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OVERVIEW OF CHRONIC URTICARIA

- **Chronic urticaria (CU) is defined as the presence of wheals and/or angioedema intermittently or continuously for ≥ 6 weeks**
- **CU affects up to 3% of the population and significantly reduces quality of life**
- **Most patients with CU do not have an identifiable cause**
- **Second generation antihistamines are recommended as first-line pharmacological treatment**

INTRODUCTION

Urticaria is a condition which is characterised by the development of wheals (hives) and/or angioedema.[1-3] International guidelines classify urticaria according to the duration and cause of the symptoms.[1] Acute urticaria has a duration of < 6 weeks, while **chronic urticaria (CU) is defined as the occurrence of wheals and/or angioedema intermittently or continuously for ≥ 6 weeks.**[1] The prevalence of CU in the general population varies from 0.5 to 3%.[1,4-7] It occurs twice as often in women than men and has a peak age of onset between 20 to 40 years.[8-10] It may resolve in many patients after a few months, however 10 to 50% of patients may have CU for > 5 years.[7,9] **CU is not life threatening but it can have a significant impact on a patient's quality of life.**[1,4-6,11] CU can also lead to significant psychological stress for the patient, while stress can also trigger or aggravate urticaria.[8]

It is estimated that approximately 50% of patients with CU present with wheals alone and 40% present with wheals and angioedema; angioedema without wheals is the main feature in 10% of patients.[4-6] It is important that CU is differentiated from other conditions where wheals and/or angioedema may be the presenting symptoms; these include anaphylaxis, auto-inflammatory syndromes and hereditary angioedema.[1,3,6]

This bulletin will review the current management strategies for CU.

PATHOGENESIS

Mast cell activation is central to the pathophysiology of CU, whereby activated mast cells release histamine and other mediators such as cytokines, prostaglandins and leukotrienes.[1,4-7] Mast cells can be activated by a variety of immunological and non-immunological triggers,[7] which result in the formation of itchy wheals (swelling of the upper layers of the dermis) or angioedema (swelling of the deeper layers of the dermis and subcutaneous tissues). Wheals consist of a central swelling of variable size, which is usually surrounded by erythema, they may be single or multiple and are associated with itching or burning; **each individual lesion generally resolves within 24 hours.**[1,4,5] Angioedema presents as less well-circumscribed tissue swellings, which may be painful and may last for up to 72 hours.[1,4,5]

Most patients with CU do not have an identifiable allergic cause, and are ultimately classified as chronic spontaneous urticaria.[1,4-6,12] It has been proposed that up to 60% of patients with CU have an underlying autoimmune aetiology (autoimmune urticaria); 30 to 50% of CU patients may produce antibodies against a subunit of an IgE receptor and up to 10% produce antibodies against IgE itself.[4-7] Many patients with CU also produce other autoantibodies such as thyroid antibodies and rheumatoid factor,[4,5] however the clinical relevance of this finding is unknown.[5]

Type I hypersensitivity or allergic reactions are rarely a cause of CU.[1] **IgE mediated food allergies can usually be excluded as a trigger unless there is a close temporal and reproducible relationship to a particular food (i.e. onset of symptoms occurs within 60 minutes of exposure).**[4] In addition, **the symptoms of food allergy do not last several days as occurs with CU.**[4] Patients with IgE-mediated food allergy also have other symptoms such as oropharyngeal itching, wheezing, vomiting or abdominal pain.[4]

Drugs including aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids can aggravate CU.[2,7,13] **Angioedema without wheals can occur in patients on angiotensin-converting enzyme inhibitors (ACEi)** and in conditions including hereditary angioedema and acquired C1 inhibitor deficiency.[4] ACEi-induced angioedema may occur within the first few weeks of commencing ACEi treatment however it may also develop after many years of uneventful drug use.[4] Afro-Caribbean patients are at increased risk of ACEi-induced angioedema, which occurs due to reduced metabolism of bradykinin. Patients usually present with swelling of the tongue, however they may also experience swelling of the lips, pharynx, larynx and viscera; fatalities have been reported. In most patients the symptoms reduce or disappear on stopping the ACEi; if the ACEi is responsible for the angioedema but not withdrawn, the patient is likely to experience more frequent and severe attacks of angioedema.[4] Angioedema has also (but more rarely) been reported in association with angiotensin receptor blockers (ARBs).[4]

There are other rare conditions which may also present with symptoms of urticaria such as urticarial vasculitis (painful and persistent individual lesions) and auto-inflammatory syndromes.[1,4]

CLASSIFICATION

Chronic urticaria, defined as the presence of wheals and/or angioedema either intermittently or continuously for ≥6 weeks, can be classified into **chronic spontaneous urticaria or chronic inducible urticaria**, (which may co-exist) as shown on table 1.[1,3] Chronic inducible urticaria occurs in 40% of patients with CU; activation of the mast cells is dependent on, and directly related to, an identifiable trigger such as heat, cold and pressure.[4,5,7,13] The wheals usually appear immediately and generally fade within 2 hours (may be longer with delayed pressure urticaria).[4,8]

Table 1: Classification of chronic urticaria subtypes[1]

Type	Description	Examples of triggers/ exacerbating factors	Tests*
Spontaneous	Spontaneous appearance of wheals, angioedema or both for ≥6 weeks	Cause unknown in the majority of cases May be exacerbated by stress, infection, drugs (e.g. NSAIDs)	FBC and differential ESR or CRP Omission of suspected drug
Inducible**	Dermographic	Minor trauma e.g. stroking skin with firm object	Provocation tests
	Cold	Swimming in cold water, cold wind, cold drinks	
	Delayed pressure	Sitting, lying, tight clothing	
	Solar	Sunshine	
	Heat	Hot bath/shower	
	Vibratory	Vibratory machinery, lawn mowing, after applauding	
	Cholinergic (due to sweating)	Exercise, emotion	
	Exercise	Physical exertion	
	Aquagenic	Contact with hot or cold water	

**- additional tests including those for infectious diseases, IgE for type 1 allergy, thyroid function tests and thyroid autoantibodies are not required unless indicated by history; ** present continuously or intermittently for ≥6 weeks*

NSAIDs – non-steroidal anti-inflammatory drugs, FBC – full blood count, ESR – erythrocyte sedimentation rate, CRP – C reactive protein

DIAGNOSIS

The diagnosis of CU is primarily clinical and is based on a detailed patient history and physical examination of the lesions to determine if they are consistent with CU and whether there are any underlying conditions.[1,4-6,14] Serial photographs of the lesions may also be helpful to document the extent and severity of the urticaria.[8] The urticaria activity score UAS7 is a validated scoring system which has been used in the clinical trial setting and also in clinical practice to determine disease activity and response to treatment.[1,5]

Table 2 outlines questions which may be helpful to include in the detailed history.

Table 2: Topics to include in history of a patient with suspected chronic urticaria[1]

Time of onset of disease	Family and personal history of urticaria
Frequency/duration of wheals and/or angioedema	Previous or current allergies
Shape, size and distribution of wheals and/or angioedema	History of infections
	Gastrointestinal symptoms
Diurnal variation	Signs and symptoms of underlying disease e.g. fever, significant malaise, arthralgia, weight loss
Associated symptoms including itch, pain of lesions	
Provoking factors for wheals and/or angioedema	Type of work
Induction of lesions by physical agents	Impact on quality of life
Drug history including use of NSAIDs and ACEi	Previous therapy for CU and response to therapy
Temporal relationship of lesions to food (within 1 hour)	Previous diagnostic procedures/results

NSAIDs - non-steroid anti-inflammatory drugs, ACEi - angiotensin-converting enzyme inhibitor

Investigations: CU is a complex disorder of mast cell degeneration. **In the vast majority of cases there is no single trigger, and extensive investigation to identify a cause is not required.**[1,5,6] Any investigation should be guided by history;[1,4-6,14] a full blood count and measurement of inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be useful to exclude underlying disease (e.g. raised ESR in urticarial vasculitis or auto-inflammatory syndromes).[5,6] Routine assessment for *Helicobacter pylori*, coeliac disease, chronic infections (e.g. hepatitis B and C) and IgE-mediated responses to allergens is **not recommended**,[5,6] unless it is indicated by the

history and examination.[1,6] Similarly, routine skin biopsies are not required in most cases of CU; they may be performed in patients when urticarial vasculitis is suspected (e.g. patients with burning or painful hives that persist for longer than 72 hours).[6] Patients with recurrent angioedema without wheals should be evaluated for hereditary angioedema and acquired C1 inhibitor deficiency (e.g. C4 and C1 inhibitor levels).[6]

Patients can be tested for dermographic urticaria by using a tongue depressor to stroke the skin firmly and induce wheal formation.[8] Physical challenge tests for cold-induced urticaria or tests for other subtypes of inducible urticaria may be considered in patients with a history of exacerbations from these triggers.[8]

MANAGEMENT OF CHRONIC URTICARIA

The management of CU requires an understanding of the clinical presentation, triggers and aggravating factors.[4] The management of CU is similar for the different subtypes and involves both non-pharmacological and pharmacological approaches.[1,6] Evidence suggests that there is a 30 to 50% remission rate in CU within the first 3 to 5 years.[5,6,8,14] Longer duration of CU is associated with more severe disease.[8,13]

Non-pharmacological management

General non-pharmacological measures include the avoidance or minimisation of nonspecific aggravating factors such as overheating and stress.[14] When drugs are suspected as a trigger for CU, they should be omitted entirely and substituted with another class.[1] **If avoidable physical stimuli are identified, the patient should be given clear instructions on avoidance strategies (e.g. avoiding cold or pressure).**[4] However, in many patients with physical CU, the threshold for the relevant trigger may be very low and total avoidance of the triggers may be impossible e.g. clothing on a patient's skin.[1] Food can usually be excluded as a cause of urticaria/angioedema if there is no close temporal relationship to a particular food trigger (i.e. if symptoms occur more than 60 minutes following exposure or contact).[4]

Pharmacological management

The pharmacological management of CU provides symptom control by reducing mast cell mediator release (e.g. histamine) and/or the effect of these mediators at the target organ; however pharmacological management does not lead to disease remission.[5,15] Table 3 outlines a step-wise approach to CU treatment. Specialist advice is recommended for third-line treatment.[1,4]

Antihistamines are inverse receptor agonists that interfere with the action of histamine, which is responsible for the majority of symptoms seen in CU.[3] **Second generation H1 antihistamines are recommended as first-line treatment** rather than first generation H1 antihistamines (e.g. chlorphenamine, hydroxyzine) which should be avoided due to their adverse effects including sedation and impaired psychomotor performance.[1,3-5,15,16] The second generation H1 antihistamines currently licensed in Ireland include cetirizine, levocetirizine, desloratadine, loratadine, fexofenadine and bilastine.[17-22] There is an absence of head to head comparison of the various antihistamines in clinical trials.[1,4,23] Individual patient responses and adverse effects may vary with the different antihistamines.[4] Guidelines recommend that **the aim of treatment is for complete symptom control and that second generation oral H1 antihistamines should be taken continuously in the lowest necessary dose rather than as required**.[4]

Once symptom control has been established, **daily treatment is advised in most patients for 3 to 6 months**, however for patients who have a long history at presentation, treatment for 6 to 12 months is advised followed by gradual withdrawal.[4]

Studies have found that a higher dose of second generation H1 antihistamines (up to 4 times the licensed dose) is an effective treatment for CU and is recommended as second-line treatment in international guidelines.[1,4,6,15] Current clinical evidence suggests that up to 67% of patients may require treatment with high-dose antihistamines.[12,15] If higher than the licensed doses of antihistamines are to be considered, incremental updosing is advised by some experts.[4]

Table 3: Recommended treatment algorithm for chronic urticaria[1,4]

First-line
Second generation antihistamines
(cetirizine, levocetirizine, desloratadine, loratadine, fexofenadine or bilastine)
↓
If symptoms persist after 2 weeks
↓
Second-line
Increase dosage of the second generation antihistamine up to 4 times the usual dose (unlicensed dose)
↓
If symptoms persist after 4 weeks
↓
Third-line
Add-on to second-line (**specialist advice required**)
montelukast or omalizumab or ciclosporin
[Short course (maximum of 10 days) of corticosteroids may also be used if required for exacerbations]

It is recommended to wait 2 to 4 weeks to allow full effectiveness, before changing to an alternative therapy – see table 3.[1] Patients should be monitored every 3 to 6 months to re-evaluate the necessity for continued or alternative drug

treatment as the severity of urticaria may fluctuate and spontaneous remission may occur at any time.[1]

Specialist advice is recommended in certain situations as shown on table 4. [4]

Table 4: Conditions where specialist advice is recommended [4]

- Diagnostic uncertainty
- Acute urticaria and/or angioedema where it is important to exclude an allergic cause
- Persistent symptoms despite treatment with regular high-dose antihistamines
- Angioedema that is persistent, recurrent or affecting the airway
- Possible diagnosis of urticarial vasculitis (lesions lasting >72 hours)
- A pregnant or breastfeeding woman who requires treatment
- Children if schooling is affected

Specialist Initiated Therapy

Leukotriene receptor antagonists: There is some evidence to show that leukotriene receptors antagonists (particularly montelukast) may be effective as add-on therapy with antihistamines (unlicensed indication).[1,3,4,11,14] Montelukast may be beneficial particularly in patients with CU aggravated by aspirin, NSAIDs and those with delayed pressure urticaria.[4,14]

Omalizumab is a monoclonal antibody that selectively binds to IgE; it has been found to be effective in patients with refractory CU in randomised controlled trials.[1,4,6,10,24] The precise mechanism of action of omalizumab in CU has yet to be determined, however it may reduce the mast cell and basophil activation mediation by IgE.[9,10] "*It is indicated for use as add-on therapy for the treatment of chronic spontaneous urticaria in adults and adolescents who have an inadequate response to H1 antihistamine treatment*";[25] the need for continued treatment should be regularly assessed.[24] Clinical experience beyond 24 weeks is limited for this indication.[10,25] Adverse effects include headache, abdominal pain, pyrexia and injection site reactions.[25]

Ciclosporin A has a moderate direct effect on mast cell mediator release and also inhibits basophil histamine release.[1,4] It has been shown to be effective in combination with antihistamines in patients with refractory CU, however it is poorly tolerated.[1,4,6,11] There are significant adverse effects associated with ciclosporin; patients require regular haematological, renal, liver and blood pressure monitoring.[3]

Corticosteroids have also been used for the treatment of exacerbations of CU (unlicensed indication), however evidence from randomised controlled trials for this indication are lacking.[1,4] Guidelines recommend a trial of a short course of systemic oral corticosteroids as **third-line therapy** or as an option for acute exacerbations; long-term use of systemic corticosteroids is not recommended.[1] **Topical corticosteroids are not recommended for the treatment of CU.**[1,4]

Other therapies

Many other alternative therapies have been used for the treatment of refractory CU however the level of evidence for their use is low.[6] US guidelines recommend, as an alternative second-line treatment, adding a first generation antihistamine at bedtime to a second generation antihistamine.[5,6] Doxepin (not licensed in Ireland) has antihistaminic properties but has sedating and anticholinergic adverse effects;[14] it is recommended as third-line therapy in US guidelines.[6]

Tranexamic acid which inhibits the conversion of plasminogen to plasmin and the production of bradykinin, may be of benefit to some patients with angioedema (without wheals) [unlicensed indication].[4] There is little evidence from randomised controlled trials to support this indication however it is used in problematic cases.[4]

H2 antihistamines have also been used as second line agents in combination with H1 antihistamines for urticaria, however the evidence for their use is lacking.[4] Recent guidelines do not recommend this form of therapy for CU.[1]

SUMMARY

CU is a heterogeneous condition which is usually diagnosed on history and clinical presentation without the need for extensive investigation. Making the diagnosis and identifying the cause of CU can be difficult; there appears to be an autoimmune involvement in up 40% of patients. Non-pharmacological management includes the avoidance of any known triggers of CU. **The mainstay of pharmacological management of CU is treatment with second generation antihistamines and if necessary at increased doses (unlicensed doses).** Specialist advice is required for third-line treatment which includes leukotriene receptor antagonists, omalizumab or ciclosporin A.

FURTHER SOURCES OF INFORMATION

Information sheets for patients on urticaria can be helpful and include:

- "What you should know about urticaria and angioedema" published by the Department of Immunology in St James's Hospital, Dublin 8 and available on http://www.stjames.ie/Patients/PatientBooklets/Urticaria_WEB.pdf.
- "Chronic spontaneous urticaria" available on The Irish Skin Foundation website http://irishskinfoundation.ie/images/uploads/CSU_Patient_FINAL_April_15_(3).pdf
- "Urticaria and angioedema" from the British Association of Dermatologists available on http://www.bad.org.uk

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