

Review Article

Urticaria and Angioedema – A Practical Perspective

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Abstract

Urticaria and Angioedema affect a significant proportion of the population. Symptoms lasting <6 weeks are defined as acute and causes include infection, and allergy. Chronic Urticaria is defined by wheals and/or swelling lasting for >6 weeks. While reversible causes such as chronic infection or medications are sometimes implicated, often no trigger is found. This is known as Chronic Spontaneous Urticaria and in the majority of patients, symptoms resolve within 1 year.

Investigations for all types of Urticaria and Angioedema are guided by the history and examination and particularly by the duration of the urticarial patches. A vasculiticurticaria is suggested when the latter last >36hours and bruising is evident as they fade. Relevant skin prick tests or specific IgE should be performed only if an allergic trigger is evident. Asymptomatic thyroid autoimmunity is frequent in CSU and suggests a possible pathogenic mechanism for the condition. Anti-helicobacter serology is indicated if there is significant dyspepsia.

Management includes treating the underlying cause if one is identified. Symptoms control is managed stepwise starting with regular non-sedating antihistamines which can be titrated up to 4 times the usual recommended dose. Montelukast can be added as a second line treatment but sometimes additional agents are needed. The newest one is an anti IgE monoclonal antibody called Omalizumab which is now used in preference to older medications such as Ciclosporin. Vasculiticurticaria requires attention to the underlying antigenic source and in addition to anti-histamines may require steroids and disease modifying agents.

ABBREVIATIONS

CSU: Chronic Spontaneous Urticaria; HAE: Hereditary Angioedema; NSAID: Non-Steroidal Anti Inflammatory Drug; ACE: Angiotensin Converting Enzyme; CU: Chronic Urticaria; AAE: Acquired Angioedema; ESR: Erythrocyte Sedimentation Rate; SLE: Systemic Lupus Erythematosus

INTRODUCTION

Urticaria and angioedema describes the sudden appearance of wheals or swellings [1]. The urticarial wheals are frequently short-lived, slightly raised, itchy red patches anywhere on the body. Angioedema describes swelling occurring slightly deeper in the skin and mucous membranes. Urticaria may affect more than 20 to 25 % of the population at some point in their lives. Most patients suffer both urticaria and angioedema although one may predominate in some patients. Urticarial patches are often pale in the centre and vary from a few millimetres to ten or more centimetres across. These patches can sometimes become confluent giving the impression of diffusely swollen, itchy red skin. They can affect any area of the body and usually last from 30 minutes to as long as 48 hours or more. Apart from the discomfort of the itching, systemic symptoms are usually absent in simple

urticaria and angioedema. Some patients may feel tired. When the individual patches of urticaria last longer than 36 hours or are associated with bruising then an inflammation of cutaneous blood vessels should be suspected as part of a cutaneous vasculitis [2]. The latter is often associated with arthralgia, myalgia and mild fever. Regardless of the aetiology, chronic spontaneous urticarial (CSU) has a major adverse effect on quality of life [3,4].

PATHOPHYSIOLOGY

The erythema, itching and swelling evident in urticaria is caused by the activation of mast cells either by antigen cross linking cell surface antigen specific IgE antibodies or possibly by anti-IgE auto-antibodies [5,6]. In some cases, there may be direct mediator release by unmyelinated nerve terminals or activation of the kinin system. Histamine appears to be the principal mediator [5] involved in the early phase response while others such as leukotrienes and prostaglandins are produced in the late phase response via arachidonic acid metabolism. Several other mediators such as complement proteins, neuropeptides, platelets, platelet activating factor, kinins, oxidative stress and various chemokines have varying importance in the different types of urticaria and angioedema [7-9]. Upregulation of substance P has been demonstrated to play a role in histamine release and

basophil accumulation in chronic spontaneous urticaria [10]. Histologically, there is dilation of small venules and capillaries, flattening of Rete pegs, and swelling of collagen fibres [2,11]. The multitude of the mediators involved explains why urticaria is sometimes poorly responsive to anti-histamines alone. The ability of the unmyelinated nerves to directly release some of the mediators [12] may explain why urticaria is sometimes precipitated by and often aggravated by stress and changes in mood [13].

Aetiology of urticaria

When trying to determine the cause of the urticaria and angioedema it is initially important to separate an acute from chronic urticaria by noting the frequency of the urticarial reactions and the total duration of the illness.

In acute simple urticarial [1], the episodes are isolated events and may be caused by food allergy, seasonal exacerbations of asthma [14], viral infection (which may be subclinical), insect bites/stings or drug reactions (aspirin, NSAIDs, penicillin etc). A causal relationship between these factors and the urticaria is often apparent from the history.

In some patients, small discrete patches of urticaria may be evident with heat or exercise and indicate a cholinergic urticaria. In other patients the urticaria may be precipitated by physical factors such as pressure, cold and sunlight. Dermatographism describes urticarial wheals when the skin is scratched. This can be a significant long term problem requiring regular anti-histamine therapy for years to control urticarial wheals sometimes evident even with rough clothing. In patients with cold urticaria, significant hypotension may occur if patients swim or bathe in cold water and care is required to avoid fatal reactions.

Chronic Spontaneous Urticaria (CSU) describes of the presence of regular (≥ 3 per week) urticarial reactions for more than six weeks [13]. In the absence of any features of vasculitis these are described as idiopathic. Allergy to specific foods or sensitivity to colourings and preservatives is almost never involved in CSU. In some patients there may be an autoimmune basis [5]; a temporary dysregulation of the immune system by a viral infection or sustained stress or strong emotions leading to autoantibodies directed against the IgE receptor (FcεRI) or against IgE itself. In either case, there is direct mast cell activation that bypasses the need for the IgE antibody to bind a specific allergen. Chronic spontaneous urticaria has been demonstrated to be associated with an atopic predisposition, and therefore, this should be assessed for routinely [15].

In western countries, worm and parasitic infestation [16,17] is rarely a cause of chronic urticaria although it should be considered if the patient has undertaken recent foreign travel. When chronic angioedema occurs in isolation of any urticaria, it is important to exclude drugs as a cause. These include ACE inhibitors e.g. Enalapril and sometimes selective serotonin reuptake inhibitors. If the patient is not taking any such medication, then the presence of infection within the sinuses or teeth should be explored and, if present, treated appropriately. Chronic Urticaria may be worsened by the use of ACE inhibitors and NSAIDs [18,19] and it is worth discontinuing or using alternatives if this is possible. Where angioedema is the sole problem, is associated with recurrent abdominal pain, difficulty breathing and occurs in a child or young adult it is important to check for hereditary

angioedema (HAE, see later). While HAE is dominantly inherited, there are cases due to new mutations in the C1 esterase inhibitor gene [20]. It is important to recognise this condition owing to the danger of airway occlusion [21].

Where a vasculitic urticaria is suspected, it is important to check for the symptoms and signs of illnesses associated with immune complex deposition and immune dysregulation accompanied by autoantibody formation. These include systemic connective tissue disorders such as SLE, chronic infection in the sinuses, lungs, urinary or gastrointestinal tract for any symptoms suggestive of a lymphoma. The role of helicobacter induced gastritis in CSU is unclear with some suggesting an important aetiological role while others have discounted it as a coincidental infection. In the experience of the authors there are certainly individuals with helicobacter infection [22] whose CSU resolves after triple treatment. It is important to determine if there are any factors that are perpetuating the urticaria [1] e.g. stress and frustration or chronic infection such as sinusitis or dental abscess.

It is important to tell patients with CSU that a cause may not be found in 70-80% even with the most detailed examination and laboratory investigation. For these patients with idiopathic urticaria a careful diary [23] may help to pinpoint possible triggers. However, patients should be warned not to let this search take over their whole life as this frequently leads to increased stress that may prolong the urticaria.

Critical points in Urticaria

If the urticarial wheals or swellings of angioedema start more than 4 hours after the previous meal then food allergy is exceptionally unlikely. In this regard patients who awake in the morning with urticaria and angioedema having gone to sleep without it almost never have food allergy as a causative factor. The exception here is the urticaria that can occur with meat allergy arising from IgE antibodies to alpha galactose 1,3 galactose [24] in the setting of tick bites.

If the urticarial wheals last more than 36 hours, fade with bruising and are accompanied by systemic symptoms of fever, arthralgia, myalgia, then an urticarial vasculitis should be suspected and a search made for an underlying chronic infection, lymphoproliferation or systemic autoimmunity.

In many individuals, stress is present in low levels and patients only become aware of its presence when specifically sought in the clinical history and when stress reduction measures improve CSU.

The dermatographism evident in some patients with CSU can persist long after the spontaneous wheals have disappeared and require long term anti-histamines. Specifically asking about the factors that precipitate the urticaria is important in differentiating the dermatographism from a continuation of the CSU.

Not infrequently patients present with no evidence of infection only for this to become apparent several months later when a dental abscess requires treatment or sinusitis contributes to headaches. Asking specifically about dental problems and postnasal discharge and previous bouts of sinusitis is important.

Investigations

When an allergen is considered of aetiological importance acute urticaria [1], it is important to confirm or exclude this by either

skin testing or blood tests that estimate the allergen specific IgE.

- Skin prick testing is rapid and relatively cheap and can utilise either commercial reagents or sometimes fresh fruit, vegetables and certain other foods. It is a remarkably safe procedure although care is required when testing in a patient with suspected anaphylaxis.
- Intradermal skin testing is used for testing for allergy to drugs, insect venom and anaesthetic agents particular.

For both types of testing, it is important that positive and negative controls are included in the testing procedure. These will assess for non-reactivity due to oral anti-histamines and certain other drugs (positive control) and non-specific skin reactivity due to dermatographism (negative control).

In patients with CSU and angioedema, a basic panel of investigations [1,13,25,26] should include the following:

- Full blood count - to check for any lymphoproliferative disease
- ESR - To assess for persistent immune activation arising from underlying autoimmunity, infection or lymphoproliferation.
- Anti-nuclear antibodies - to check for any underlying connective tissue disorder.
- Anti-thyroid antibodies - anti-thyroid peroxidase ab may be found in 10-25% of patients with CU with some having overt hypothyroidism requiring treatment.

Serum vitamin D analysis - patients with very low levels of circulating vitamin D appear to be prone to CSU [27-29]. The precise mechanism is unclear but vitamin D3 has powerful immune regulatory properties [30].

Serum immunoglobulins and electrophoresis analysis - this is especially important in the elderly and if angioedema is the sole problem as a monoclonal gammopathy of unclear significance or very rarely other lymphoproliferative processes may underlie 'acquired angioedema' (AAE).

Complement C4 assessment is the best way to screen for hereditary angioedema (HAE) or indeed acquired angioedema arising from an underlying lymphoproliferative process. Levels that are well within the normal range virtually exclude both. If the C4 level is low, then a serum C1 esterase inhibitor analysis should be performed. If the latter is low, then referral to an Immunologist to assess for HAE or AAE is indicated. Most cases of slightly low C4 in otherwise healthy people are due to one or more C4 null genes.

Other investigations would be based on any clinical symptoms and may include:

- Anti-helicobacter serology or helicobacter stool antigen where this is significant dyspepsia
- Sinus and/or Chest X ray if any evidence of chronic sinusitis or chest infection
- Rheumatoid factor or anti-CCP antibodies if patient has an inflammatory arthritis

Autologous serum intradermal skin testing if autoimmune basis of CSU requires confirmation [31]

Serum Clusterin has been suggested as a reliable prognostic

marker for antihistamine treatment responsiveness [32].

In patients with CSU in which the urticarial patches last less than 6 hours and there is no indication of underlying medical disease, it has been suggested that no blood tests are required at least initially. However, if the condition continues for more than 1 year or is not responding to regular antihistamine therapy in double dosage then it is suggested that the above blood tests are undertaken.

TREATMENT

The best treatment for urticaria and angioedema is clearly to identify the cause and avoid it. Where this is not possible, the main aim of treatment is to provide symptomatic relief and suppression of the urticarial wheals. In all patients with CSU stress has the ability to aggravate and perpetuate the condition and thus stress reduction therapy is important as a long term measure. In time many patients come to recognize the role of stress in their condition and will undertake important lifestyle changes that ameliorate this factor. Recently vitamin D3 supplementation [28] has been shown to have a beneficial effect and if serum levels are low then replacement therapy can be helpful in the long term (Figure 1).

Symptomatic treatment [1,13,33] for CSU should commence with a regular non-sedating antihistamine tablet. A short acting sedating antihistamine may be useful if the attacks are nocturnal or if a persistent urticaria disrupts sleep. The vast majority of the newer anti-histamines are very safe even in patients with cardiac problems. There are individual variations in efficacy and tolerance. Most patients notice none or few side effects and the therapy may be continued for many years without long-term complications. They should be reassured that high dose second-generation, non-sedating antihistamines are exceptionally safe.

The antihistamines commonly used in the clinic are:

- Cetirizine or Levocetirizine
- Fexofenadine
- Loratadine
- Mizolastine (contraindicated in patients with cardiac problems or patients on macrolides and imidazoles).
- Chlorphenamine (may be used in very young children and in pregnancy)

Several different types of antihistamines may need to be tried to see which one works best with the fewest side effects. They often need to be used at doses higher than those used for allergies. Alternatively, combining different antihistamines may be worth trying. Sedating anti-histamines should be taken at night and non-sedating ones should be taken during the daytime. It is important to tell patients that anti-histamines provide symptomatic relief of their symptoms while waiting for the urticaria to resolve. In some patients the addition of a leukotriene receptor antagonist, such as montelukast, may be worth considering although the evidence that it provides any benefit is very limited [34].

For acute urticaria, a brief course of oral prednisolone therapy may be tried at a dose of 25mg daily for 5 days before reducing the dose by 5 mg every two days thereafter. Doses of 25mg or less of prednisolone are only rarely associated with psychosis.

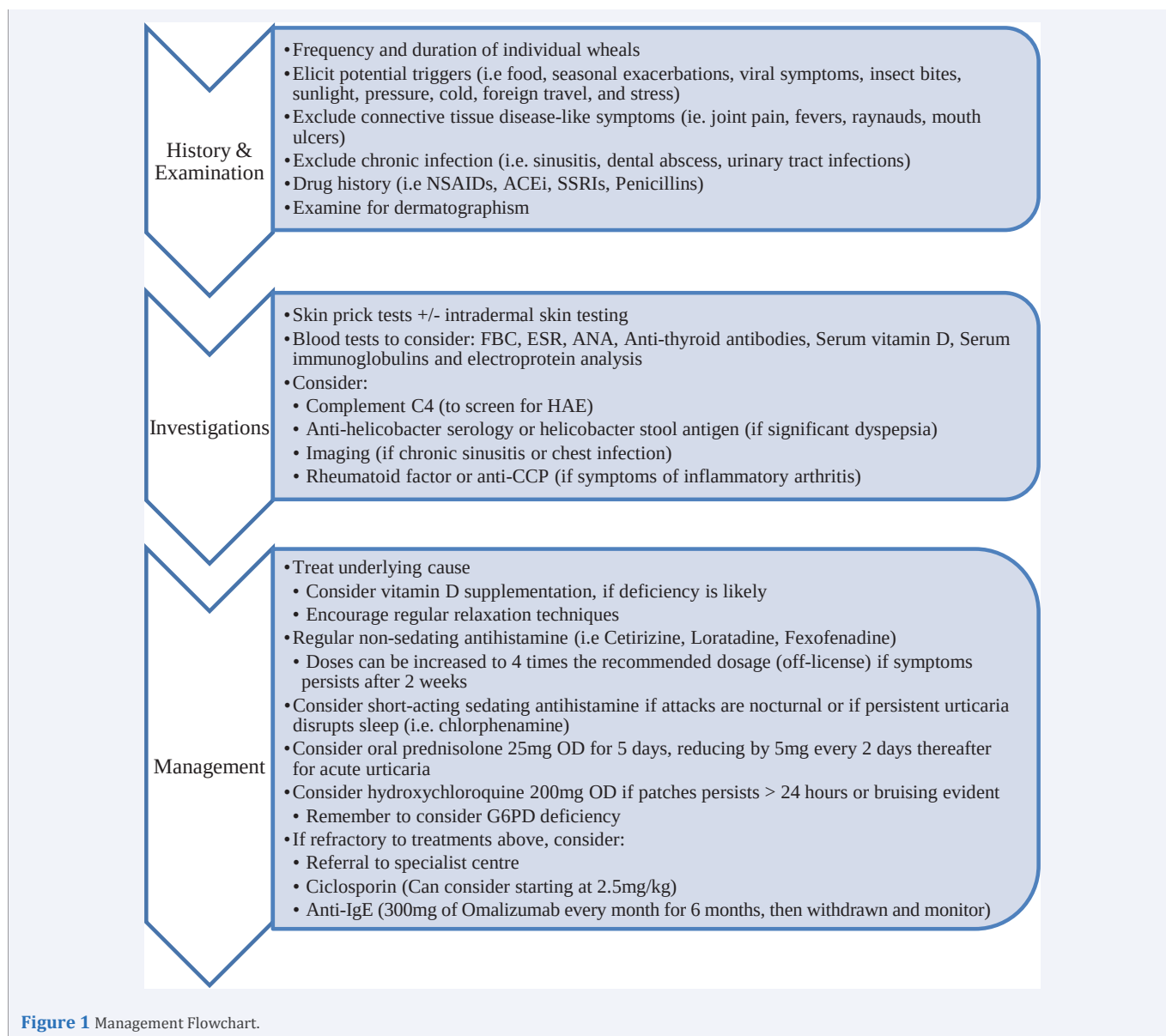


Figure 1 Management Flowchart.

When anti-histamines used at double the conventional dosage have failed or provided only partial symptomatic relief then an H2 antagonist such as Famotidine or Ranitidine may be considered. However, the evidence that these provide benefit is very limited and some consider that they work only by reducing the hepatic degradation of any conventional anti-H1 anti-histamine that is being used.

In patients in whom the urticarial patches persist for more than twenty-four hours or there is bruising evident, hydroxychloroquine at 200mg daily should be considered. Before commencing this treatment, it is important to make sure that patients of Mediterranean, Asian and African origin have normal levels of red cell Glucose-6-Pyruvate Dehydrogenase. The patient's near vision should also be checked [35] and the results recorded in the notes as this therapy can in rare cases alter vision. However, this is usually only observed at higher doses used for several years. Patients should be warned that hydroxychloroquine works slowly and that little benefit may be

observed in the first 2 to 4 weeks. The therapy then increases in effect for a further 4-6 months and should be continued for between 6-12 months.

Patients not responding to the above medication may benefit from treatment with dapsone, colchicine and very occasionally with ciclosporin, intravenous immunoglobulin, and histaglobulin [36]. Anthelmintic treatment should be considered in travellers with relevant travel history [37]. These treatments are more effective in patients whose urticarial wheals last longer than 8-12 hours as this suggests immune activation being of critical importance in the aetiology of the skin problem. Chronic cold urticaria has been shown to respond to doxycycline [38].

More recently, anti-IgE therapy using omalizumab has shown significant and rapid benefit in several trials on CSU [6,13,35,39,40]. Referral to a local Anti-IgE centre within Immunology, Dermatology or Allergy Clinic is often necessary and patients are offered the treatment if they have not responded

to high dose anti-histamine therapy combined with anti-leukotriene receptor therapy and other immunomodulatory therapy. The urticaria activity score over seven days (UAS7) needs to exceed 28 for at least 2 weeks before this treatment to be offered on the NHS in the UK. The UAS7 is derived from the number of wheals and the extent of the itching scored as mild, moderate or severe. Treatment with omalizumab [40] is offered subcutaneously as a fixed dose of 300mg every month for 6 months in the first instance. The treatment is then withdrawn to see if the urticaria has resolved but may be continued long term if significant urticarial activity continues and remains unresponsive to high dose anti-histamine therapy. Omalizumab has been demonstrated to have very good efficacy in reducing not just symptoms, but also reducing socio-economic burden of chronic spontaneous urticaria [41].

PROGNOSIS

Acute simple urticaria and angioedema has a very good prognosis and well over 90% will not have a further attack. This is particularly so in children. In others, the attacks may occur sporadically over a few days, weeks, months or years. However, the tendency in each case would be for a gradual resolution over a period a few months. It is important to note the trend rather than the severity of an individual episode. Urticaria with varying degrees of angioedema lasting a few days and not associated with specific foods is often the result of a viral infection in children and this type only rarely recurs. Clearly, acute urticaria and angioedema arising from a specific food or drug allergy will only recur if there is continued or further exposure.

When urticaria becomes chronic with recurrent episodes occurring over at least three months, the prognosis becomes less favourable the longer the overall duration of the urticaria. Nevertheless, 60-70% with CU patients will be entirely free of their attacks by one year. The figure is slightly less when the urticaria is accompanied by angioedema and less so at about 30-40% if angioedema occurs without urticaria. Several factors can perpetuate the urticaria becoming chronic including the stress and anxiety associated with having a skin condition that can cause cosmetic disfigurement and one which is uncomfortably itchy and highly unpredictable. If the patient can be encouraged to relax and be optimistic that the problem will go, then this frequently encourages a resolution of the problem. In any event, patients should be reassured that simple urticaria, no matter how often it occurs or how long it persists, does not indicate that they have any serious underlying illness. The simple blood tests mentioned above will certainly help in emphasising this point. There is an association with chronic idiopathic urticaria and future risk of hypertension [42], however the mechanism of this phenomenon remains unclear.

When urticaria has been brought on by physical stimuli [43] such as physical pressure, vibration, cold or sunlight the prognosis is more guarded. In this case, the urticaria tends to resolve in fewer than a quarter of all such patients. Regardless, all patients can be offered symptomatic relief with either regular or intermittent anti-histamine therapy. Clearly, all such patients should avoid the physical stimuli that provoke their urticaria. A case report shows delayed pressure urticaria to be responsive to SSRI [44]. Patients whose urticaria is induced by cold (so called

cold urticaria) deserve special counselling. These patients should be cautioned against swimming or taking a cold bath or shower as collapse and occasional fatalities have occurred from massive histamine release.

The Future

Chronic spontaneous urticaria remains poorly understood from the perspective of its aetiology and the mediators responsible. Its relationship to psychological stress merits further evaluation. Future areas of research include investigating the global epidemiology of both acute and chronic urticaria and its' socio-economic consequences [1]. This could help determine predisposing factors and expand our currently limited knowledge. Pathophysiology will need to be further elucidated to develop and identify histological markers, activating factors and serum biomarkers. Qualitative research could include identifying psychological impact associated with urticarial diseases. Controlled multicenter studies looking specifically at adjuvant therapy would be beneficial to guide future management of urticaria.

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