Urticaria – diagnosis and management

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Educational aims

- To make a more confident clinical diagnosis of urticaria
- To increase familiarity with the commonest causes and triggers of urticaria
- To update the knowledge on management of urticaria

Key words
Urticaria, angioedema, oral antihistamines, omalizumab

Abstract

Urticaria is a common and characteristic skin condition presenting with wheals and/or angioedema. It may be acute or chronic and has various causes and triggers. Patients with urticaria are often referred to allergy clinics to find out 'what they are allergic to'. Urticaria may impact significantly on a patient's quality of life. Its management involves identifying and removing causes or triggers, together with oral antihistamines as first line treatment for symptomatic control. Omalizumab is a recently licensed expensive treatment option for patients with urticaria resistant to oral antihistamines, and has shown a high success rate and good safety profile.

Introduction

Urticaria, also known as 'nettle rash' or 'hives', is a reaction pattern that gets its name from the Latin word for nettle (*urtica*). The nettle is a weed with stinging hairs that causes contact urticaria. Urticaria describes a reaction pattern with characteristic features and may have many causes or triggers. It is described as acute if it lasts less than 6 weeks, or chronic if it lasts 6 weeks or longer. Some patients have episodic acute intermittent urticaria lasting for hours or days and recurring over months or years.

Urticaria is a very common condition, occurring across all age ranges. It has a lifetime prevalence of approximately 20% in the general population. The chronic form affects 1-3% of the population.[1] When severe and extensive, it often prompts patients to seek treatment in the emergency department; in fact, it is the most common skin disease treated in the emergency department. Patients with urticaria may also seek advice from their pharmacist. Most new-onset urticaria resolves spontaneously within days or a few weeks. However, at least 20% of chronic urticaria patients with symptoms severe enough to warrant hospital referral remain symptomatic 10 years after first presentation.[2] Although rarely life-threatening, chronic urticaria leads to both misery and embarrassment and has a significant impact on an individual's quality of life.[3]

Box 1 summarizes the main clinical features of urticaria.[4-6] It is typical of patients with urticaria to have no evident lesions at the time of their doctor's visit. In this situation, a good history is sufficient to make the diagnosis. Patients may also bring photos of their rash to the clinic.

The characteristic urticarial wheals affect the superficial skin layers (papillary dermis). When the submucosa, the deeper reticular dermis and subcutaneous tissues are involved, the resulting deep swelling is called **angioedema**. This is often most notable in the eyelids and lips. These swellings can be painful rather than itchy. Urticarial wheals and angioedema often coexist, but either can occur separately. Unlike wheals that individually resolve within 24 hours, angioedematous swellings can persist for a few days. Disfiguring when they occur in the skin, they can be extremely alarming and occasionally life-threatening when they occur in the oropharynx.

Urticaria needs to be differentiated from other medical conditions where

Box 1: Clinical features of urticaria

- Pink, non-scaly, itchy or sometimes burning swellings (wheals) that can occur anywhere on the body and blanche with pressure.
- Lesions of urticaria can be polymorphic and vary from several millimetres to large, continuous plaques.
- Individual wheals do not last longer than 24 hours, fading without a trace and without scars, but new wheals may continue to appear for days, months or even years.
- Patients with urticaria tend to rub their skin rather than scratch, so heavily scratched skin is rarely, if ever, a consequence of urticaria.
- Patients show no or minimal systemic symptoms. Patients often feel fatigued, especially during relapses, but headache, dizziness, syncope, or respiratory, gastrointestinal or arthralgic symptoms are rare.

wheals, angioedema, or both can occur as a symptom, for example skin prick test, anaphylaxis, or hereditary angioedema.

Pathogenesis

The *mast cell* is the primary agent in the pathogenesis of urticaria. Mast cell stimulation results in the release of both preformed (*histamine*) and newly formed mediators (prostaglandins) from cytoplasmic granules, which cause wheal formation, vasodilatation, oedema (due to increased microvascular permeability) and erythema. Mast cells release chemoattractants for other cells (for example eosinophils and neutrophils) that are also involved in wheal formation. A number of agents may be involved in the pathogenesis of urticaria, which may explain why antihistamines are not always effective therapy.[7]

Release of mediators by mast cells may be caused by both immune and nonimmune mechanisms. All mast cells express high-affinity IgE receptors (FceRIs) that enable their involvement in IgE-dependent allergic reactions. When IgE forms a complex with FceRI on the mast cell to which an allergen binds, degranulation occurs. Examples of IgE-mediated urticaria include acute urticaria secondary to foods (for example peanuts, eggs, shellfish), animal dander, stinging insects, some medications (for example beta-lactam antibiotics) and latex.

Mast cell degranulation also occurs through a variety of other mechanisms. Some agents, such as opioids and radiocontrast media, cause mast cell degranulation directly through nonimmunologic means. In chronic spontaneous urticaria (CsU, previously called chronic idiopathic urticaria), there appears to be persistent activation of mast cells in the skin, but the precise mechanism is unknown. Functional auto-antibodies against the FceR1 on the mast cell surface have been demonstrated in 30–40% of patients with chronic urticaria suggesting an autoimmune basis. This variant of chronic urticaria is described as chronic autoimmune urticaria (CaU). Patients with CaU tend to follow a more aggressive course and often require more aggressive therapy.[8]

The commonest type of angioedema without wheals is histaminergic.

Angioedema without wheals is a cardinal feature of hereditary angioedema (HAE), which is bradykinin-mediated and typically involves subcutaneous sites, gut and larynx. In Types I and II HAE, levels of C4 and C1 inhibitor (functional and/or antigenic) are low.[9]

Commonest causes and triggers of urticaria and angioedema

Acute urticaria

A definitive inciting agent can be identified in about 50% of cases of acute urticaria and angioedema. Infections, medications and food were identified as the commonest causes.[4] Acute urticaria is considered to be a classical manifestation of viral infection in general, especially in children, but also in adults.[10] When the trigger is a viral upper respiratory tract infection (URTI), the patient should be informed of the self-limiting duration of the disorder. Other viruses (for example hepatitis or herpes viruses) or infections (including streptococcal infections and chronic parasitic infections) may also be possible triggers.

Drug triggers

Acute urticarial reactions from drugs are common. The commonest drugs to trigger urticaria are nonsteroidal anti-inflammatory drugs (NSAIDs), salicylates, codeine and antibiotics, especially penicillins, cephalosporins, tetracyclines and sulphonamides. Urticaria usually comes on within a few hours of exposure to the drug. A notable exception is angioedema secondary to angiotensin converting enzyme (ACE) inhibitors (refer to Box 2).[5]

Box 2: Angiotensin converting enzyme (ACE) inhibitor-induced angioedema

- ACE inhibitors can cause angioedema without wheals resulting in airway compromise. The patient usually presents with swelling of the tongue, but the lips, pharynx, larynx and viscera may also be involved.
- Fatalities are reported and, hence, it is mandatory to recommend that the ACE inhibitor is withdrawn.
- ACE inhibitors are contraindicated in individuals with a history of angioedema with or without wheals.
- The mechanism underlying the angioedema is likely to be due to the reduced metabolism of bradykinin.
- Angioedema associated with angiotensin receptor blockers has been occasionally reported and hence their use in individuals with ACE inhibitor-related angioedema has been questioned but is not contraindicated.
- The incidence of ACE inhibitor-induced angioedema may be as high as 0.68%.
- Most cases were initially thought to occur in the first weeks of treatment, but it is now appreciated that later onset angioedema, occurring after many years of uneventful drug use, is quite common.
- The episodes of angioedema may persist for several months after withdrawal of the ACE inhibitor without undermining the validity of the drug-related diagnosis.
- Individuals who do not improve even after several months of stopping the ACE inhibitor are likely to have an alternative explanation for their angioedema and were coincidentally taking an ACE inhibitor.
- There are no routine investigations to distinguish responders from non-responders to ACE inhibitor withdrawal. If the ACE inhibitor is responsible but is not withdrawn, the attacks may become more severe and frequent.

Food triggers

Acute urticarial reactions to food are believed to be common and many go unreported. Food allergy should be considered in acute urticaria and urticaria in children. Such foods as tree nuts, peanuts, eggs, shellfish, and tomatoes should be considered (the involvement of food additives or preservatives is controversial). Urticarial reactions may not be to the basic nutrient but to other constituents such as spices. Usually, reactions occur within minutes or a few hours but sometimes allergic urticaria develops many hours after food ingestion. This may occur due to slow absorption or metabolism of food, or because the mechanism is IgG-mediated. Urticaria occurs consistently after every exposure to the problem food. A careful history is normally adequate to determine if a particular food is causing urticaria in a patient. Testing for serum IgE to the food is occasionally performed to help confirm a clinical suspicion. Rarely, allergic reactions to food may occur only if intake is followed by exercise, with neither the food nor exercise alone inducing wheals. Substances reported to cause this include wheat, hazelnuts and shellfish. Box 3 summarizes some important features of IgE-mediated food-induced urticaria/angioedema.[5]

Chronic urticaria

Most cases of chronic urticaria are thought to have an autoimmune origin. Autoimmune conditions (including thyroid disease, vitiligo, insulin-dependent diabetes, rheumatoid arthritis, and pernicious anaemia) are associated more frequently with chronic urticaria patients having functional autoantibodies than in those without autoantibodies. URTI and psychological factors, including stressful events, are thought to aggravate chronic urticaria. Rarely is food allergy the cause of chronic urticaria and food can typically be excluded on the basis of the clinical history. Alcohol can aggravate chronic urticaria by its effect of vasodilation.[5]

Inducible urticarias

Inducible urticarias are responsible for approximately 20-30% of cases of chronic urticaria. In some patients, the triggering stimuli are the predominant cause of the condition, whereas in other patients it is an incidental factor in a case of chronic urticaria. Inducible urticarias are reproducible with the appropriate stimuli and can be identified with a thorough history and sometimes challenge testing. In many patients, the condition gradually improves and clears after several years, for example after 2-3 years, but the duration is usually quite unpredictable.[11]

- Patients with *symptomatic dermographism* (writing on the skin) can be diagnosed in an office setting by stroking the skin with a firm object, such as a tongue depressor. This action provokes a typical, itchy, wheal-and-flare response within a few minutes, usually resolving within an hour.
- Patients with *cholinergic urticaria* get numerous small pruritic wheals after sweating, for example following exercise or emotion.
- Patients with *delayed pressure urticaria (DPU)* suffer from erythema and swelling, associated with itch and/or pain, typically 4-6 hours after a pressure stimulus.
    - Examples of pressure stimuli include standing, walking, sitting on a hard surface, using tools (such as a screwdriver or a hammer), hand-clapping, carrying a handbag or wearing tight-fitting clothes, especially at the waistline. Patients with DPU may be significantly limited in activities of daily life.
    - Lesions can occur anywhere, but are especially common on the hands and feet. They may persist for three days and may be associated with flu-like symptoms.
- Patients with *cold urticaria* develop an urticarial rash and/or angioedema within 2-5 minutes of being exposed to cold, cold water, cold wind and cold objects. Symptoms usually last for a few hours. In very severe cases, hypotension, shock, collapse and even death may occur, often after swimming in cold water.
    - Cold urticaria may be primary (idiopathic) or secondary to an underlying haematologic (for example cryoglobulinaemia or chronic lymphocytic leukaemia) or infectious disease (for example varicella or glandular fever); most cases are idiopathic.
- *Contact urticaria* refers to the onset of urticaria within 30-60 minutes of contact with an inciting agent, for example latex, plants (including the stinging nettle), animals (caterpillars, dander), medications and food (for example fish, garlic, onions, tomato).
- Other forms of inducible urticaria include *aquagenic urticaria, vibratory urticaria* and *solar urticaria*.

Some conditions that may be confused with urticaria

- *Arthropod bites*. Pruritic papules and papulovesicles with a central punctum appear on exposed skin and usually take more than 24 hours to resolve. Sometimes arthropod bites trigger a hypersensitivity reaction called *papular urticaria*. In this case, the itchy red papules can come up even under tight clothes, in areas away from the bites.
- *Polymorphic light eruption* (PLE). This is a reaction to the sun, coming up after minutes or hours of sun exposure, typically on skin that is having its first exposure to the spring or summer sun. Lesions last for several days. PLE usually becomes less of a problem as the summer progresses, as the skin gets 'hardened' to the sun. PLE is much commoner than solar urticaria, in which wheals develop within 5-10 minutes of sun exposure and usually resolve within an hour.
- *Urticarial vasculitis*. In this variant of vasculitis, lesions look like urticarial wheals, but they burn rather than itch, last longer than 24 hours and tend to leave a bruise-like stain on fading. Urticarial vasculitis is usually confirmed by taking a skin biopsy and is investigated as for other forms of vasculitis.

Box 3: IgE-mediated food-induced urticaria/angioedema

- Symptoms typically occur reproducibly within 60 min of exposure to the offending food rather than coming on overnight or being present first thing in the morning.
- Symptoms do not last several days.
- Additional symptoms are usually present, such as oropharyngeal itching and discomfort, wheezing, vomiting or abdominal pain.

- *Scombroid food poisoning*. This is a foodborne illness that results from eating spoiled (decayed) fish, especially mackerel, tuna, bluefish, mahi-mahi, bonito, sardines, anchovies, and related species of fish that were inadequately refrigerated or preserved after being caught. It resembles an allergic reaction, but is actually due to histidine that exists naturally in many types of fish, which is broken down by bacteria into histamine at temperatures above 16°C. Histamine is not destroyed by normal cooking temperatures, so even properly cooked fish can be affected. Symptoms consist of skin flushing (especially of the face, spreading to the torso), facial sweating, throbbing headache, burning-peppery taste sensations in the mouth and throat, abdominal cramps, nausea, diarrhoea, palpitations, a sense of unease, and, rarely, collapse or loss of vision. Symptoms usually occur within 10–30 minutes of ingesting the fish and are generally self-limited, but respond quickly to oral antihistamines.[12]

Clinical history and examination

A detailed history in a patient with urticaria and/or angioedema is essential. Note should be made of the nature, site and duration of individual wheals, and whether they are itchy or painful. The circumstances of onset and any triggers should be noted, together with the frequency and pattern of recurrence. A family history and detailed drug history are important, as well as response to previously attempted treatments. The clinical history often identifies relevant triggers and directs any further investigations.

Laboratory investigations

The diagnosis is based primarily on the clinical presentation. The need for investigations to elucidate a possible underlying cause should be guided by the history, but may not be necessary in patients showing a good response to antihistamines. Complete blood count (CBC) and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) are often performed routinely in patients with chronic urticaria.[6]

In patients with angioedema without urticaria, and who are not on ACE inhibitors, it is important to rule out C1 esterase inhibitor deficiency. A normal plasma C4 during an attack or normal C4, C1 inhibitor, and C1 inhibitor function between attacks, will typically exclude this.[5]

Management

In patients with acute urticaria and associated shortness of breath, suggesting respiratory involvement and a diagnosis of angioedema, the patient should be monitored in the emergency department until normal airway function is restored. Adrenaline should be used when laryngeal angioedema is suspected.

An adrenaline autoinjector is rarely required and should only be considered if there is a history of significant angioedema affecting the upper airway (rare in angioedema with urticaria). The patient should then be shown how to use the device and provided with a written self-management protocol. For patients with a known history of hereditary angioedema, C1 esterase inhibitor concentrate, ecallantide, or icatibant should be administered as soon as an angioedema attack is recognized.

Acute urticaria restricted to the skin and chronic urticaria do not require hospitalization and can be managed with outpatient care. Inpatient care for angioedema is usually not necessary when timely treatment is administered.[5,6]

General measures

Any triggering foods or drugs identified from the history should be withdrawn. Aggravating factors such as heat, tight clothing, stress, overtiredness and alcohol, as well as trigger stimuli for physical urticaria should be avoided if possible. It is important to reassure anxious patients that the eruption is not a hallmark of cancer, HIV infection or other underlying disease.

Certain medications, such as aspirin and NSAIDS, are reported to exacerbate urticaria in patients with chronic urticaria resulting from other causes. Their avoidance in favour of paracetamol as an analgesic should usually be recommended because these drugs aggravate chronic urticaria in about 30% of patients. Patients taking low-dose aspirin for its antithrombotic properties can usually continue regular treatment, although non-aspirin alternatives, such as clopidogrel, are available. It is good practice to recommend avoidance of codeine and other opiates in view of the enhanced skin test reactions to codeine found in chronic urticaria, but the value of this is unclear. It is common to see exacerbations of chronic urticaria at the time of minor viral infections, and it may be difficult to differentiate between a flare caused by the illness and a flare caused by medication taken for it.[5,6]

Oral antihistamines

Oral antihistamines active against the H1 receptor remain the mainstay of treatment in patients with urticaria, providing control of symptoms.[3,4] There are several on the market. First-generation (sedating) antihistamines and their recommended adult doses include chlorphenamine (4mg every 4-6 hours), diphenhydramine (25-50mg every 4-6 hours), hydroxyzine (25-100mg daily) and promethazine (25mg nocte). Second-generation (non-sedating or minimally sedating) antihistamines with their licensed adult doses include acrivastine (8mg, 1-3 times a day), bilastine (20mg daily), cetirizine (10mg daily), desloratadine (5mg daily), fexofenadine (180mg daily), levocetirizine (5mg daily), loratadine (10mg daily), mizolastine (10mg daily) and rupatadine (10mg daily).

Individual patient responses and side-effects to antihistamines vary. Due to the absence of head-to-head comparisons in clinical trials, none can be recommended over others, but non-sedating or minimally sedating antihistamines are generally preferred. The older first-generation sedating antihistamines have pronounced anticholinergic effects and sedative actions on the central nervous system, which last longer than 12 hours, whereas the antipruritic effects last only for 4-6 hours. Many interactions have been described for these sedating antihistamines with alcohol and drugs affecting the central nervous system. They can also interfere with rapid eye movement sleep and impact on learning and performance.[13]

It is recommended that modern second-generation H1-antihistamines are to be used as first-line treatment of urticaria because of their good safety profile.

The usual once-daily dose may be increased incrementally in resistant cases up to 3-4 times the recommended dose (off-label). Updosing with a single antihistamine is preferable to mixing different antihistamines. Patients should be advised that antihistamines work best when they are taken regularly.[14] In patients with chronic urticaria, treatment for 6 or even 12 months is advised, with gradual withdrawal over a period of weeks. Safety data is available for

Box 4: Oral antihistamines in children

- Cetirizine and desloratadine are licensed for the treatment of chronic urticaria in children from 1 year of age.
- Loratadine and levocetirizine are licensed for the treatment of children 2 years and older.
- Acrivastine, bilastine, fexofenadine, mizolastine and rupatadine are licensed for use in children over 12 years.
- Desloratadine, levocetirizine, loratadine and cetirizine are available in syrup formulations.
- The metabolism of cetirizine in children is different to that in adults; hence, this drug should be taken twice daily.
- First-generation sedating antihistamines should be avoided due to the risk of psychomotor impairment, impacting on the child's safety and education. Those licensed for use in childhood include diphenhydramine, hydroxyzine, promethazine and chlorphenamine.

oral antihistamines taken continuously for several years. For patients with infrequent symptoms, treatment may be taken as required or even prophylactically (for example prior to an important event such as a wedding or a work presentation).

A trial of up to fourfold dose of modern second-generation H1-antihistamines is recommended as second-line in the algorithm of treatment.

Box 4 summarizes the use of oral antihistamines in children, while Box 5 indicates the recommended antihistamines in pregnancy and during breast-feeding.[5]

Treatment in resistant cases

Oral corticosteroids may occasionally be required in short rescue courses for angioedema affecting the mouth or for severe exacerbations of chronic urticaria that have not responded to full-dose antihistamines. Examples are 30-40 mg of prednisolone daily for 1-3 days reducing to zero over 10 days, or 30-40 mg daily for 3-7 days. Prolonged daily treatment with oral corticosteroids nearly always leads to severe systemic toxicity accompanied by poor control of urticaria and severe rebound on attempts to withdraw.[5,6]

Third-line treatment for resistant cases includes cyclosporine, montelukast and omalizumab. Efficacy of ciclosporin A in combination with a modern second-generation H1-antihistamine has been shown in placebo-controlled trials as well as open controlled trials. This drug does have a high incidence of adverse effects, but it has a far better risk/benefit ratio than long-term use of oral corticosteroids. Anti-leukotrienes such as montelukast may be useful in urticaria patients who are sensitive to aspirin. *Omalizumab* is a recently licensed humanized monoclonal anti-IgE antibody indicated in patients with spontaneous and autoimmune chronic urticaria who have persistent symptoms despite high-dose antihistamines. It is expensive and requires monthly injections but appears well-tolerated. It is effective in approximately 80% of individuals with persistent and resistant symptoms, leading to a rapid improvement. Currently, treatment is recommended for 6 months, but typically relapses occur when treatment is discontinued.[15,16] Figure 1 illustrates the EAACI/GA2LEN/EDF/WAO (2013 revision and update) recommended treatment algorithm for urticaria.[6]

Some other (off-label) treatment options for resistant cases include dapsone, mycophenolate mofetil and methotrexate. Tranexamic acid may benefit patients with antihistamine-resistant angioedema without wheals. Due to the migrating nature of urticarial wheals, topical steroids are not indicated. Cooling antipruritic lotions such as 2% menthol in aqueous cream can, however, be soothing.

Conclusion

In patients with urticaria, the history and physical examination are crucial while undirected laboratory examination is typically fruitless. Although acute urticaria often has an identifiable trigger (foods, drugs, virus), chronic urticaria frustratingly tends to remain idiopathic. About 30–40% of patients with chronic idiopathic disease appear to have an autoimmune aetiology. Second-generation H1 receptor antihistamines represent the first-line therapy for urticaria.

Box 5: Oral antihistamines in pregnancy and breastfeeding

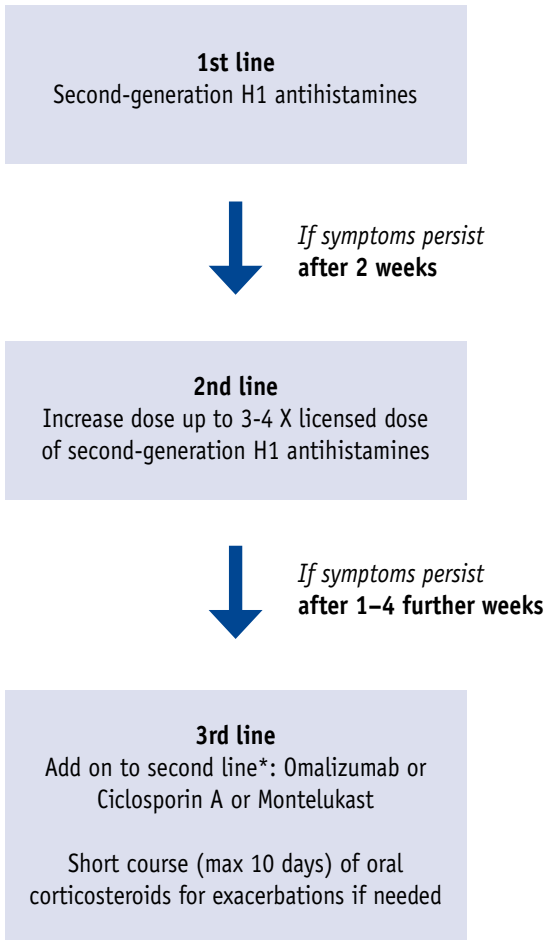
- If an antihistamine is required in pregnancy, the lowest dose of loratadine, cetirizine or chlorphenamine should be used. Loratadine and cetirizine have been assigned a category B by the US FDA. Hydroxyzine is specifically contraindicated in early pregnancy.
- If an antihistamine is required during breastfeeding, it is recommended that either cetirizine or loratadine are taken at the lowest dose. Whenever possible, chlorphenamine should be avoided during breastfeeding as it may cause drowsiness and poor feeding.

Key points

- A diagnosis of urticaria is usually easily made from the clinical history
- Triggers and aggravating factors can often be elicited by taking a good history without the need for testing
- Any potential triggers or aggravating factors should be removed where possible
- Modern second-generation oral antihistamines are indicated as first-line treatment in patients with urticaria, with updosing if necessary
- Omalizumab (anti-IgE) is a new treatment option in patients who do not respond to oral antihistamines or second-line treatment options

Figure 1: The EAACI/GA2LEN/EDF/WAO (2013 revision and update) recommended treatment algorithm for urticaria[6]

**The order of third-line treatments does not reflect preference*



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