

The GP's role in urticaria

- What is the place of allergy testing in patients with urticaria?
- How should antihistamines be used for optimum results?
- What non-pharmacological interventions are likely to help?



Figure 1
Solar urticaria in a child
[AUTHOR PLEASE – WOULD YOU CARE TO ADD AN EXTRA CAPTION LINE OF USEFUL CLINICAL INFO?]

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Urticaria control is the most difficult of all dermatological problems presenting to the GP. Patients with chronic urticaria usually feel abandoned by their GP and dermatologist, and can become extremely depressed with the constant itching and unsightly rash, which may persist or periodically recur for many years.

Urticaria predominantly affects adult females and up to 20 per cent of the general population sometime during their lifetime. It presents as a diffusely raised, itchy wheal and flare reaction that migrates over the skin surface.

All forms of urticaria may occur in association with deeper skin swelling or angioedema and, equally, angioedema may occur in isolation with no apparent urticaria. When this hereditary angioedema (HAE) is seen possible deficiency of

the C1-esterase inhibitor enzyme should be considered.

• **Classifying urticaria** We classify ordinary urticaria as acute when the rash duration appears for under six weeks, and chronic when it persists for over six weeks.

The actual cause of acute ordinary urticaria is relatively easy to identify, as the trigger seems immediately apparent and the reaction is reproducible. Examples include: shellfish, penicillin, insect or latex allergy, and the rash associated with a streptococcal or viral hepatitis infection.

This is the only form of urticaria where allergy testing by means of skin-prick or RAST blood tests may be helpful.

In chronic ordinary urticaria it is far more difficult to identify a specific trigger, and in over 50 per cent of cases no cause is ever identi-▶



VIERING/MEDICINE

Figure 2 Urticarial wheals [AUTHOR PLEASE – YOUR WHEEL IMAGE WAS TOO LOW RES TO PUBLISH. IS THIS AN ACCEPTABLE REPLACEMENT, AND WOULD YOU CARE TO ADD AN EXTRA LINE OF USEFUL CLINICAL INFO?]

fied: we then label this chronic idiopathic urticaria (CIU). A fraction of chronic ordinary urticaria cases may be triggered by systemic illnesses such as autoimmune thyroid disease, collagen vascular disease, chronic parasitic infections, chronic sinusitis, *Helicobacter pylori* and chronic dental infections.

Over one-third of individuals with chronic urticaria display autoantibodies directed against IgE or the mast cell IgE receptor. These autoantibodies trigger mast cell

degranulation and histamine release, and make this form of chronic urticaria extremely difficult to control.

Sustained daily intake of food additives (benzoates, sulphites and azo dyes) can lead to chronic urticaria, but true food allergy is unlikely to cause chronic ordinary urticaria, and exhaustive food allergy testing is not helpful.

Physical urticaria is due to an external physical trigger and has a familial tendency. In its most benign form it commonly presents as linear dermatographism after firmly stroking the skin. Other reproducible physical stimuli that act as triggers include heat and exercise (cholinergic urticaria), cold, sun exposure (solar urticaria), vibration, deep pressure (delayed pressure urticaria) and water exposure (aquagenic urticaria – extremely rare).

The lesions occur within minutes of the stimulus (except delayed pressure) and disappear rapidly within an hour or two.

Just to complicate matters, physical urticaria often occurs in conjunction with chronic ordinary urticaria.

In contact urticaria, an immediate IgE-mediated allergy occurs after skin contact with fresh food,

pet saliva or latex and settles within a few hours. Children frequently develop discretely grouped itchy papular urticaria following insect bites.

Urticarial vasculitis is a rare condition that presents with painful non-migratory lesions that persist for over 24 hours, often with fever, purpura and arthralgia. Skin biopsy and specialist referral are required. It is associated with underlying autoimmune connective tissue diseases and serum sickness, systemic lupus erythematosus and Sjögren's syndrome should be considered.

Urticaria pigmentosa, which may occur in children, is a diffuse, dark freckle-like rash that urticates on

'Urticarial vasculitis requires skin biopsy and referral'

rubbing the skin and is due to excess mast cells in the skin (cutaneous mastocytosis).

Exercise-induced urticaria may be food allergy related. Hypersensitivity to wheat, celery or shellfish ►

Table 1 Foods with high vasoactive amine (histamine) content

Fish
Mackerel, tuna, smoked salmon, sardines, pickled herring
Cheese
Emmental, Parmesan, Camembert, Cheddar, Stilton
Cured meat
Salami, dried ham, smoked sausage, chicken liver
Fruit and vegetables
Aubergine, spinach, red beans, avocado, bananas, dates
Alcohol
Red wine, cider, real ales
Others
Marmite, soy sauce, tomato ketchup

as well as aspirin or alcohol ingestion may manifest with urticaria and even anaphylaxis occurring after exercise (if that food is eaten within four hours prior to exercise).

If a specific urticaria trigger can be identified, then avoidance is the most desirable action, but very often no underlying cause is ever identified. The main thrust of management should then be to provide support and alleviate symptoms while the urticaria slowly 'burns' itself out and resolves, only to recur again – a process that may take many years.

•Pharmaceutical management of urticaria

•Antihistamines The second-generation non-sedating antihistamines are the mainstay of current urticaria treatment and doubling the normal recommended dose is often necessary to obtain symptom control (for example, daily cetirizine 10–20mg, loratadine 10–20mg or fexofenadine 180–360mg). Once the urticaria is controlled, the dose can be slowly reduced.

The addition of sedating antihis-

tamines such as chlorpheniramine or hydroxyzine may help if optimal control is not achieved and will reduce sleep disturbance from itching.

Tolerance to antihistamines can develop and it may help to periodically rotate through different antihistamines.

Ketotifen can be effective in children with its antihistamine and mast-cell stabilising properties. If it is necessary to use antihistamines in pregnancy, chlorpheniramine, though sedating, is safest. Gastric histamine H₂-blockers such as ranitidine 150mg bd offer additional antihistamine effects if used together with conventional antihistamine medication and can be used for long periods of time.

•Oral steroids Although prednisolone (>30mg) is most effective in the short term for rapid symptom relief, long-term use will lead to undesirable side-effects and sometimes problematic rebound urticaria on withdrawal. Occasionally long-term alternative-day regimens may be necessary to control chronic recalcitrant urticaria.

'Montelukast is particularly useful in aspirin-sensitive individuals'

•Steroid-sparing options The tricyclic antidepressant doxepin (10–50mg daily) has histamine-blocking properties and is useful as an adjunct, especially if there is co-existent depression with the urticaria. Doxepin cream (Xepin) used topically also has anti-pruritic properties.

The leukotriene receptor antagonist montelukast (10mg at night) and the 5-lipoxygenase inhibitor zileuton (600mg every 6–12 hours) have been used with some success, and are most effective when used in



Figure 3 Diffuse urticaria (?) [AUTHOR PLEASE – YOUR DIFFUSE URTICARIA IMAGE WAS TOO LOW RES TO PUBLISH. IS THIS AN ACCEPTABLE REPLACEMENT, AND WOULD YOU CARE TO ADD AN EXTRA LINE OF USEFUL CLINICAL INFO?]

combination with non-sedating antihistamines or doxepin. Montelukast is particularly useful in aspirin-sensitive individuals (who are prone to urticaria, nasal polyps and asthma), but may cause gastrointestinal disturbances.

Oral sodium cromoglycate may dampen food-related exercise-induced urticaria, while those with exercise-induced anaphylaxis or severe angioedema should carry an EpiPen (adrenaline auto-injector) and avoid vigorous exercise.

Stress (public speaking, examinations, exercise and arguments) may trigger cholinergic urticaria, and propranolol will reduce symptoms.

Other drugs such as colchicine, warfarin, nifedipine, danazol, dapsone and sulfasalazine have been tried over the years with varying success in chronic urticaria.

Auto-immune thyroid disease ►

Urticaria

Clinical focus

• Urticaria predominantly affects adult females and up to 20 per cent of the general population sometime during their lifetime. We classify ordinary urticaria as acute when the rash duration appears for under six weeks, and chronic when it persists for over six weeks. Physical urticaria is due to an external physical trigger such as heat, cold, pressure or exercise and has a familial tendency

• The actual cause of acute ordinary

urticaria is relatively easy to identify, as the trigger seems immediately apparent and the reaction is reproducible. This is the only form of urticaria where allergy testing by means of skin-prick or RAST blood tests may be helpful. In chronic ordinary urticaria it is far more difficult to identify a specific trigger, and in over 50 per cent of cases no cause is ever identified

• If a specific urticaria trigger can be

identified, then avoidance is the most desirable action, but very often no underlying cause is ever identified. The main thrust of management should then be to provide support and alleviate symptoms while the urticaria slowly 'burns' itself out and resolves, only to recur again – a process that may take many years

• The second-generation non-sedating antihistamines are the mainstay of current urticaria

treatment and doubling the normal recommended dose is often necessary to obtain symptom control (for example, daily cetirizine 10–20mg, loratadine 10–20mg or fexofenadine 180–360mg). Once the urticaria is controlled, the dose can be slowly reduced. The addition of sedating antihistamines such as chlorpheniramine or hydroxyzine may help if optimal control is not achieved and will reduce sleep

disturbance from itching. Tolerance to antihistamines can develop and it may help to periodically rotate through different antihistamines

- Although prednisolone (>30mg) is most effective in the short term for rapid symptom relief, long-term use will lead to undesirable side-effects and sometimes problematic rebound urticaria on withdrawal. Occasionally long-term alternative-day regimens may be necessary to control chronic recalcitrant urticaria

- If there is a poor response to conventional and histamine medication, reconsider urticarial vasculitis and review the diagnosis of ordinary urticaria

with associated urticaria may respond to oral thyroxine supplementation, even if biochemically euthyroid.

Immune suppressive therapy such as cyclosporin or methotrexate is effective, but cyclosporin can cause serious side-effects such as renal impairment and uncontrolled hypertension.

Other expensive third-line treatments include intravenous immunoglobulin administration and serum plasmapheresis at a specialist centre.

•Iatrogenic triggers Aspirin-containing flu remedies, and other non-steroidal anti-inflammatory (NSAI) medication such as ibuprofen and diclofenac, as well as codeine and opiate-containing analgesics, should be avoided. If essential, aspirin-sensitive individuals seem to tolerate the newer cyclooxygenase-2 selective inhibitors or COX-2 NSAI medications such as rofecoxib and meloxicam.

Paracetamol is the only analgesic and flu treatment that can safely be used in urticaria.

ACE inhibitor anti-hypertensives are a common trigger for angioedema and urticaria, especially lisinopril, ramipril and enalapril. ACE inhibitors may suddenly trigger angioedema after long periods of asymptomatic use. The angiotensin-II receptor antagonists (ACE2) such as valsartan and candesartan are less likely to induce

angioedema and urticaria.

Oestrogen replacement therapy (HRT) may trigger angioedema and urticaria and should be used with caution in urticaria.

•Advice for patients The following should be recommended:

- Resist the temptation to rub the itchy and painful lesions
- Try to keep cool at all times and wear loose-fitting clothing
- Avoid all alcoholic drinks, many of which non-specifically trigger urticaria
- Try to reduce stress with relaxation exercises and yoga
- Minor viral illnesses, menstrual periods and oestrogen may aggravate urticaria
- Keep the skin well moisturised with bland emollients
- Avoid non-specific physical triggers such as excess heat, cold, exercise and rapid temperature changes
- All forms of salicylate including toothpaste, wintergreen muscle rubs and peppermints should also be excluded
- There seems to be scant evidence to show that homeopathy benefits the management of urticaria, although the poor response to conventional treatment and the chronic, disabling nature of urticaria causes dissatisfaction and fuels exploration of alternative medical practices
- Apply calamine, aqueous cream with menthol one per cent or ten

per cent crotamiton (Eurax) lotions to soothe the skin

- Avoid topical antihistamine creams (mepyramine, antazoline, diphenhydramine) as these are potent skin-contact sensitisers
- Topical steroid creams are of no value in ordinary urticaria
- Avoid multivitamin preparations containing additives and colourings that may non-specifically aggravate urticaria
- Dietary advice** Patients should avoid food colourings (such as tartrazine), additives (including sodium benzoate and sulphites) and natural salicylate sources (including berry fruits, spices, wine and Ceylon tea).

Many patients with chronic urticaria derive benefit from a low vasoactive amine diet. Histamine contained in foods such as dark fish, fermented cheese and cured meats may trigger vasodilatation and flushing and perpetuate urticaria. Avoidance of these foods will help reduce itch and flushing (see table 1).

Recommended reading and websites

- 1 Greaves M, Kaplan A (eds). Urticaria and Angioedema. Manhattan, USA: Marcel Dekker Inc, 2004
- 2 Joneja JV (auth). Dietary Management of Food Allergies and Intolerances. 2nd edition. Burnaby, British Columbia, Canada: J A Hall Publications, 1998
- 3 Durham S (ed). ABC of Allergy. London, England: BMJ Publishing, 1998
- 4 Allergy and Allergies Agency website <http://www.allergy-network.co.uk/urticaria.htm>
- 5 Prodigy Urticaria website <http://www.prodigy.nhs.uk/guidance.asp?gt=Urticaria>