Managing urticaria

Urticaria is a common condition encountered in the community. The key points in management are to classify the nature of the urticaria and to identify the possible triggers. Despite many advances in understanding the pathophysiology of the condition, antihistamines are still the mainstay of treatment.

DENISE C. HSU
BSc, MB BS

CONSTANCE H. KATELARIS
MB BS, PhD, FRACP

Dr Hsu is an Immunology Registrar at Campbelltown Hospital, Sydney South West Area Health Service. Professor Katelaris is Professor of Allergy and Immunology at Macarthur Clinical School, University of Western Sydney, Sydney, NSW.

Urticaria is a common condition, affecting 15 to 25% of the population at some point in their lives. Causes are many and varied. It can cause a great deal of distress as it is intensely pruritic, with significant disfigurement, and its occurrence is unpredictable. It can have a profound impact on patients' sleep, work and social lives.

Definition of urticaria

Urticaria is characterised by the occurrence of pruritic, raised lesions with surrounding erythema that are transient (lasting less than 24 hours) and resolve without scarring (Figure). Angioedema is characterised by swelling involving the lower dermis and subcutis. It is also transient but generally longer lasting than urticaria. Angioedema occurs in 40 to 50% of patients with urticaria.

Urticaria and angioedema occur due to increased permeability of capillaries and small venules triggered by mediator release (especially histamine) as a consequence of mast cell degranulation. This may result from immunological or nonimmunological triggers.

Types of urticaria

The time course differentiates the subcategories of spontaneous urticaria and determines the investigations and treatment involved. Acute urticaria lasts for less than six weeks. Chronic urticaria occurs on most days of the week and persists for months or years.

It is important to differentiate physical from spontaneous urticaria. Physical urticaria is provoked by external physical stimuli, usually soon after contact (except in the case of delayed pressure urticaria). Examples are listed below.

- **Dermographism** is the most common type of physical urticaria, affecting 5% of the population. Whealing is induced by shearing forces on the skin.
- **Cholinergic urticaria** is the next most common form of physical urticaria, often affecting

IN SUMMARY

- **Acute urticaria tends to have identifiable triggers.**
- **A careful history to identify possible triggers is the most useful diagnostic tool in patients with new-onset urticaria.**
- **A trigger or cause is not found in most patients with chronic urticaria despite extensive investigations.**
- **Chronic urticaria caused by physical triggers can be identified by history alone and rarely needs any further investigations (with the exception of cold urticaria, where investigations for an underlying cause is necessary).**
- **It is essential to differentiate chronic urticaria with angioedema from angioedema without urticaria and from urticarial vasculitis as these conditions are associated with different underlying pathology.**
- **Investigations should be tailored to individual patients.**
- **Antihistamines are the mainstay of treatment for urticaria.**

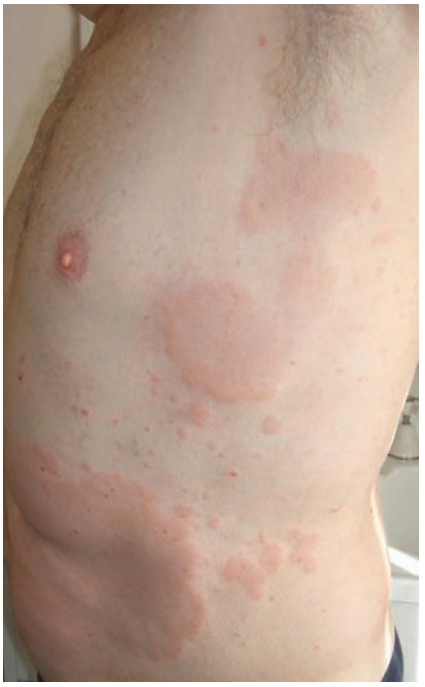

Figure. Urticaria.

young adults. It is usually triggered by changes in core temperature such as that occurring with exercise, hot baths and stress. Symptoms are usually mild, transient and reversed by temperature modification. In most patients, explanation and avoidance of triggers is sufficient management.

- **Delayed pressure** urticaria is characterised by deep painful swelling occurring four to eight hours after exposure to pressure. It typically involves the palms, soles and buttocks.
- **Cold urticaria** is stimulated by a sudden drop in skin temperature.
- **Heat urticaria** is elicited by an increase in skin temperature.
- **Solar urticaria** is elicited by light of wavelengths between 280 to 760 nm and is due to serum factors acting as IgE-dependent photoallergens.

There are usually no serious underlying conditions associated with the physical urticarias, thus extensive investigation is unrewarding. The exception is cold urticaria, which in a minority of patients can be triggered by underlying infections, neoplasia or autoimmune disease.

It is important to remember that more than one type of urticaria can coexist in a patient.

Differential diagnoses

Urticarial vasculitis should be considered if individual lesions last longer than 24 hours, are burning or painful, or leave residual scars or hyperpigmentation. If urticarial vasculitis is suspected, a skin biopsy is prudent to confirm leukocytoclastic vasculitis. Patients with suspected urticarial vasculitis should be referred to an immunologist or dermatologist for further investigations to exclude associated underlying conditions such as hepatitis B, hepatitis C and autoimmune diseases. Treatment often involves immunosuppression with corticosteroids initially followed by maintenance therapy withimmunomodulatory, cortico - steroid-sparing agents.

Urticarial dermatitis may also resemble urticaria, but it is more superficial and individual lesions persist for days to weeks. The condition is usually linked to eczema but can be drug induced.

Recurrent angioedema without urticaria is a condition with a separate list of differentials. The most common cause is ACE inhibitor therapy. This can occur after years of uneventful use of ACE inhibitors.

Hereditary or acquired C1-esterase inhibitor deficiency is another differential to consider. Patients with this rare condition require specific counselling and management and will benefit from early referral to an immunologist.

Causes of urticaria

Acute urticaria

Acute urticaria tends to have identifiable triggers and often patients do not present to their doctor.

In the paediatric population, acute urticaria is most often associated with viral upper respiratory tract infections. The urticaria may recur with each episode of infection. Another common cause of acute urticaria is IgE mediated food allergy, with milk, egg and nuts being the most frequent food allergens identified.

In the adult population, IgE mediated food allergy and reactions to medications are the most common causes of acute urticaria.

Medications can induce urticaria through many different mechanisms. Reactions to penicillins and cephalosporins are IgE mediated. Reactions to NSAIDs and aspirin occur due to inhibition of cyclo-oxgenase and resultant imbalance between prostaglandins and leukotrienes. Reactions to opioids, radiocontrast media and vancomycin are mediated by direct mast cell degranulation.

Table 1 lists some common causes of spontaneous acute urticaria.

Chronic urticaria

Unlike acute urticaria, chronic urticaria is unlikely to be IgE mediated. An external cause for the condition cannot be found

Table 1. Common causes of spontaneous acute urticaria

IgE mediated	
Food allergy – e.g. peanut, tree nuts, seafood, egg, milk	
Hymenoptera venom – e.g. bee, wasp, ant	
Medications – e.g. penicillins, cephalosporins	
Complement mediated	
Postviral infections	
Direct mast cell degranulation	
Radiocontrast media	
Opioids	
Vancomycin	
Imbalance of arachidonic acid metabolism	
NSAIDs	
Aspirin	

in at least 80 to 90% of patients with chronic urticaria. However, within the group of previously termed chronic idiopathic urticaria, 35 to 50% of patients have been found to have complement activating autoantibodies directed at the IgE receptor (FcεRIα).[1] Currently, there is no readily available diagnostic test for the presence of these antibodies.

Many conditions are associated with chronic urticaria. There is increased prevalence of both thyroid disease and subclinical thyroid autoimmunity in patients with chronic urticaria. However, it remains unclear whether the presence of thyroid autoimmunity is an independent risk factor for chronic urticaria. Chronic infections that have been implicated include hepatitis A, hepatitis B and, more recently, *Helicobacter pylori* infection.[2] Other conditions such as systemic lupus erythematosus and neoplasia have also been identified as rare causative factors for chronic urticaria.

Although many patients attribute their chronic urticaria to food allergy, IgE mediated reaction to foods is an unusual cause of chronic urticaria. True IgE mediated food reaction tends to occur within one hour of ingestion, the culprit food is usually identifiable and symptoms are reproducible on re-ingestion of the same food. The role of adverse food reactions secondary to the ingestion of natural food ingredients or food additives in the development of chronic urticaria is controversial. Reported frequencies of positive reactions to food additives vary greatly among studies, ranging from none to more than 80% of studied populations.[3]

Evaluation of patients with urticaria

History taking is the most important tool for identifying the cause for urticaria. A thorough history of known allergies, food ingested, medication use, recent illness and occupational exposure should be obtained (Table 2).

Investigations

Acute urticaria is, by definition, self-limited and requires minimal laboratory evaluation. Skin prick tests with suspected allergens are useful if an IgE-mediated allergic reaction is suggested by the history.

Large numbers of laboratory tests are often performed to elicit possible triggers of chronic urticaria. This is based on the belief that the impact of chronic urticaria on an individual's quality of life makes the screening of a low prevalence underlying disease justifiable. However, a recent systematic review of more than 6000 patients with chronic urticaria found no relation between the number of identified diagnoses and the number of laboratory tests performed.[4]

Laboratory tests should be tailored individually and requested based on clues in the history. Many experts recommend routine differential blood count, erythrocyte sedimentation rate and C-reactive protein measurement. Screening for thyroid hormones, thyroid autoantibodies and antinuclear antibodies can be requested if the history is suggestive in chronic urticaria.

Treatment

In the treatment of urticaria patient education is paramount. It is important to explain to patients that there are usually no health threatening underlying triggers and that the condition tends to be chronic so that patients need to learn how to manage it.

Treatment should be directed at avoiding known triggers and alleviating symptoms. NSAIDs, aspirin, opioid analgesics,

Table 2. Important questions to answer in history taking

Time course of lesions

When did the lesions start?

For how long have the lesions been recurring?

How frequent are the attacks?

Nature of the lesions

Are the lesions pruritic or painful?

How long does each lesion last on the skin?

Is there residual scarring or pigmentation?

Is there associated angioedema?

Are there symptoms suggestive of generalised allergic reaction?

Are there symptoms suggestive of physical urticaria?

Identifying the triggers

Is there a history of drug allergy?

Which medications is the patient taking?

Has the patient recently commenced any medications?

Is there a history of food allergy?

Is there a clear relation between the urticaria and eating?

Has the patient recently had a viral infection?

Is there a relation between the urticaria and the menstrual cycle?

Impact on quality of life

Is sleep, work or social life affected?

Previous therapy

Has the patient responded to previous therapy for the urticaria?

overheating, excessive alcohol intake and stress should also be avoided as these can aggravate the condition.

Acute urticaria resolves spontaneously within six weeks. In the interim, antihistamines are useful for symptomatic relief. Acute urticaria may be the initial manifestation of a more generalised allergic reaction. More intensive intervention such as the use of adrenaline is necessary if symptoms and signs of anaphylaxis are present.

Most symptoms of urticaria are mediated mainly by H_1-receptors. The regular use of antihistamines (H_1-receptor antagonists) has the best evidence of efficacy and remains the mainstay in management of chronic urticaria.[5] All patients who have frequent symptoms should use antihistamines on a daily basis rather than 'as needed'. The effect of antihistamines in urticaria is dose dependent, and many patients will require double the recommended doses. Antihistamines have a good safety profile and are usually well tolerated. Poor response to antihistamines is more common in patients with physical urticaria and those with urticarial vasculitis. Nonresponders to one antihistamine may respond well to another.

There is often a misconception that sedating antihistamines are more effective than less sedating antihistamines. However, meta-analyses have demonstrated that this is not the case. The use of the newer, less sedating antihistamines is preferred as these medications have less frequent adverse reactions and they also inhibit cytokine release from basophils and mast cells. Table 3 lists antihistamines commonly used in the treatment of urticaria.

Table 3. Antihistamines commonly used for the treatment of urticaria

Newer less sedating antihistamines

Cetirizine (Alzene, Zilarex, Zyrtec) – adult dosage: 10 mg daily

Desloratadine (Claramax) – adult dosage: 5 mg daily

Fexofenadine (Chemists' Own Fexo, Fexal, Fexotabs, Tefodine, Telfast, Xergic) – adult dosage: 180 mg daily

Loratadine (Alledine, Allereze, Chemists' Own Loratadine, Claratyne, Hexal Lorano, Lorapaed, Lorastyne) – adult dosage: 10 mg daily

Older sedating antihistamines

Cyproheptadine (Periactin)

Dexchlorpheniramine (Polaramine)

Dimenhydrinate (Dramamine)

Diphenhydramine (Snuzaid Gels and Tablets, Unisom Sleepgels)

Pheniramine (Avil)

Promethazine (Gold Cross Antihistamine Elixir, Phenergan, Sandoz Fenezal)

Trimeprazine (Vallergan)

The addition of an H_2-receptor antagonist (e.g. ranitidine 150 mg twice daily or famotidine 40 mg once daily) is often the next step due to the adjunctive effect of blocking both histamine receptors. A small number of patients derive added benefit from this regimen.

The tricyclic antidepressant doxepin (Deptran, Sinequan), 10 to 25 mg at night, is often useful in more resistant cases as it has both H_1-receptor and H_2-receptor antagonist properties. Its sedative action is also useful if sleep disturbance from pruritus is a major problem.

Glucocorticoids are effective in the treatment of urticaria. However, due to the many side effects and the chronicity of the condition, they should only be used with caution in patients with severe acute exacerbations and for as short a time as possible.

The addition of a leukotriene-receptor antagonist (zafirlukast [Accolate] or montelukast sodium [Singulair]) to antihistamine treatment may be effective in some patients. Cyclosporin (Cicloral, Neoral, Sandimmun; a corticosteroid-sparing agent) may be considered in patients with severe chronic urticaria requiring a corticosteroid for control. It may also be very effective in cases where urticaria is mediated by underlying immune processes. Both leukotriene-receptor antagonists and cyclosporin should be initiated in consultation with an immunologist.

Several other drugs have been used in patients with urticaria with success, but robust evidence of efficacy is lacking. These include hydroxychloroquine (Plaquenil), dapsone, sulfasalazine (Pyralin EN, Salazopyrin), tacrolimus (Prograf), methotrexate (Methoblastin), cyclophosphamide (Cycloblastin, Endoxan),

continued

Table 4. Steps to treating patients with urticaria

Step 1. Treat patient with an H_1-receptor antagonist. Ensure the patient takes regular, adequate doses.
Step 2. If there is no improvement, add an H_2-receptor antagonist to the regimen.
Step 3. If there is no improvement and/or if symptoms are causing sleep disturbance, add doxepin to the regimen. Also consider the patient's diet and whether he or she has a chronic infection or thyroid autoimmunity.
Step 4. If there is still no improvement, refer the patient to an immunologist or other appropriate specialist for consideration of treatment with a leukotriene-receptor antagonist, cyclosporin, hydroxychloroquine or other immunomodulating agent.

interferon, and plasmapheresis and intravenous immunoglobulin.

Table 4 summarises the steps in the treatment of urticaria.

Other treatment modalities

Elimination diet

A diet containing low levels of natural and artificial food substances for three to six months has been shown to achieve spontaneous remission of urticaria in about 50% of patients.[6] However, as mentioned previously, there is little evidence that adverse food reaction is an important cause of chronic urticaria. Many patients are therefore subjected to unnecessary dietary restrictions, some even to the extent of malnutrition. Thus it is important to conduct an elimination diet under supervision of a dietitian and to discontinue this after a few weeks if there is no improvement.

Eradication of persistent infections

Clinically identifiable chronic infections should be eradicated. A systematic review on chronic urticaria and *H. pylori* infection showed that remission is more likely following eradication.[7] Chronic urticaria may take eight to 12 weeks to settle after eradication of infection.

Thyroid hormones

Small studies have shown that treating patients who have both chronic urticaria and thyroid autoimmunity with thyroxine (Eutroxsig, Oroxine) leads to significant improvement in their urticaria.[8] Some of these patients were euthyroid. However, before more conclusive evidence is available, routine administration of thyroxine to euthyroid patients with chronic urticaria and thyroid autoimmunity cannot be recommended.

Course of chronic urticaria

Chronic urticaria of unknown aetiology spontaneously remits in 47% of patients after one year. Patients with physical urticaria have more persistent disease, with only 16% undergoing spontaneous remission after one year.[9]

When to refer

Referral to an immunologist or other appropriate specialist is advisable for patients with the following:

- chronic angioedema without urticaria
- suspected urticarial vasculitis
- urticaria poorly responsive to a combination of H_1- and H_2-receptor antagonists.

Summary

Urticaria is often encountered in the general practice setting. Although acute urticaria tends to be easy to manage, caring for patients with chronic urticaria can be challenging and at times frustrating as a cause is not usually identifiable even after extensive investigations. Symptoms can be severe and persistent over months or years and the condition can have a great impact on a patient's quality of life. With increased understanding of the autoimmune basis of chronic urticaria and the role played by chronic infection and diet, treatment of chronic urticaria will become more satisfying and successful. MT

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DECLARATION OF INTEREST. None.