MedicineToday 2012; 13(12): 20-25

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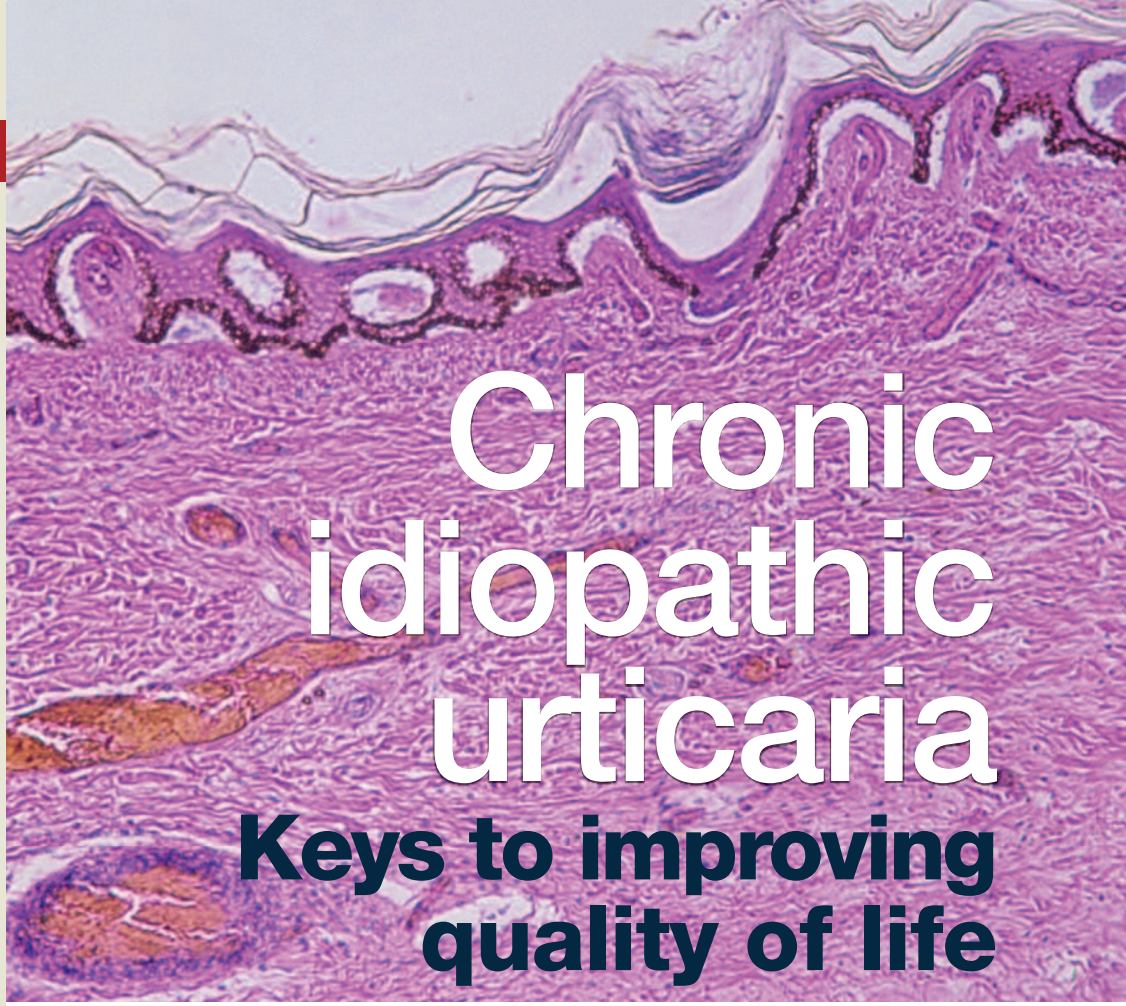

Chronic idiopathic urticaria

Keys to improving quality of life

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The intense pruritus and evanescent skin lesions of urticaria are poorly tolerated by patients, and long-term disease can lead to sleep disturbances, anxiety and reduced quality of life. Nonsedating antihistamines, patient education and psychological support form the basis of management.

Key points

- **Urticaria is a relatively common condition, affecting a quarter of the population at some time.**
- **Although chronic idiopathic urticaria is a nonlife-threatening condition, it can be associated with significant emotional distress and reduction in quality of life.**
- **Oral second generation (nonsedating) antihistamines are the mainstay of treatment and compliance is a key factor in the management of this condition.**
- **Patients require education regarding the nature of urticaria and psychological support for the associated emotional distress.**

Urticaria, or hives, is a transient pruritic skin eruption caused by the release of histamine and other mediators from the dermal mast cells. A quarter of the general population will experience urticaria at least once in a lifetime. When urticaria occurs daily or almost daily for longer than six weeks, it is termed chronic urticaria. Although the exact incidence is unknown, the average prevalence is thought to be about 0.1 to 3%, with a male to female ratio of 1:2.

CATEGORIES OF CHRONIC URTICARIA

Chronic urticaria can be broadly classified into the following three categories:

- physical urticaria
- chronic idiopathic urticaria (including autoimmune urticaria)
- urticarial vasculitis.

Treatment of each type is aimed at relief of symptoms.[1] This article will focus on chronic idiopathic urticaria.

Physical urticaria

Approximately 20% patients with chronic urticaria have a physical trigger, such as cold, heat, pressure or vibration, for the condition. Dermatographism and cholinergic urticaria are two of the most common forms of physical urticaria. Careful identification of the cause is important, and once diagnosed, no further investigations are necessary.

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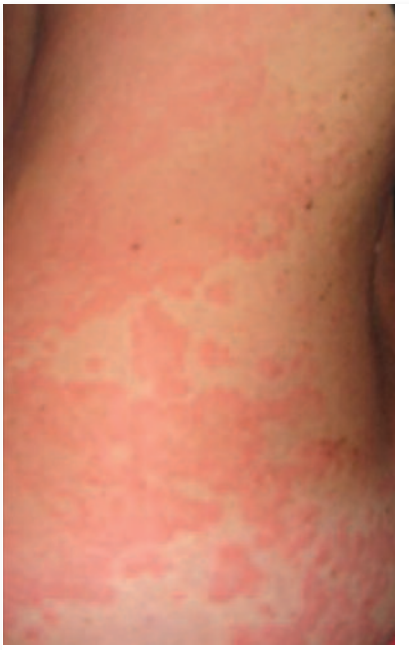
Chronic idiopathic urticaria

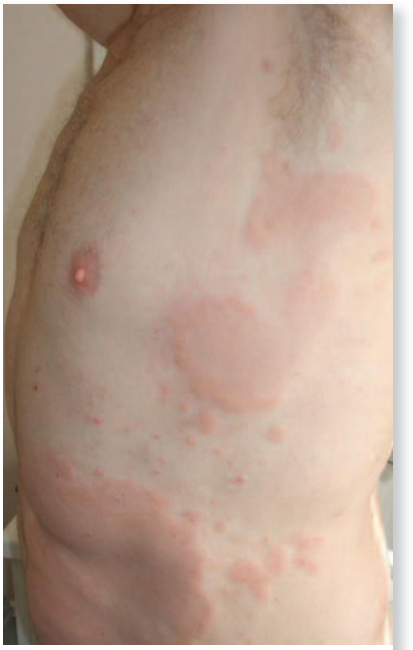
About 80% of patients with chronic urticaria come under the category of chronic idiopathic urticaria, and around 50% of these patients have associated angioedema. The disease may show a relapsing and remitting pattern, with an average duration of three to five years. Some 20% of cases remain symptomatic, even after 20 years.

Circulating IgG antibody against the subunit of the IgE receptor can be identified in 35 to 45% of patients. Also, an anti-IgE IgG antibody can be found in an additional 5 to 10% of cases.[2,3] The remaining 50% of people with chronic idiopathic urticaria do not have any detectable autoantibodies; however, autoimmunity remains the likely aetiology.

Chronic idiopathic urticaria per se is not a life-threatening condition. Even when associated with angioedema, there is rarely any airway compromise. However, optimal management is essential because of the distressing nature of the condition.

The major symptoms of chronic idiopathic urticaria are intense pruritus and evanescent skin lesions that can result in temporary disfigurement poorly tolerated by patients (Figures 1 and 2). Chronic urticaria can also lead to sleep disturbances, anxiety and reduced quality of life. It has been demonstrated that patients with chronic idiopathic urticaria have health scores similar to those of patients with coronary artery disease.[4]





Figures 1 and 2. The typical lesions of urticaria.

Urticarial vasculitis

Urticarial vasculitis is a rare condition and is characterised by painful rather than itchy lesions that respond poorly to antihistamines and usually last more than 24 hours. Patients may experience constitutional symptoms such as arthralgia or arthritis, and investigations may suggest an autoimmune aetiology (e.g. a positive test for antinuclear antibodies [ANA], low complement levels).

IS CHRONIC URTICARIA A FOOD-RELATED PROBLEM?

Most patients consider certain food additives are the prime cause for their urticaria and may try avoiding different types of food by using various elimination diets. Well-conducted, controlled studies of such interventions are scarce; at best about 5% of individuals with chronic urticaria may have a food intolerance contributing to their condition.[5]

Some patients may experience an exacerbation of urticaria after consuming alcohol (via vasodilatation and the histamine-releasing properties of alcohol) or taking aspirin or NSAIDs (via perturbation of leukotriene pathways). Patients may be cautioned about the possibility of these agents producing a marked episode of urticaria. There is no evidence to suggest that chronic urticaria is due to an IgE-mediated reaction.

IS CHRONIC URTICARIA DUE TO AN INTERNAL MALIGNANCY?

Except for isolated case reports, there no data to support the theory that an internal malignancy may cause chronic urticaria.

WHAT IS THE ROLE OF *HELICOBACTER PYLORI*?

There have been several publications in the past implicating *Helicobacter pylori* infection as

the cause of chronic urticaria, including reports of improvement after eradication. Many recent studies have failed to reproduce this result and the link, if any, remains controversial. However, *H. pylori* eradication may be attempted in those patients with chronic urticaria who are infected with *H. pylori*, especially those with symptoms of dyspepsia.[6]

CHRONIC IDIOPATHIC URTICARIA AND AUTOIMMUNE THYROID DISEASE

Antithyroid autoantibodies (mainly antithyroid peroxidase) are found in 27% of patients with chronic idiopathic urticaria, and 19% have abnormal thyroid function.[7,8] There is no strong evidence to suggest that treating the underlying thyroid dysfunction alters the course of the disease, although some reports suggest improvement in the clinical picture after thyroxine treatment.[9]

STRESS AND CHRONIC IDIOPATHIC URTICARIA

A few controlled studies have evaluated the relation between psychological factors and chronic idiopathic urticaria, and have failed to demonstrate whether psychological factors are causal or develop as a consequence of a distressing condition.[10] These studies also failed to demonstrate any relation between the degree of emotional stress and the severity of urticaria.

WHICH INVESTIGATIONS ARE USEFUL FOR SUSPECTED URTICARIA?

The investigations listed below are of assistance in patients with possible urticaria.

- Full blood count, C-reactive protein and biochemistry may be useful to exclude underlying conditions. Results of these tests are usually within the normal range in patients with chronic idiopathic urticaria.
- Antithyroid peroxidase antibodies; if results are positive, thyroid function tests.
- *H. pylori* screening, especially if the patient has associated gastrointestinal symptoms.

Patients with an autoimmune aetiology will have more aggressive disease and be resistant to treatment. There are no readily available in vitro tests to assist with the diagnosis of autoimmune urticaria.

MANAGEMENT

Management of urticaria consists of a several steps once any underlying causes and/or triggers have been eliminated. These steps are:

- pharmacological therapy
- patient education
- psychological support.

Pharmacological therapy

The main aim of pharmacological therapy for urticaria is symptomatic relief, thereby improving the patient's quality of life. Compliance is the key factor. As patients may continue to experience urticaria while taking medications to treat it, it is crucial to educate the patient about this possibility, with emphasis on the relief of pruritus and restoration of a good sleep pattern rather than complete elimination of urticaria.

An algorithm showing recommended pharmacological treatment of urticaria is provided on page 24.

First-line agents

Oral antihistamines. Oral antihistamines (also known as H_1-antihistamines because they are H_1-receptor antagonists) have been available for the past 60 years for the management of chronic urticaria and remain the mainstay of treatment. Current evidence recommends the use of the nonsedating second generation antihistamines (cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine).[1] First generation antihistamines, which have more sedating effects than the second generation antihistamines, are not recommended as first-line treatment because of their impact on alertness.

Oral antihistamines may be used alone or in combination, as listed below.

- Monotherapy: use of a nonsedating antihistamine in an adequate dose. Expert guidelines recommend that the dose can be increased to up to four times the regular dose, although this is off-label use.[1]
- Combination antihistamines:
  - the combination of a morning dose of a nonsedating antihistamine with an evening dose of a sedating antihistamine
  - the combination of a nonsedating H_1-antihistamine with an H_2-antihistamine (an H_2-receptor antagonist) such as cimetidine or ranitidine (off -label use). Studies have shown only modest benefit with this combination in idiopathic urticaria.[11]

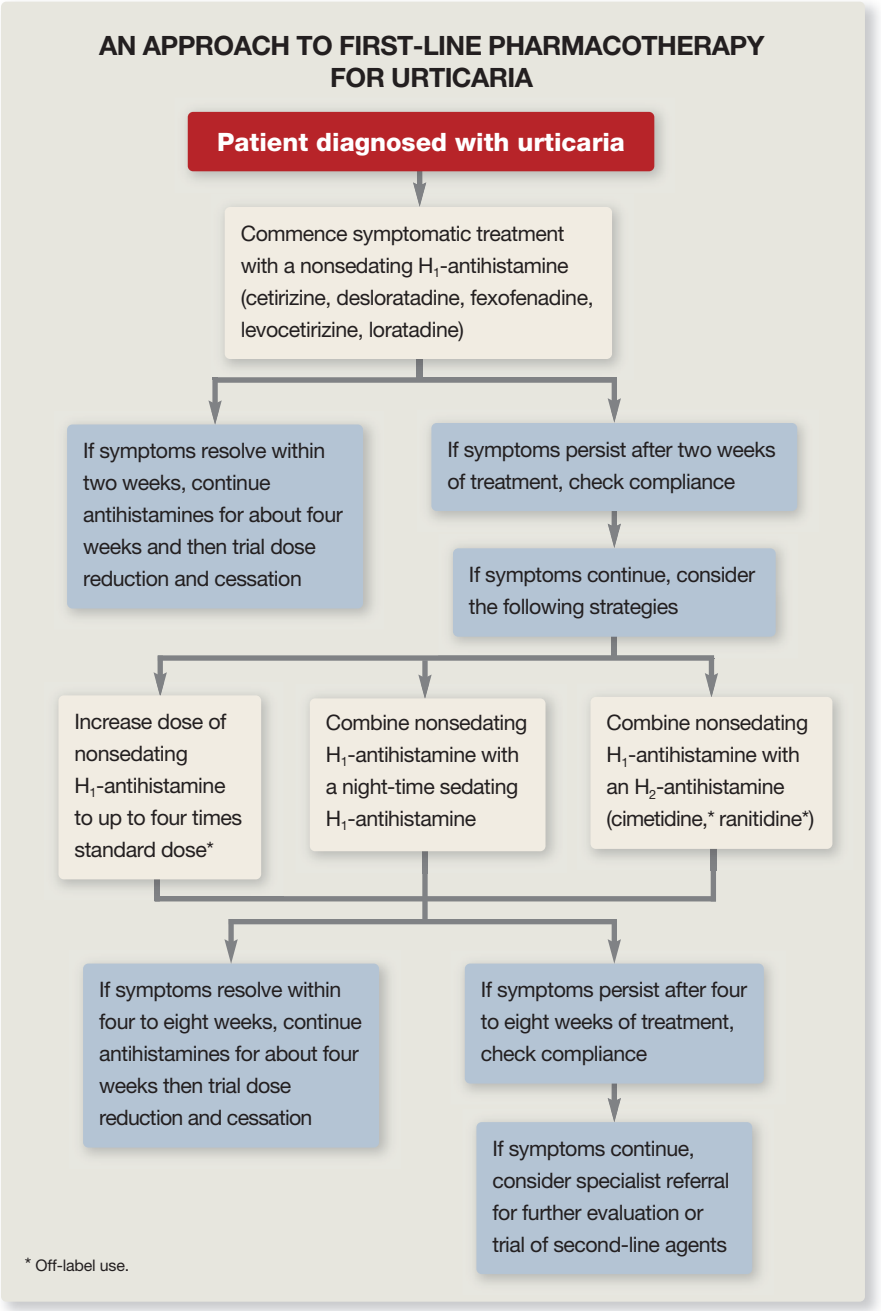
If urticaria clears completely for four weeks, then a trial of back-titrating medication can be attempted. If wheals do not reappear, treatment may then be withdrawn.

Leukotriene inhibitors. Compared with placebo, the leukotriene antagonist montelukast was found to be superior in patients with chronic idiopathic urticaria, although there is no evidence to support any benefit once maximal H_1-blockade has been achieved.[12] (Montelukast is not TGA indicated for urticaria.)

Oral corticosteroids. Oral corticosteroids such as prednisolone may alleviate the symptoms of chronic urticaria when used in the short term in patients with exacerbations. Long-term use is not recommended because of the inevitable side effects of corticosteroid use.[1,13]

Second-line agents

Cyclosporin. The efficacy of cyclosporin in combination with H_1-antihistamines for the treatment of chronic urticaria has been demonstrated in clinical trials.[14] Cyclosporin exerts a direct effect on mast cell mediator release. However, specialist referral, careful patient selection and



monitoring are required because of its potential side effects, especially renal impairment. (Cyclosporin is not TGA indicated for urticaria.)

Omalizumab. A recent multicentre trial has shown that omalizumab (an anti-IgE monoclonal antibody) is effective in the treatment of selected patients with chronic urticaria. However, the cost of this medication and lack of clarity regarding the duration of treatment precludes its regular use.[15] (Omalizumab is not TGA indicated for urticaria.)

Others. Many other drugs have been used in chronic idiopathic urticaria, including tricyclic antidepressants (doxepin), ketotifen, hydroxychloroquine, methotrexate, tranexamic acid, sulfasalazine and dapsone. Various case series have reported some benefit of treatment with these drugs, but there is no high level of evidence for efficacy for any of them.[13,16-19] Doxepin may help with sleep and anxiety.

Special circumstances

Children. Although chronic urticaria is uncommon in very young children, an antihistamine is required when it does occur. Cetirizine has been shown to have an excellent safety profile in young children (infants aged 6 to 11 months).[22] Some formulations of cetirizine and fexofenadine are TGA indicated for the treatment of chronic idiopathic urticaria in children aged 6 months and older.

Pregnancy. Any systemic therapy should be used with caution in pregnancy. Cetirizine and loratadine have not been associated with birth defects in small studies and are generally preferred if an antihistamine is required for the treatment of chronic urticaria in pregnant women.[23-25]

Other therapeutic options

Various other treatment modalities have been trialled in the management of chronic idiopathic urticaria, including phototherapy, intravenous immunoglobulin and plasmapheresis.[20,21] The lack of convincing data restricts the use of these therapeutic options to a trial of treatment in the most severe, resistant cases.

Patient education

Patient education plays a vital role in the management of chronic urticaria. Patients should be informed about the nature of the disease, especially the fact that it may persist for months or even years. They should be told that the cause of this condition is unlikely to be allergy or a serious condition such as malignancy. It is useful to discuss triggers for flares, and also to stress the important role of psychological stress, highlighting the need to manage this.

Emphasis should be given to the need to comply with medication for good control. Patients should be warned about the sedative effects, including driving risks, of first generation antihistamines if

they are prescribed. In general, avoidance of alcohol and NSAIDs should be advised as these agents may worsen urticaria.

Psychological support

Only a few published papers are available on psychological interventions in patients with chronic idiopathic urticaria. Tricyclic antidepressants have been used in the past because of their H_1-receptor blocking activity. Most of the published literature suggests the use of tricyclic antidepressants (for their H_1-receptor blocking activity) and relaxation techniques.[26]

WHEN TO REFER TO A SPECIALIST

Referral to an immunologist or allergist should be considered for patients who have the following:

- chronic urticaria and/or angioedema and who fail to respond to standard treatment
- suspected urticarial vasculitis
- aggressive urticaria with airway angioedema.

CONCLUSION

Chronic idiopathic urticaria is a common condition that can persist for months and can result in significant reduction in the quality of life. Nonsedating antihistamines are the mainstay of treatment and patient education is crucial. MT

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COMPETING INTERESTS: None.