

URTICARIA AND RELATED ALLERGIC DISORDERS

NETTLE – *URTICA URENS*



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‘Weals or wheals’ are raised white areas on the skin with reddened margins, which may result from sharp blows, or may be a symptom of nettle-rash

CORE TUTORIALS IN DERMATOLOGY FOR PRIMARY CARE

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PREQUEL: A SYSTEMATIC APPROACH TO DIAGNOSING SKIN CONDITIONS

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URTICARIA AND RELATED ALLERGIC DISORDERS**

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Urticaria, derived from the Latin for a “nettle”, was first described by Hippocrates. At first glance it might appear contentious to include the urticarias as a “core” subject in general practice dermatology. However, I make no apology! Urticaria may be the least well recognised of what I like to term the “four horsemen of the allergic apocalypse” – asthma, eczema, and allergic rhinitis being the others, but its frequency, impact on quality of life and its traditionally poor management make it an obvious contender for inclusion.

THE URTICARIAS

Like all allergy related disease, it is irrefutable that the urticarias are on the increase. Reasons for this remain unclear and are likely multifactorial. Statistically, however, the lifetime risk of suffering from acute urticaria is around 20%¹ and that of chronic urticaria 2-3%.² Quality of life assessments demonstrate significant impacts on both objective functioning and subjective well-being, scoring urticaria highly, equating with severe eczema and coronary heart disease and indeed higher than psoriasis.

URTICARIA



Urticaria, akin to eczema, is a general term that can be clearly sub classified into varying different classical patterns. For simplicity in this article, the sub-divisions will be acute, chronic, physical, angioedema, and urticarial vasculitis. As with the eczemas, there is a huge potential for areas of overlap.

Pathophysiologically, urticarias are mediated by mast cell degranulation and release of histamine. However, other chemotactic agents are also involved, such as cytokines. Antihistamines, although remaining the mainstay of treatment as monotherapy, are therefore not always completely successful in achieving complete symptom control.

DIAGNOSIS

I was always taught that history taking was the most important component of establishing accurate diagnoses. Never has this been more true than when establishing a diagnosis of urticaria, also known as hives or “nettle rash”. By its very nature, the rash may not be apparent on any one day, but a good history should leave the clinician in little doubt as to the problem in a straightforward presentation of urticaria. History should focus on the periodicity and transience of the rash, the appearance of raised, itchy wheals, their flitting nature lasting less than 24 hours and leaving skin of **normal** appearance, with no scaling or scarring. Some exceptions to these general rules are explored later in the article.

We must all be aware, as clinicians, that it is human nature for our patients to need to recognise the cause for their “allergic” rash and reduce uncertainty. Some go to great lengths to pursue this and often inadvertently mislead the physician with theories of what is causing their problem. Some become obsessed with their diet or environment and many a domestic pet has had a finger firmly, but erroneously, pointed in their direction! I hope that on finishing reading this article, the clinician may have some facts and figures to hand to combat such ignorance and hysteria!

Basic history should, however, include the following in addition to the nature and appearance of the rash as detailed above. Indeed, some specialist centres assess urticaria with very comprehensive questionnaires to exclude underlying cause or provoking factors.

Areas to be explored are as follows:

- General health – with special reference to co-existing chronic systemic disease, especially thyroid/autoimmune, reticuloses or carcinoma and hepatitis status.
- Occupational history.
- Drug history – **all** regular/intermittent medication including all over-the-counter drugs, particularly aspirin.
- Family history of atopy/angioedema.
- Hobbies/pets.
- Any recent acute illness, especially infection/infestation/inflammation.
The association of these processes with urticaria shows conflicting results.
- Any **consistent** provoking factors, particularly physical/acute food/contact reactions or cyclical (menstrual) pattern.
- Areas of the body most frequently affected.
- Any associated symptoms e.g. wheeze, abdominal pain, vomiting or diarrhoea.
- Foreign travel/seasonal variation.

Is there a **clear** relationship to anything ingested, injected, implanted or inhaled?

Classic urticaria is divided into acute and chronic, the latter being rather arbitrarily defined as lasting in excess of six weeks. There are some significant differences between the two.

1. ACUTE URTICARIA – Affected individuals are much more likely to have an atopic background. Many will have raised IgE levels and causation is much more likely identifiable, although this can still only be established in less than 50% of cases. IgE mediated food allergy is extremely rare as a cause of chronic urticaria.

Commonest aetiologies are Type I immediate hypersensitivity allergic food reactions and also drug reactions.

Most commonly implicated foods are:

- Fish, including shellfish (31%)
- Strawberries and raspberries (10%)
- Eggs (5%)
- Wheat (3%)
- Meats (2%)
- Nuts (12%)
- Citrus fruits (8%)
- Tomatoes (5%)
- Alcohol (3%)

Most commonly implicated drugs are:

- Antibiotics
- Codeine
- ACE Inhibitors
- Aspirin
- Morphine
- NSAIDs

Less common pharmacological causes include:

- Local anaesthetic
- Blood products
- Radiocontrast media

Colourings and preservatives, particularly tartrazine and benzoates only constitute a very small number (2-4%)



Insect bites and stings can produce both papular and generalised urticaria; uncommonly, life-threatening anaphylaxis can develop – an average of four deaths per year occur in England and Wales as a consequence of wasp and, less commonly, bee stings.

There remains, however, a very powerful patient perception that foods are implicated as a cause; this far exceeds true confirmed reactions.³ There is, however, a rare but serious type of reaction related to certain foods, in combination with exercise which can potentially induce anaphylactic shock.

Acute contact urticaria can be mediated both via immune and non-immune mechanisms (i.e. without prior sensitisation). Foods have already been discussed. Other possible causes are plant, animal and chemical contacts, e.g. latex. Such reactions can be differentiated from contact dermatitis by the short time scale with reactions occurring between a few minutes and one hour. There is also the lack of skin scaling so characteristic of an eczematous reaction. Certain foods can also demonstrate cross reactivity e.g. kiwi and avocado.

PAPULAR URTICARIA



2. CHRONIC URTICARIA – Defined as recurrent or persistent urticarial rashes lasting in excess of six weeks. This has been variously titled ordinary urticaria and chronic idiopathic urticaria but the current correct term is chronic spontaneous urticaria (CSU). Cause is rarely established (2-4%) and the majority are now considered to be autoimmune mediated. Autoantibodies can be identified in a third of cases. Foods and additives are rarely implicated;⁴ a history of atopy less likely and IgE levels are usually normal. Unless dictated otherwise by history, investigations should be kept to a minimum; this is discussed further on page 6. The physician should be optimistic and upbeat regarding prognosis; 50% self resolve within six months. However, 10% can persist for over ten years!

3. PHYSICAL URTICARIAS aka INDUCIBLE/ATTRIBUTABLE URTICARIA – These comprise approximately 20% of all urticarias. A wide range of differing physical stimuli are implicated and confirmation is by provocative testing. Most common of the physical urticarias is the cholinergic variety – small, intensely itchy, monomorphic urticariated papules, less than 0.5 cm, which appear after episodes of exercise or emotional stress.



Other physical urticarias are listed below.

- **Pressure/delayed pressure urticaria** – can occur between 30 minutes and 9 hours after provocation; one of the few urticarias that can last in excess of 24 hours.
- **Cold urticaria** – can be replicated by an ‘ice cube’ test. This involves applying an ice cube for 3-5 minutes; there is an occasional risk of anaphylactic shock and death with sudden total immersion in cold water.
- **Solar urticaria** – can be differentiated from other types of sun-induced dermatoses by its sudden onset within minutes of exposure, with symptoms lasting several hours.

Other types of rarer physical urticaria include vibratory, heat and aquagenic urticaria.

Dermographism – Literally “writing on the skin”. This can be a feature in a wide range of urticarias but can be induced in 5% of the normal population.

DERMOGRAPHISM



4. ANGIOEDEMA – This is a clinical presentation characterised by deep-seated subcutaneous swellings, with or without mucous membrane involvement; these are **not** itchy. Less commonly, there are systemic symptoms e.g. wheezing or abdominal pain. About half have an associated urticaria. Symptoms can present for several days. This condition can be potentially life threatening if there is laryngeal/tracheal oedema. Acute food and drug allergy can be implicated; be particularly aware of ACE inhibitors where the mechanism is thought to be due to inhibition of bradykinin breakdown.



Rarely, this condition can be hereditary due to C₁ esterase inhibitor deficiency. Inheritance is autosomal dominant and enquiries should be made to include family history. Onset is usually evident before the age of 40 and there is no coexistent urticaria.

Even more rarely, C₁ esterase inhibitor deficiency can be acquired; this is associated with various systemic diseases including autoimmune conditions, such as systemic lupus erythematosus and also lymphoproliferative disease. If C₁ esterase inhibitor deficiency is suspected, C₄ levels should be checked; a normal result excludes the diagnosis. To differentiate between hereditary and acquired C₁ esterase deficiency, where a C₄ will be low in both conditions, a C₁q will be low in the hereditary form and normal in the acquired form.

ANGIOEDEMA – WASP STING



ANGIOEDEMA – INSECT BITE



5. URTICARIAL VASCULITIS – The literature suggests that this comprises up to 5% of chronic urticaria; however, it is not widely recognised in primary care. There are some clear indicators in the history, most importantly the urticarial lesions will often persist in excess of 24 hours and last frequently for several days. Patients may complain of pain and burning in addition to itching. The lesions can fade to leave bruising. Henoch-Schönlein purpura is a type of urticarial vasculitis. There are often systemic symptoms and there is an association with other diseases, especially of an autoimmune flavour. A biopsy demonstrates a leucocytoclastic vasculitis histologically.



INVESTIGATIONS

REMEMBER – These are a distant second to good history taking!

ACUTE URTICARIA – IgE levels and specific CAP fluoroimmunoassays, formerly known as RAST tests (radioallergosorbent tests), can be carried out to a wide range of possible food, plant and animal triggers. However, these are relatively expensive, have poor specificity and should not be done routinely. Occasional dietary challenge and prick tests can be helpful to unravel difficult cases. There is a common misconception that patch testing is useful – this is **not helpful** in the investigation of urticaria, which is essentially a type 1 immediate hypersensitivity reaction while patch testing is to define type 4 antibody/antigen reactions.

CHRONIC URTICARIA – As most cases are idiopathic, comprehensive tests are not indicated unless history dictates. A full blood count and an inflammatory indicator, such as viscosity or CRP would be a simple baseline. Abnormalities here may indicate the possibility of an underlying infection which would need further investigation although in real practice this is a rare association. A raised eosinophil count may indicate parasitosis, and a stool examination may be indicated. An additional case may be made to check liver and thyroid function, as such abnormalities can occasionally present as chronic urticaria.

Other tests are reserved for specific situations e.g.

- **Cold urticaria** – may require cryoglobulin estimation.
- **Urticarial vasculitis** – requires a biopsy and further investigations as indicated.
- **Angioedema** – may require complement and C₁ esterase inhibitor levels as previously discussed.

N.B. Chronic persistent urticariated plaques are a well recognised prodrome of bullous pemphigoid in the elderly. Bear this in mind in higher risk age groups, especially if the skin progresses to frank blistering.

TREATMENT

The fundamental cornerstone for the treatment of all urticarias are antihistamines. Pharmacokinetically, these act as mast cell stabilisers. Certain types of urticaria may require additional specific approaches. Topical antihistamines/steroids are **not** of use. Likewise, courses of oral steroids for the majority of acute/chronic urticaria, although frequently prescribed, are not appropriate. Certain exceptions are discussed on page 8. The newer second generation antihistamines are very effective and well tolerated drugs. The use of first generation antihistamines should be an exception. Antihistamines, however, often disappoint in the treatment of some physical urticarias.

Personally, I think there is very little to choose between the different preparations available, either on price, efficacy or convenience. However, it is worthwhile swapping patients to different preparations if the first chosen is ineffective. It is well acknowledged that individual patients seem to do better on one preparation than another, although I know of no strict scientific reason for this. First generation antihistamines still have a place, especially for the treatment of intractable night-time itch. Chlorphenamine (Piriton) is considered the safest in pregnancy, purely as a consequence of experience.

A profile of the present available antihistamines follows below. It is important to note that in all accidents where ingested medication is implicated, a third involved antihistamines!



ANTIHISTAMINE PROFILES

NAME	PROS	CONS
bilastine (Ilasten®)		
cetirizine dihydrochloride (non-proprietary) Zirtek® Allergy	Additional properties – inhibits leucocyte activity – specifically useful in delayed pressure (DPU) and urticarial vasculitis	Can be sedating (8.5/1000) Renally excreted – dose needs adjusting if abnormal kidney function
levocetirizine dihydrochloride (non-proprietary) Xyzal®		
loratadine (non-proprietary)		
desloratadine (non-proprietary) Neoclarityn® (metabolite of loratadine)	Non-sedative	
fexofenadine hydrochloride (non-proprietary) Telfast®	Non-sedative – doesn't cross blood/brain barrier – available in 3 strengths	
mizolastine (Mizollen®)		– may affect QT interval and induce cardiac arrhythmias
rupatadine (non-proprietary) (Rupafin®)		

My normal practice is to introduce a non-sedating antihistamine and increase the dose according to response with the exception of mizolastine which is not suitable for up-dosing. It is common dermatological practice to use 2, 3 and even a maximum of 4 times the recommended doses of antihistamines for resistant cases of urticaria, although there are some contraindications for certain categories of patient and these should always be checked by the prescriber. Sedating antihistamines should be used with caution if there is a history of BPH, urinary retention or angle closure glaucoma.

Cetirizine has the shortest time to reach maximum concentrations in the body which can be theoretically advantageous in order to achieve rapid symptom control.

If there is failure to control symptoms, then switching to a different brand and titrating the dose again, can be useful. If again this fails, then consideration of second line drugs/treatments listed below should be considered.

When treating chronic spontaneous urticaria during pregnancy/breast feeding consider chlorphenamine, loratadine or cetirizine after the first trimester. In young children, desloratadine and chlorphenamine are licensed from 1 year and over and loratadine and cetirizine from 2 years and over.

SECOND LINE DRUGS/TREATMENTS

- **H₂ blockers** – Histamine₂ receptors are not exclusive to the GI tract, combining H₁ and H₂ blockade, for example, with famotidine can sometimes be helpful.
- **Doxepin** – This is a tricyclic antidepressant with potent antihistaminic properties. It is useful when there is coexistent agitation/sleeplessness.
- **Mast cell stabilisers** e.g. ketotifen and nifedipine – these are rarely effective.
- **Prednisolone** – This can be useful in special situations e.g. severe angioedema and delayed pressure urticaria and selectively for episodes of disabling acute urticaria, but should **not** be used routinely or as a long term strategy.
- **Ciclosporin** – This can be useful in intractable chronic spontaneous urticaria (CSU) and cold urticaria under specialist supervision.
- **Leukotriene antagonists (e.g. montelukast)** – These seemed to show some early promise in the treatment of CSU in combined therapy but the subsequent evidence base is weak. Montelukast appears to be the most effective.
- **Exclusion diets** – Selected patients only – these will need strict monitoring both by specialist and dietician.
- **Danazol** – Indicated for treatment of cholinergic urticaria and angioedema/C₁ esterase deficiency.
- **Omalizumab (Xolair)** – This is a recently introduced injectable therapy for very resistant CSU with inadequate response to H₁ antihistamine. It requires careful supervision probably best done in secondary care.

As a simple aide-mémoire, I have set out a diagrammatic diagnostic and management plan for urticaria (see overleaf). I hope this may be useful for quick reference.

MANAGEMENT GUIDELINES

CHRONIC URTICARIA MANAGEMENT GUIDELINES

DIFFERENTIAL DIAGNOSIS

- Insect bite.
- Pemphigoid.
- Dermatitis herpetiformis.
- Toxic erythema.
- Erythema multiforme.

URTICARIA PRESENTATION

- Transient, usually pruritic pink papules or wheals.
- Anywhere on the skin surface.
- Variable shape and size.
- Last 6 to 24 hours before resolving.
- Occasionally associated with angioedema.
- Less than 6 weeks treat as acute urticaria.
- More than 6 weeks treat as chronic urticaria.

Associated with cold, pressure, sunlight, exercise, water, vibration or stroking of skin?

YES

NO

Wheals greater than 24 hours?
Painful rather than itchy?
Residual purpura?
Systemic features (fever, nephritis, arthralgia)?

YES

NO

Is there angioedema in the absence of urticaria?

YES

NO

GENERAL MANAGEMENT PRINCIPLES

- Diagnosis is made primarily from history and clinical features.
- Explain the nature of the condition and often no cause is found.
- Avoid aspirin, codeine, morphine and other trigger factors.
- Minimise stress, overheating, alcohol, tight clothing.
- Exclusion diet when indicated by history.
- Non-sedating antihistamines are the treatment of choice for most urticarias.



CLASSIFICATION OF CHRONIC URTICARIA

PHYSICAL URTICARIAS

- Diagnosis by history and clinical findings alone.
- COLD: itchy pale or red wheal at site of cold surface.
- PRESSURE: large painful or itchy red swelling at site of pressure appearing a few hours after contact, e.g. soles, palms or waist.
- SOLAR: itchy pale or red swelling at site of exposure to UV.
- CHOLINERGIC: itchy small <5mm monomorphic pale or pink papular wheals on trunk, neck or limbs after exercise or hot shower.
- DERMOGRAPHISM: itchy linear wheals soon after stroking of skin.
- OTHERS: aquagenic, vibratory, contact e.g. latex allergy.

URTICARIAL VASCULITIS

- Diagnosis by history, clinical examination and investigations.
- Elevated ESR.
- Elevated acute phase proteins.
- Biopsy shows vasculitis (leucocytoclastic).
- Check FBC, ESR, ANF, Hep status, urinalysis, C₃ and C₄.

HEREDITARY ANGIOEDEMA (C₁ ESTERASE DEFICIENCY)

- Diagnosis by history, clinical findings and investigations.
- Is the patient on an ACE inhibitor (causes reduced bradykinin breakdown)?
- Low serum C₄ suggests C₁ esterase disorder.
- If low C₄ perform C₁q (low = hereditary, normal = acquired).

CHRONIC SPONTANEOUS URTICARIA (CSU)

- Diagnosis by history, clinical examination and investigations.
- 50% due to an autoimmune mechanism, testing only in reference centres for IgG autoantibody to IgE receptor involves autologous serum skin test.
- Concentrate on food and drug history, especially seafoods, nuts, fruits, eggs, milk, food additives, aspirin and other NSAID's, opiates, penicillin.
- Is there an occupational trigger?
- Check FBC, ESR, LFT, stool for parasites if eosinophilia.
- If initial tests -ve, proceed to thyroid function tests, ANF to consider SLE, Hepatitis B and C serology, urine analysis.
- Skin prick tests or CAP fluoroimmunoassay (formerly known as RAST) if specific trigger suspected – (This is more useful in investigation of acute urticaria with associated atopy).

SPECIFIC MANAGEMENT

- Remove cause.
- H₁ non-sedating antihistamine.
- Stepwise addition of sedating H₁ antihistamine and H₂ antihistamine.
- Consider short course prednisolone for severe pressure urticaria (2 weeks).

- Refer to a dermatologist.
- Trial dapsone, colchicine or indomethacin.
- Short course prednisolone if required.
- Need to exclude underlying systemic disease e.g. SLE.

- Refer to a dermatologist.
- May need adrenaline 0.5-1.0 ml 1:1000.
- May need anabolic steroids e.g. danazol and antifibrinolytic e.g. tranexamic acid.
- Urgent referral if airway compromise.

- Remove cause.
- H₁ non-sedating antihistamine e.g. loratadine.
- Stepwise addition of sedating H₁ antihistamine e.g. chlorphenamine and H₂ antihistamines e.g. famotidine.
- Consider doxepin or mast cell stabiliser such as nifedipine.
- Try to avoid short courses of prednisolone.
- Refer to a dermatologist.

CRITERIA FOR REFERRAL

- 1). Severely affected and resistant to treatment.
- 2). History of anaphylaxis/severe angioedema.
- 3). Urticaria associated with refractory systemic disease.
- 4). Urticarial vasculitis.
- 5). When history indicates either special investigation e.g. prick testing, challenge diets, or special treatment e.g. exclusion diets.

TEACHING POINTS

- 1). The lifetime risk of suffering from acute urticaria is around 20%¹ and that of chronic urticaria 2-3%.²
- 2). Causes of chronic urticaria are not usually identifiable.
- 3). Steroids are rarely indicated in the treatment of urticaria.
- 4). Good history taking is of paramount importance in the diagnosis of urticaria.



USEFUL CONTACT

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Legal category: Class I medical device.

Further information is available from: Dermal Laboratories Ltd, Tatmore Place, Gosmore, Hitchin, Herts, SG4 7QR, UK.

Date of preparation: April 2022.

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Adverse events should be reported. Reporting forms and information can be found at yellowcard.mhra.gov.uk. Adverse events should also be reported to Dermal.

References: 1. Comparison of the skin hydration of Doublebase Once emollient with Epaderm Ointment in a 24-hour, single application study, in subjects with dry skin. Extract report summarising skin hydration results for wiped off sites. Data on file. Dermal Laboratories Ltd, Hitchin, UK. Epaderm® Ointment is a registered trademark of Mölnlycke Health Care. 2. Antonijević MD & Karajčić J. Ointments or a gel emollient? Randomised and blinded comparison of the hydration effect on *ex-vivo* human skin. Data presented at the 17th European Academy of Dermatology and Venereology (EADV) Symposium, May 2022, Ljubljana, Slovenia.

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