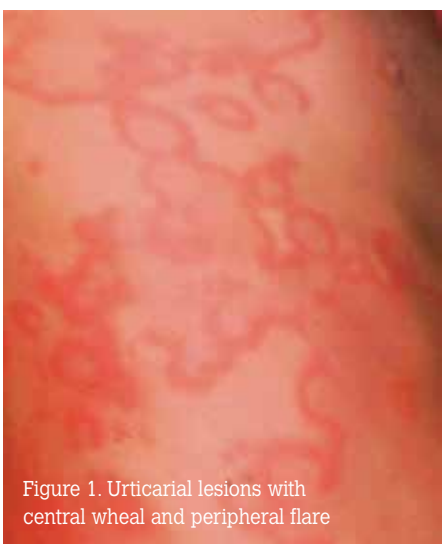

Figure 1. Urticarial lesions with central wheal and peripheral flare

Table 1. Causes of acute and chronic urticaria

Acute	Chronic
Food	Idiopathic
Medication	Autoimmune
Insect sting	Physical
Viral infection	Urticarial vasculitis
Contact	Thyroid autoimmunity
	Connective tissue disease
	Mastocytosis
	Infection
	Hormonal

or in association with other forms of urticaria. Patients describe linear wheals that occur at sites of stroking or scratching. Most patients do not seek medical attention as the lesions are not usually pruritic. Cholinergic urticaria is characterised by the appearance of small, 1–3 mm wheals precipitated by a rise in core body temperature as occurs with exercise, emotional stress, and heat exposure.

Cold urticaria follows exposure to cold air and water and can be associated with systemic reactions such as hypotension; fatalities such as drowning have been reported.[5] Cold urticaria is usually idiopathic but may be associated with cold dependent serum protein disorders such as cryoglobulinemia or following infections such as infectious mononucleosis. A familial form with an autosomal dominant mode of inheritance is rare. This form presents in infancy and is associated with a range of specific debilitating systemic symptoms.

Delayed pressure urticaria involves cutaneous erythema and swelling that occurs 4–6 hours after pressure stimulus is applied, such as that from: constrictive clothing (eg. underwear), shoes, seatbelts, handbags, and from tools used in manual labour. Patients often describe burning and pain instead of, or in addition to, pruritus. The swelling can last several hours to several days and may be accompanied by arthralgias. These patients usually have concomitant chronic idiopathic urticaria and angioedema.

Exercise induced urticaria and anaphylaxis is rare. It is characterised by the development of large wheals, flushing and fatigue and particularly if exercise continues, may be accompanied by angioedema, gastrointestinal symptoms and hypotension. Food dependent, exercise induced anaphylaxis is a related condition in which symptoms develop only if exercise takes place within a few hours of eating, and in most cases, only if a specific food is eaten in the pre-exercise period. Rarer forms of physical urticaria include solar urticaria, aquagenic urticaria and vibratory angioedema. The various forms of physical urticaria can be confirmed with the appropriate stimulus test if required[6] (*Table 2*).

Urticarial vasculitis

Urticarial vasculitis accounts for up to 5% of CU cases and is mediated by immune complex deposition in blood vessel walls. The condition has a female preponderance and a peak incidence in the fourth decade of life. Patients may describe lesions that are burning or painful rather than pruritic and purpuric or pigmented.[7] Individual lesions may last for up to 72 hours. Patients in whom CU is suspected, can circle a new lesion and monitor the length of time to its disappearance. Systemic features such as fever, arthritis, chronic obstructive pulmonary disease/asthma, scleritis/uveitis, glomerulonephritis and abdominal pain may be present. Skin biopsy for both histopathology and direct immunofluorescence reveals leukocytoclastic vasculitis and perivascular deposition of immunogloubulin, complement and fibrin. Laboratory investigation may reveal hypocomplementemia (C3, C4), raised inflammatory markers (erythrocyte sedimentation rate and C-reactive protein), and positive antinuclear antibody.

Most cases are idiopathic, however the condition is associated with a range of medications, connective tissue diseases (systemic lupus erythematosis, Sjogren syndrome), infection (hepatitis B, hepatitis C, Epstein-Barr virus), lymphoproliferative disorders, malignancy and physical urticaria. Initial testing for these conditions includes hepatitis B surface antigen, hepatitis C antibody, and electrophoretogram/immunoelectrophoretogram. Beyond these tests, the authors recommend further investigation for secondary causes only if clinically indicated.

Systemic disorders

Thyroid functions tests and thyroid autoantibodies should be performed to exclude autoimmune thyroid disease. Autoimmune thyroid disease, especially Hashimoto disease, is associated with CU and angioedema. Up to 26% of patients with CU have antithyroid antibodies compared to 3% of healthy subjects.[8] The presence of urticaria however, does not necessarily correlate with thyroid function in these patients. Those patients with CU accompanied by circulating thyroid autoantibodies and normal thyroid function are often poorly responsive to standard therapies for urticaria and may have more persistent disease. The role of these autoantibodies in patients with normal thyroid function is not clear.

Other systemic diseases are rare causes of CU and include systemic lupus erythematosis and other connective tissue diseases, mastocytosis, Schnitzler syndrome (monoclonal gammopathy) and cryopyrinpathies (autoinflammatory syndromes from genetic defects in the cryopyrin protein that cause familial cold urticaria). Apart from thyroid stimulating hormone and thyroid autoantibodies, further investigations for these systemic manifestations should be performed only if clinically indicated.

Infection

Simple viral infections are common causes of acute urticaria in children as a result of immune complex formation but are rarely associated with

Table 2. Testing procedures for physical urticaria

Physical urticaria	Testing method
Dermographism	Stroking skin firmly with a narrow pointed object
Cold	Ice cube test for 5 minutes
Cholinergic	Exercise for 15–20 minutes or emersion of leg in a 44°C bath
Delayed pressure	Sandbag test using 7 kg of weight for 15 minutes
Exercise	Exercise for 15–20 minutes +/- skin tests/RASTs for food allergens
Solar	Specific wavelength light exposure
Localised heat	Test tube of water at 44°C for 5 minutes
Vibratory	Vibration with a laboratory vortex for 4 minutes
Aquagenic	Water compress

the chronic form.[9] Human immunodeficiency virus, bacterial infection and parasitic infestation are rare causes of CU.

Hormonal

Progesterone containing oral contraceptives, hormone therapy, or endogenous progesterone may be rarely associated with cyclic urticaria, with or without other types of skin rash. Lesions appear before menses and resolve following its completion.[10] Skin testing +/- oral challenge to progesterone can be performed to confirm the diagnosis. Pruritic urticarial papules and plaques of pregnancy is an urticarial, pruritic eruption that develops in and around the abdominal striae in about 0.5% of pregnancies.

Less well established causes

The association between *Helicobacter pylori*, candidal infection, malignancy, food intolerance and CU have been reported but not well substantiated. Investigation for these conditions is not routinely recommended. In contrast to acute urticaria, IgE mediated food allergy is rare in the chronic form and skin testing is futile and can lead to an inaccurate diagnosis of a food allergy and unnecessary dietary restriction. An elimination diet to exclude the remote possibility of an intolerance to food chemicals should ideally be performed by a specialist in close collaboration with a dietician that has expertise in the area.

Chronic idiopathic urticaria

In the majority of cases no cause can be found, and hence, the diagnosis of chronic idiopathic urticaria is made. A subset of patients have autoantibodies to the high affinity IgE receptor, or rarely, anti-IgE antibodies.[11] Autologous serum skin testing for these autoantibodies is performed in a few specialised centres using an intradermal injection of a patient's serum and observing for a wheal and flare reaction. More recently, in vitro tests measuring basophil and mast cell activation have been introduced in a few specialist laboratories as a means of detecting surrogate markers of autoimmune urticaria.

Treatment

An approach to the treatment of CU is outlined in *Figure 2*.

Reassurance

It is important to reassure the patient that, in the vast majority of cases, CU is not associated with malignancy and is not usually life threatening. Except for those patients with cold or exercise induced anaphylaxis, most patients with CU are not at risk of airway obstruction or anaphylaxis. Information for patients with urticaria and angioedema can be downloaded from the Australasian Society of Clinical Immunologists and Allergists website (see *Resource*).

Nonpharmacological treatment

Physical triggers should be avoided. Patients with cold urticaria should be warned never to swim alone and similarly, those with exercise induced anaphylaxis, never to exercise alone. These patients should also be prescribed an adrenaline auto-injector. Certain medications such as aspirin, related nonsteroidal anti-inflammatory agents and opiates, which can cause or exacerbate urticaria in some patients, should also be stopped if possible. Avoidance of excessive heat, spicy foods or alcohol may also be useful in some patients.

Pharmacological treatment

In most cases of CU a specific cause is not found and hence the primary objective is the relief of symptoms. Pharmacological therapy may not completely relieve symptoms and this should be conveyed to the patient.

Oral antihistamines

Symptoms of urticaria are predominantly mediated by H1 receptors on cutaneous nerves and endothelial cells as a result of histamine release from mast cells. This means that second generation, nonsedating antihistamines are the first line treatment of CU.[12] Drugs in this class include loratidine, desloratidine, cetirizine and fexofenadine. Comparative data regarding the relative efficacy of these antihistamines show similar benefits. Often patients require more than the recommended single daily dose, however, in the authors' experience,

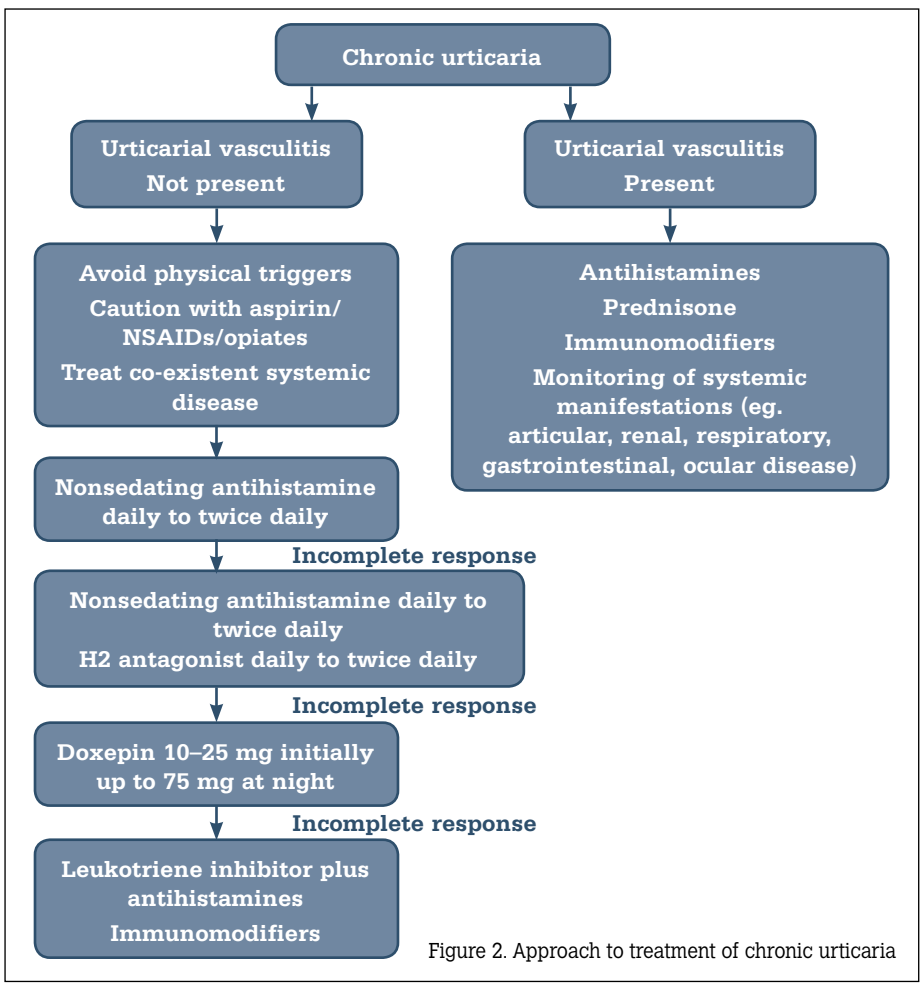

Figure 2. Approach to treatment of chronic urticaria

increasing the dose beyond a twice daily regimen is rarely beneficial. Prophylactic therapy rather than symptomatic therapy may better stabilise mast cells and hasten resolution of CU. Sedation at higher doses may be evident in some patients.

Data regarding the safety of antihistamines during pregnancy reveals that chlorpheniramine is the first generation antihistamine of choice and loratadine or cetirizine as the second generation antihistamine of preference.[13] The reassuring human data for loratadine and cetirizine in a large number of patients and the potential for sedation or performance impairment with first generation antihistamines suggest that these second generation antihistamines are a feasible alternative for pregnant women.

The addition of an H2 receptor antagonist may be effective when added to H1 receptor antagonists in the 10–15% of patients who are unresponsive to H1 receptor antagonists alone. The options include ranitidine, nizatidine, famotidine and cimetidine at daily to twice daily dosing. The side effect profile of cimetidine, including its numerous drug interactions, limits its utility in this setting.

First generation antihistamines have a limited role in CU because of excessive sedation. However, cyproheptadine is especially useful in cold urticaria, and first generation antihistamines are useful when nocturnal symptoms interfere with sleep. Patients should be specifically warned of impairment of fine motor and driving skills.

Doxepin has very potent H1 and H2 antihistamine activity and initiated at doses of 10–25 mg at night and increased to up to 75 mg/day in patients unresponsive to combined H1 and H2 blockade.[14] Its utility is restricted by sedation and weight gain. High doses may prolong the QT interval.

Oral corticosteroids

Prednisone is often prescribed for short term relief of severe urticaria that is unresponsive to high dose antihistamines. However, the side effects of corticosteroids preclude their use in the long term management of CU.

Treatment of underlying systemic disease

Patients with thyroid autoantibodies and hypothyroidism may benefit from thyroid hormone replacement.[15] Some reports suggest that euthyroid patients with CU and thyroid autoantibodies should also be treated with thyroxine.[16] The authors advise against this because of the potential risk of osteoporosis.

Table 3. Treatments for refractory urticaria

Leukotriene modifiers +/- antihistamines
Sulfasalazine
Dapsone
Hydroxychloroquine
Colchicine
Cyclosporin
Mycophenolate mofetil
Omalizumab (anti-IgE monoclonal antibody)
Plasmapheresis

Treatments for histamine resistant disease

A number of medications have been used to treat CU unresponsive to high dose antihistamines. They act as anti-inflammatory agents and/or immunomodulators, immunosuppressives (*Table 3*). A review of other agents is beyond the scope of this article. Patients who require these medications should be reviewed by a specialist.

Summary of important points

- Chronic urticaria is relatively common and causes distressing pruritus that can last from weeks to years.
- Careful history taking and physical examination is the cornerstone of assessment.
- Apart from thyroid stimulating hormone and thyroid autoantibodies, further evaluation of CU with provocation tests, laboratory investigation and skin biopsy should only be performed if clinically indicated.
- Allergy is very rarely a cause of CU; skin tests/RASTs are rarely indicated.
- First line treatment involves reassurance, avoidance of exacerbating factors and nonsedating antihistamines.
- Patients with urticarial vasculitis, associated systemic diseases or refractory disease may require further evaluation and alternative treatments by a specialist.

Resource

The Australasian Society of Clinical Immunologists and Allergists (ASCIA): www.ascia.org.au.

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