

CHRONIC URTICARIA – BACK TO BASICS

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ABSTRACT

Urticaria must be classified as either acute or chronic. Acute urticaria lasts less than six weeks and in the paediatric population it is largely in response to a viral infection. Chronic urticaria lasts longer than six weeks and may be episodic or difficult to control, requiring high-dose antihistamines or other adjuvant therapy. The diagnosis of chronic urticaria requires a good clinical history, differential diagnoses to be considered and limited special investigations. The 2018 EAACI guideline introduces biologic agents early in the course of treatment, but these may not be available to patients in state-funded care.

INTRODUCTION

Urticaria is a condition characterised by oedema of the superficial dermis, which may present as wheals. Angioedema is swelling in the deeper layers of the skin. Urticaria may occur as the only type of lesion in combination with angioedema and rarely as angioedema alone. The typical phenotype of chronic spontaneous urticaria is an intensely pruritic, macular or papular rash with central swelling and surrounding erythema which classically moves around the body with no residual hypo- or hyperpigmentation of the skin. There may be residual trauma from the scratching but, once resolved, it should not leave any pigmentation or ecchymoses.

Urticaria is a common presentation in general practice and needs to be classified as either acute or chronic. Acute urticaria lasts less than six weeks and has a number of potential causes; but it is largely infection-related in the paediatric population. Chronic urticaria (CU) has a population prevalence of 0.5–5%,¹ in studies from North America and Europe, and an incidence estimated at 1.4% per annum.¹ There are currently no data from African populations. CU has a female preponderance in the adult population. It may be either chronic spontaneous urticaria (CSU) or chronic inducible urticaria (CIU) – the latter was previously termed 'physical urticaria'. Conditions associated with CSU are shown in Table I.

TABLE I: CONDITIONS ASSOCIATED WITH CSU

Autoimmune disorder	Coeliac disease, Sjogren syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 diabetes mellitus (DM), thyroid autoantibodies with or without normal thyroid function ²
Gastrointestinal (GIT) disorders	<i>Helicobacter pylori</i> , bowel parasites, gastritis, reflux oesophagitis ³
Malignancy	More studies are needed to define this possible association

AN APPROACH TO A PATIENT WITH CHRONIC URTICARIA (> 6 WEEKS)

1. ENSURE THE RASH IS URTICARIAL: WHAT IS THE NATURE OF THE LESION?

The lesions must be pruritic and have the classic central swelling with surrounding erythema.³ These lesions may be 1 mm to a few centimetres in diameter, as lesions may coalesce. Patients will often have photographs of the lesions as they evolve on their personal cellular telephone, which will aid diagnosis. The response to antihistamines may be a useful aid to the diagnosis of CU.

TABLE II: WHEN TO CONSIDER A SKIN BIOPSY?

- Suspected urticaria pigmentosa/mastocytosis
- Suspected urticarial vasculitis
- When lesions are atypical or poorly responsive to antihistamines
- Systemic symptoms are present which are not categorised above

2. IS THERE ASSOCIATED ANGIOEDEMA?

Urticaria and angioedema may exist together in 40%⁴ of patients with CSU. In 50% of patients isolated urticaria occurs and in 10% isolated angioedema.⁴ Angioedema may exist as part of CU but it is imperative that patients presenting with angioedema alone be investigated for C1-esterase inhibitor deficiency, either acquired or hereditary. Adult patients, or those on angiotensin-converting enzyme (ACE) inhibitors, must be investigated for drug-induced angioedema.

3. ARE THERE ASSOCIATED SYSTEMIC SYMPTOMS?

CU may be the presenting symptom of an underlying systemic disorder. It is important to elucidate the general health in the patient and to ask specifically about constitutional symptoms such as fever, unexplained weight loss, arthritis and arthralgia.

Specific associations with *H pylori* infection should encourage clinicians to enquire about symptoms of dyspepsia or a history of gastric ulcers. Patients with coeliac disease may present with



Figure 1: Urticarial vasculitis

CU. Possible clues in the history of an undiagnosed patient may be vague gastrointestinal disturbance, bloating, diarrhoea and gluten intolerance.

Urticarial vasculitis (UV) may present as skin-only manifestations or urticaria with systemic symptoms. UV may present as urticaria which burns rather than itches, is poorly responsive to antihistamines, leaves residual pigmentation or ecchymoses and usually has dermal oedema which last 3–7 days.⁵ A biopsy is required to make this diagnosis. The associated systemic features are outlined in Table III.

TABLE III: THE SYSTEMIC MANIFESTATIONS OF UV⁹

SYSTEM	CLINICAL MANIFESTATIONS
Musculoskeletal	Arthralgia and arthritis
Renal	Proteinuria, haematuria indicative of a number of subtypes of glomerulonephritis
Pulmonary	Cough, dyspnoea, haemoptysis, pleuritic, pleural effusions, asthma, chronic obstructive pulmonary disease
Gastrointestinal	Abdominal pain, nausea, vomiting and diarrhoea
Ophthalmologic	Episcleritis, uveitis, conjunctivitis
Cardiovascular	Rarely pericarditis, tamponade, valvular disease
Neurologic	Idiopathic intracranial hypertension, aseptic meningitis, cranial nerve palsies, peripheral neuropathy, transverse myelitis

4. IS THERE A FAMILY HISTORY OF URTICARIA?

Patients who experience onset of an urticarial rash in childhood, or a family history of rashes and systemic symptoms, require the exclusion of an autoinflammatory condition. CU usually lasts 3–5 years, whereas an autoinflammatory condition usually starts in childhood and is lifelong.⁶

5. IS THERE AN IDENTIFIABLE TRIGGER: STIMULUS BY FOOD OR DRUG(S)?

Patients who have noticed an association with a specific food will require a detailed history to ascertain the likelihood of an IgE-mediated reaction. A blood-specific IgE or a skin-prick test (SPT) will be required to detect sensitisation in order to confirm a diagnosis of IgE-mediated food allergy, which is rare. A food diary may help with the diagnosis of food-additive sensitivity and may be supported by positive cellular antigen stimulation tests (CAST).

Non-IgE-mediated hypersensitivity may exist to some naturally occurring ingredients or food additives, which may respond to a pseudoallergen and histamine-free diet. These diets are currently unproven in well-designed studies.³

Drug allergy is a more complicated diagnosis which requires testing with either SPTs, drug-specific IgE or basophil activation testing.

6. PAST MEDICAL HISTORY, INCLUDING KNOWN ALLERGIES, CHRONIC MEDICAL CONDITIONS AND ALL MEDICINES – BOTH PRESCRIPTION AND OVER-THE-COUNTER

Patients may be forthcoming only about prescription drugs, but all medicines ingested should be recorded as part of the history-taking. Non-steroidal anti-inflammatory drugs (NSAIDs) may cause or aggravate CSU. As part of the diagnostic work-up, any drug thought to be aggravating CSU should be eliminated in order to form an opinion on the effect on the chronic condition.

7. OCCUPATION AND HOBBIES

Patients may have a physical or contact trigger related to their occupation or hobbies. It is important to include this as part of the clinical history. Patients with vibratory angioedema may present with itching and swelling after mountain biking; avid gardeners may present with urticaria on the hands where they have been in contact with an eliciting trigger.

8. OTHER TRIGGERS – MENSTRUATION, STRESS, EXERCISE, INFECTIONS

Attacks of CU may be triggered by stress and exercise or exacerbated by infection. Patients in whom sex hormones act as a trigger may flare for the week prior to menstruation, during pregnancy, on oral contraceptive or hormone-replacement therapy or for the duration of fertility treatment.

THE INDUCIBLE URTICARIAS

The physical or inducible urticarias are a subgroup of CU that are produced by a defined stimulus. It is postulated that there is heightened sensitivity of the mast cell to the physical stimulus which, when provoked, degranulates and produces urticaria and angioedema. Some patients may be triggered by multiple stimuli.

There is a 1% prevalence of CU and 20–30%⁷ of these patients have an inducible urticaria. These conditions may be tested for by inciting a reaction by various office investigations listed below (Table IV).

TABLE IV: OFFICE INVESTIGATIONS FOR THE INDUCIBLE URTICARIAS.⁷

INDUCIBLE URTICARIA	TEST
Dermographism	Stroke the skin with a clean, pointed object. A wheal will appear within five minutes and will resolve by 30 minutes Fric® test ⁹
Local heat	Test tube of water at 44°C applied to the arm
Delayed pressure	1. History 2. Office test: 5 kg weighted rod laid over the forearms for 20 min, then patient to observe the site over the next 24 hours 3. Sling with a 3 cm strap containing a 7 kg weight hung from a patient's forearm for 20 min
Cholinergic	1. History 2. Exercise challenge ¹³
Solar	1. History 2. Exposure of the patient's forearm to sunlight for a short period
Aquagenic	Wet compress applied to the upper body at 35°C for 30 min
Cold	Ice-cube test
Vibratory	1. History 2. Vibratory stimulus

Dermographism or dermatographism is the most common of the inducible urticarias: in this instance, patients develop a wheal-and-flare reaction to firm stroking or scratching of the skin. This may be either pruritic or non-pruritic. The Fric test® or friction test dermatographometre, is an instrument that may be used as an alternative to the ballpoint pen to assess the threshold of symptomatic dermatographism. This test has four plastic prongs of varying lengths (2.5 to 4 mm) which are used to induce dermatographism.^{8,9}

Local heat urticaria is rare. It occurs when there is localised urticaria in an area of the skin that has been exposed to heat, usually within minutes of exposure.

Delayed-pressure urticaria or angioedema classically develops four to six hours after stimulus to the area. This may be an erythematous area with burning and swelling, and less commonly pruritus. The angioedema may last for several hours.

Cholinergic urticaria is precipitated by generalised heating of the body, which may be due to exercise, a hot bath or humid environments. This type is classically smaller, with wheals of 1–3 mm which appear and may coalesce into erythematous patches on the skin. Special mention should be made of the entity of exercise-induced anaphylaxis which occurs with physical exertion. The wheals in this condition will be larger than with cholinergic urticaria.¹⁰ Food-dependent exercise-induced anaphylaxis occurs a few hours after a patient exercises after having consumed a specific food. It is important to differentiate these conditions from cholinergic urticaria.

Aquagenic urticaria is a rare disorder which occurs when water touches the skin. The lesions in this type are identical to those in cholinergic urticaria. Onset is usually 20–30 minutes after exposure to water and may resolve within one hour after the removal of the stimulus.¹¹

Solar urticaria usually presents with areas of erythema, which may itch or burn when patients are exposed to sunlight. This occurs within minutes of exposure to sunlight and may occur directly onto bare skin or through clothing made from light fabric. This may progress to urticaria if the stimulus is not removed.¹²

Patients with cold urticaria may develop both it and angioedema after exposure to cold objects, liquids or even cold air, with a minority of patients developing systemic symptoms. Patients with systemic reactions are at risk for anaphylaxis. Patients with cold urticaria are at risk of drowning if they swim unsupervised in cold water.

DIAGNOSTIC WORK-UP OF PATIENTS WITH CHRONIC URTICARIA

A thorough, focused clinical history should be sufficient for a patient presenting with CSU. Any questions that raise concern of an alternative diagnosis should prompt investigation and referral to dermatologists for a biopsy. The current guidelines are to perform a full blood count with differential and a

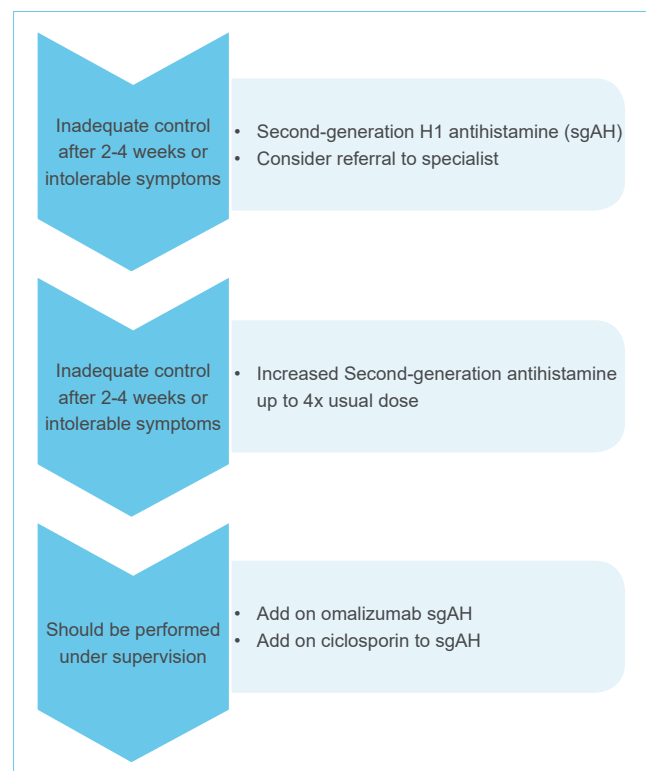


Figure 2: EAACI/WAO treatment algorithm for chronic urticaria²

C-reactive protein and/or an erythrocyte sedimentation rate (ESR).³ Current recommendations are not to do routine testing for thyroid autoantibodies, coeliac disease or *H pylori* infection.¹¹ The autologous serum skin test (ASST) is positive only in 30% of patients with autoimmune urticaria and therefore of uncertain diagnostic usefulness in clinical practice.¹¹

MANAGEMENT

AVOIDANCE

Patients with CSU should be advised to avoid known triggers of their condition – stress, heat, exercise – and should be warned to expect exacerbations of a previously controlled disease during viral infections. The management of inducible urticaria should involve advice regarding avoidance of the physical stimuli.

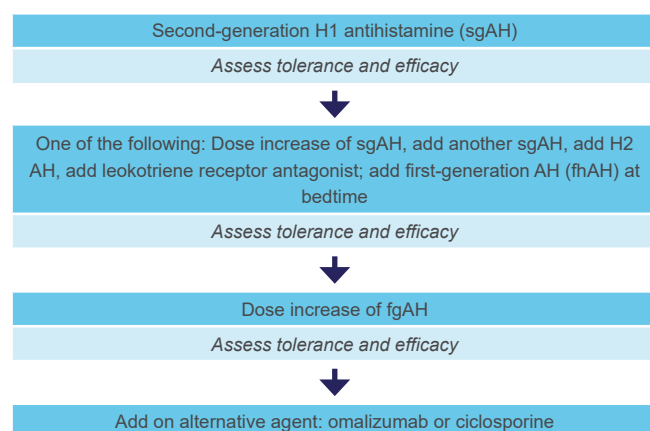


Figure 3: AAAAI treatment guideline 2014 chronic urticaria¹

PHARMACOTHERAPY

The second-generation H1 antihistamines are first-line therapy for patients with CU but they have variable to no success with some of the inducible urticarias. This may be escalated up to four times the standard dose (see Figure 3). The addition of omalizumab as step 3 has major cost implications¹⁴ for state patients or those in the private healthcare system. Current practice at the Red Cross War Memorial Children's Hospital Allergy Clinic is based on the American Academy of Asthma Allergy and Immunology (AAAAI) guideline of 2014, which involves the addition of an H1 antihistamine of a different class, or a leukotriene receptor antagonist or H2 antihistamines, as step 2 in the management of CU. Step 3 of this guideline is to escalate the H1 antihistamine doses and step 4 is the addition of omalizumab or ciclosporin.¹ Possible alternative biologic therapy is beyond the scope of this article, and readers are therefore referred to the 2018 review by Ntshalintshali et al.¹⁶

SPECIAL CONSIDERATIONS

Delayed-pressure urticaria may require the addition of a leukotriene receptor antagonist or even omalizumab, if available. Patients with aquagenic urticaria who do not respond to antihistamines have been treated with propranolol in a small case series.⁶ An adrenaline autoinjector should be prescribed for patients with cold urticaria and systemic symptoms.

DECLARATIONS OF CONFLICT OF INTEREST

The author has no conflict of interest.

This article has been peer reviewed.

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