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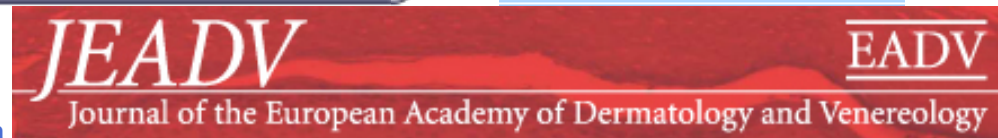
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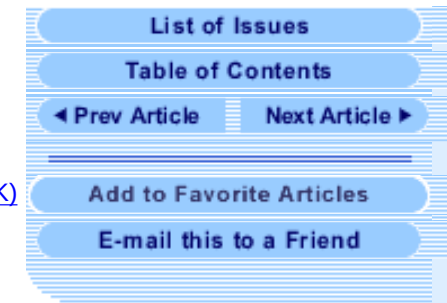
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Chronic urticaria: diagnostic recommendations

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Abstract

A group of European recognized dermatologists – the European Working Group on the Diagnosis of Chronic Urticaria – met on 12 March 1999 to discuss best practice for assessing and diagnosing patients with chronic urticaria. These are their recommendations. The recommendations will be valuable for the majority of cases, but are not exhaustive and may not include every possible precipitating factor.

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Introduction

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Chronic idiopathic urticaria is a diagnosis readily given where there is no obvious cause for persistent urticarial wealing. However, physicians should not be deterred from searching further for an underlying cause and should be guided by clues revealed in the patient history and physical examination.

Urticaria is a widespread, debilitating condition characterized by itchy lesions or weals. There is little accurate information on the prevalence of the disease, but it is thought to affect 15–23% of the US population and, internationally, the numbers are likely to be similar. ¹ The lesions are transient, pale or red skin swellings usually surrounded by erythema. The shape and size of the lesions vary, they can occur anywhere on the body and usually last less than 24 h. ² Deep, subcutaneous or submucosal swellings characterize angioedema that often coexists with urticaria. These swellings may last longer than urticarial weals because of their size and may be less itchy. They usually affect the lips, eyelids and tongue, but can occur anywhere.

Urticaria can be classified initially by the duration of the episode – acute lasting up to 6 weeks and chronic urticaria for more than 6 weeks. Chronic urticaria predominantly affects adults and is about twice as common in women as men. ¹ Up to 40% of patients with chronic urticaria lasting more than 6 months will still suffer from weals 10 years later. ¹ Chronic urticaria tends to follow a remitting and relapsing course and is often worse at night.

Chronic urticaria is an extremely distressing and disabling condition for the patient. A recent study has reported that the degree of disability experienced by a chronic urticaria patient – personal, social and occupational – is comparable with that of patients with severe coronary artery disease awaiting surgery. ³

Subtypes of urticaria can be identified by history and investigation, although where there appears to be no identifiable cause, the condition is termed idiopathic urticaria. However, it should be noted that, on closer inspection, much 'idiopathic' urticaria does have an underlying cause. Diagnosing the type of urticaria may be complicated by the presence of a combination of different types. An overview of the principal features of the most common urticarias is given in [Table 1](#).

Classification of urticaria

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Pathogenesis

Degranulation of dermal mast cells causes secretion of histamine and other mediators, leading to redness, oedema, flare and itching. Specific cell surface receptors, such as the high-affinity IgE receptor, are involved in the mechanism that triggers mast cell degranulation. Histologically, neutrophils, eosinophils and mononuclear cells, mainly arranged perivascularly, are present.

Allergic urticaria

Wealing may result from an allergic IgE-mediated reaction to a foreign stimulus such as: bee and wasp stings; blood products; food such as shellfish, fruit, nuts, dairy products and spices. In its most severe form, this reaction is seen as acute anaphylaxis, but a less severe response may cause urticaria without any systemic symptoms. Allergic urticaria can be mimicked by aspirin and non-steroidal anti-inflammatory drugs (NSAIDs).

☐ Dominique Tennstedt**Key words:** **Key words:**☐ chronic urticaria☐ diagnosis☐ idiopathic urticaria☐ recommendations

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Involvement of a food allergen can be investigated by the measurement of specific IgE in serum and skin prick tests (conducted with caution). Henz and Zuberbier have also claimed that the use of an exclusion diet avoiding preservatives, dyes and natural pseudoallergens resulted in remission for many patients (73%). ⁴

Drug-induced urticaria

Urticaria may be caused by drugs such as penicillin, aspirin, NSAIDs, morphine and codeine. Aspirin and NSAIDs are common causes of non-IgE-mediated urticaria.

Contact urticaria

Contact with various substances can result in local urticaria within a few minutes to an hour after contact. Reactions are commonly mild. Food preparation or wearing latex rubber gloves are common causes of contact urticaria on the hands. It can occur as both an immunological and non-immunological reaction. Non-immunological reactions may occur *de novo* after handling substances like ammonium, persulphate (hair perming solution), cinnamic aldehyde and benzoic acid (often found in cosmetics and food), although many other substances can also cause such reactions.

Papular urticaria

Papular urticaria results from hypersensitivity to bites from certain insects, such as mosquitoes, gnats, fleas and mites. It presents as grouped weals or papules mainly on exposed skin, especially the legs, arms, head and neck. Each papule usually shows a punctum. They are intensely itchy and often excoriated unlike other types of urticaria.

Physical urticarias

The physical urticarias are characterized by reproducible wealing that occurs following a specific physical stimulus. They occur in at least 50% of patients with chronic urticaria and a patient may suffer from more than one physical urticaria at one time. ⁵ The physical urticarias can be categorized into the following.

Dermatographism, immediate/delayed pressure urticaria and vibratory angioedema (fig. 1)

These may be caused by mechanical trauma such as friction (e.g. stroking the skin), pressure (e.g. tight clothing) and vibration, respectively. Symptomatic dermatographism results in the appearance of itchy weals 5–10 min after light stroking of the skin. Reactions may also occur at sites where clothing rubs against the skin. Itching may be severe in this condition. Delayed pressure urticaria (DPU) occurs an hour or more after sustained pressure to a particular site on the body. Tight clothing is a particularly common cause of DPU. The swellings may be itchy, burning or painful. In contrast to other physical urticarias, in which the weals are short lived (< 1 h), weals associated with DPU are persistent. Vibratory angioedema is an uncommon condition in which itchy, short-duration swellings are caused by vibration, for example by firmly gripping the handle of a lawnmower or motorcycle handlebars.

Cholinergic urticaria

This arises from stimulation of the sweat glands following exercise, emotion or heat. Weals are usually small (2–4 mm), itchy and surrounded by flares. They may occur anywhere on the body and appear within minutes of the stimulus. ⁶

Image Previews

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Table 1 Common types of urticaria – features and investigations at a glance ¹



[Full Size]

fig. 1 Dermographic urticaria — upper back of a 54-year-old man. (Source: Diepgen TL, Eysenbach G et al.....

Cold urticaria

Symptoms occur within minutes of cooling the skin. Cold weather or handling cold objects commonly initiate a reaction. The usual test for this involves challenge testing with an ice cube on exposed skin for about 10 min.

Solar urticaria

Exposure of the skin to natural or artificial sunlight induces immediate wealing.

Aquagenic urticaria

This occurs after contact with water of any temperature.

Once the physical cause has been identified by challenge testing, further investigation will be of little value and management/treatment can be initiated. The physical urticarias, with the exception of DPU, usually respond well to H₁ antihistamine treatment.

Chronic 'idiopathic' urticaria (CIU)

This is the most common diagnosis made for urticaria, given when diagnoses of urticarial vasculitis and predominant physical urticarias have been excluded. ⁷ Physicians should not be deterred by negative laboratory investigations and should continue the search for clues in a carefully taken history and examination.

A small proportion of patients (< 5%) may prove to be reactive to certain food additives. An even smaller number of cases may be associated with parasite infestation. It is worthwhile doing a differential white blood cell count to reveal any eosinophilia. If present, this should prompt stool examinations for ova and parasites.

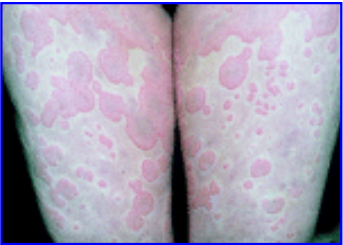
The high rate of comorbidity of CIU with other forms of urticaria, such as dermatographism and DPU, should also not be overlooked. ⁸

Recent evidence has suggested a further subgroup of chronic urticarias relating to circulating histamine-releasing autoantibodies. As many as 30–60% of CIU patients may have circulating autoantibodies, predominantly IgG1 and IgG3, specific for the α subunit of the high-affinity IgE receptor (FcεRIα). A proportion of CIU diagnoses may in fact have an underlying autoimmune pathogenesis. ^{5,9,10} Identifying this subgroup of patients has practical implications for their treatment, with immunotherapy being of value in such cases. ⁵

Angioedema

Angioedema is a deeper form of urticaria and is associated with urticaria in about half of CIU patients. ⁵ The swellings involve subcutaneous or submucosal tissue and, being larger, last longer than urticarial weals and are less itchy. Swelling is often localized around the lips, eyelids, tongue, hands, feet, pharynx and genitals. Involvement of the upper airways can lead to life-threatening situations.

Hereditary angioedema is a rare condition (< 1% of all angioedema cases) caused by an autosomal dominant genetic defect. It has no associated wealing. Stress or trauma are often involved in prompting an episode. A prolonged history of repeated cutaneous or mucosal angioedema warrants screening for a hereditary or, rarely, acquired deficiency of the C1 esterase inhibitor by measuring plasma concentrations of complement C4.



[Full Size]

fig. 2 Urticaria vasculitis – upper legs of a 58-year-old female patient. (Source: Diepgen TL, Eysenbac...

A detailed checklist form for suspected urticaria. The form includes sections for: 1. Lesions (location, duration, individual lesions, size, color, wheal appearance, frequency, chronic nature, body sites affected, itchiness, and healing). 2. Associated symptoms (food intake, exercise, stress, and other factors). 3. History of symptoms (onset, duration, and associated conditions). The form is designed to be filled out by a healthcare provider to gather comprehensive patient history.

[Full Size]

fig. 3 Suspected urticaria – patient history checklist.

Urticarial vasculitis (fig. 2)

Diagnosis of urticarial vasculitis is suggested by longer lasting lesions (3–7 days) and residual bruising as the weals fade. Weals may be painful and associated with a burning sensation. ¹¹ Some patients may also show signs of systemic disease including arthralgia, abdominal or chest pain, eye inflammation, lung and renal disease. Many cases of urticarial vasculitis are idiopathic, but it may be associated with conditions such as connective tissue disease (particularly systemic lupus erythematosus), serum sickness, complement abnormalities and hepatitis B or C infection. ¹¹

Confirmation of a diagnosis of urticarial vasculitis can only be done by skin biopsy to show histological evidence of vasculitis. Systemic involvement should be investigated. The most common laboratory abnormalities reported are an elevated erythrocyte sedimentation rate (ESR), hypocomplementaemia and circulating immune complexes. It is also worth noting that about 60–80% of cases occur in women. ¹¹

Diagnosis summary

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Identifying the type(s) of urticaria requires a detailed patient history. A brief checklist of elements to remember when evaluating the patient is given in fig. 3. Key steps and investigations for diagnosis are presented in fig. 4.

It may be useful to initiate a patient evaluation by considering the duration of individual weals and specifically whether each lesion lasts longer than a day. ⁵ Consideration should also be given to the appearance of the lesions – size and colour, and the location of the lesions on the body. Attention should be paid to possible precipitating causes, such as medications, including aspirin and other NSAIDs, and possible insect bites/stings.

When physical urticaria is suspected, appropriate challenge testing should be performed to confirm the diagnosis. If physical urticaria is then found to be the predominant cause of symptoms, further investigations (such as those outlined in fig. 4) are of little value.

Conditions requiring specialist referral: ¹²

- severe, life-threatening allergy, e.g. peanut or latex allergy
- urticaria lasting beyond 6 weeks (chronic)
- features of urticarial vasculitis
- associated systemic features
- poor response to antihistamines
- angioedema involving the airways.

Investigations

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Complete blood count with differential analysis and measurement of ESR and (in cases of associated angioedema) serum complement C4 level should be carried out at the patient's first visit.

- Eosinophilia – suggests that the stool should be examined for ova and parasites.



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fig. 4 Key steps for investigating chronic urticaria. Reproduced with permission from Greaves MW. *N En...*

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- Elevated ESR – suggests that a skin biopsy may show evidence of urticarial vasculitis, particularly where individual weals last longer than 24 h.
- Skin biopsy – should be taken from the edge of the weal and should include clinically normal and abnormal skin. Skin biopsy should be taken if weals last longer than 24 h, if marks are left on the skin, if lesions are more painful than itchy or if there is a poor response to treatment with antihistamines.
- Low complement C4 level – necessitates investigation of C1 esterase inhibitor level (and activity) to confirm hereditary angioedema.
- Skin prick testing – rarely used except (with care) to confirm food and certain drug reactivities in acute allergic urticaria.

Where food or food additives are considered to be possible causes, double-blind, placebo-controlled challenge testing should be initiated.

Where autoantibodies against Fc ϵ R1 α are thought to be involved, 0.05 mL of autologous serum is injected intradermally into the forearm. A serum-induced weal with a mean diameter 1.5 mm larger than that resulting from a control injection (phosphate-buffered saline) indicates a positive result.

¹³ Confirmation of autoantibody involvement requires histamine release from the basophils of a healthy donor on incubation with the patient's serum. This requires participation by a specialist allergy or dermatology unit.

Controversies/confusion

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The coexistence of chronic urticaria and physical urticaria, particularly dermatographism and DPU, is a frequent cause of diagnostic confusion. It is therefore important to establish the presence of physical urticaria with appropriate challenge testing, as future investigations and treatment may be affected. Overlooking urticarial vasculitis is a common diagnostic pitfall. Acute contact allergic dermatitis may resemble angioedema.

Treatment overview

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Advice to be given to patients where appropriate

- remove identifiable cause(s)
- explanation, information and reassurance
- minimize stress, overheating and alcohol
- avoid aspirin, codeine and morphine
- angioedema patients should avoid angiotensin-converting enzyme inhibitors
- exclusion diet (only when indicated from history), e.g. exclude food additives such as colourings and preservatives.

Pharmacotherapy

First line

- non-sedating antihistamine

- if poor response (with regard to itching), a sedating antihistamine at night may be of value
- if poor response, adding an H₂ antihistamine may be valuable
- reconsider diagnosis – could symptoms be a result of urticarial vasculitis or DPU (which respond poorly to antihistamines)? ²

With histamine being the main mediator of urticaria, H₁ antagonists are naturally the first-line treatment for itching and wealing. In order to prescribe antihistamines effectively, the diurnal periodicity of the symptoms, particularly itching, needs to be established for each patient.

Second line for special indications:

- systemic steroids: short-term for severe exacerbations of urticaria (prolonged use should be avoided); for urticarial vasculitis
- adrenaline for severe angioedema. ²

Third line

- immunomodulatory treatments, including cyclosporin and intravenous immunoglobulin ¹⁴– under investigation in specialist centres for the most severe, recalcitrant urticaria
- plasmapheresis. ¹⁵

Conclusions

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Urticaria is one of the most distressing and frustrating dermatological conditions. The disease may have a significant impact on the patient's quality of life, including lost work days and impaired social relationships. Although about three-quarters of cases are thought to be idiopathic, a careful assessment of patient history, appropriate challenge testing and laboratory investigations may reveal a causative factor for the predominant symptoms. With identification of such factors (e.g. pressure, cold, food additives, etc.), the patient can be reassured and advised to avoid such triggers. Treatment options and future investigations are also dependent on initial assessments.

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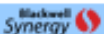
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