

The urticaria spectrum: recognition of clinical patterns can help management

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Summary

Urticaria has diverse clinical presentations and causes. The implication of classifying urticaria primarily by clinical presentation rather than aetiology is that management can be focused on specific clinical problems without extensive investigations. Management pathways may involve nonpharmacological measures and drug interventions, which can be grouped into first-, second- and third-line therapies. Stronger, but potentially more risky, second- and third-line approaches may be justified for patients who do not respond to first-line therapy with antihistamines even though it may not be possible to define a specific aetiology, such as autoimmune urticaria, with confidence.

The urticaria spectrum

The term 'urticaria' is often taken to be synonymous with weals and is regarded as being distinct from deeper swellings called angio-oedema which tend to be pale and painful rather than pruritic. In practice, there is often a spectrum of manifestations ranging from superficial pink, itchy weals in the upper dermis merging with angio-oedema of the subcutaneous and submucosal tissues. It is common for weals and angio-oedema to occur in the same patient but angio-oedema may occur without weals and this has specific implications for potential causes and management. Mucocutaneous swellings are often a feature of anaphylaxis and urticaria can very occasionally progress to anaphylaxis. I prefer to use urticaria as a wider term for the disease process to encompass the full spectrum of short-lived mucocutaneous swellings that may occur rather than the narrower descriptive use for an eruption of weals. This simplifies the clinical classification since it is implicit that urticaria may present with weals, angio-oedema or a mixture of the two, unless specified

otherwise. The concept of a disease continuum embraces rare entities, such as food- and exercise-induced anaphylaxis and vibratory angio-oedema, which are usually grouped with the physical urticarias even though weals are not a defining feature.

Clinical classification of urticaria

Most urticaria that fluctuates continuously from one day to another without a consistent physical trigger, behaves similarly with respect to weal duration, range of severity and skin biopsy findings whatever the aetiology or disease duration. This 'ordinary' pattern of urticaria may have diverse aetiologies including autoimmunity, allergy, pseudoallergy and infection although the majority will remain idiopathic after investigation. This pattern can nearly always be distinguished from urticarias triggered reproducibly by a physical stimulus, angio-oedema occurring without weals, urticarial vasculitis, contact urticaria and rare urticarial syndromes (such as Muckle Wells syndrome and Schitzler syndrome) by history taking, simple physical challenge tests in the clinic and skin biopsy if vasculitis is suspected¹ (Fig. 1). These patterns are not mutually exclusive and may overlap with one another, particularly the ordinary and physical urticarias. An example of this is the concurrence of delayed pressure urticaria in up to 40% of chronic 'idiopathic' urticaria

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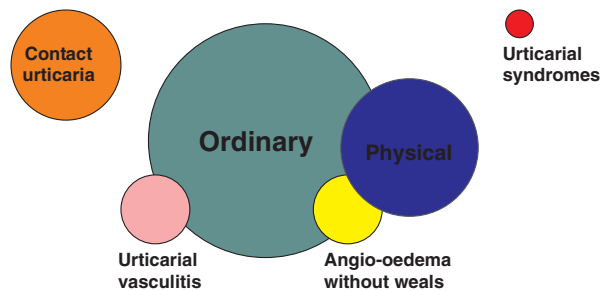


Figure 1 Clinical classification of urticaria into six main patterns. The size of each circle gives a very approximate pictorial indication of the frequency of occurrence although it should be noted that urticarial syndromes are very rare. Contact urticaria is relatively common in the community but is not often the reason for referral to hospital clinics. Ordinary urticaria includes patients with different aetiologies, including autoimmunity, allergy, pseudoallergy and idiopathic disease who, nevertheless, present with a similar clinical picture. Overlap between ordinary urticaria, physical urticarias, angio-oedema without weals and urticarial vasculitis may occur.

patients.² The cause of physical urticarias can hardly ever be established so their management hinges on avoidance of the trigger stimulus (once it has been established) and pharmacological treatments. Angio-oedema *without* weals, on the other hand, is often idiopathic but may be caused by C1 esterase inhibitor deficiency or medication, including angiotensin converting enzyme inhibitors (ACEIs) and nonsteroidal anti-inflammatory drugs (NSAIDs). It is therefore important to distinguish these cases from the much more common presentation of angio-oedema *with* weals that may occur in other patterns of urticaria because their management will almost certainly be different. Urticarial vasculitis should be regarded, more correctly, as a leukocytoclastic small vessel vasculitis than urticaria but is, nevertheless, usually included in classifications of urticaria because its clinical presentation may be hard to distinguish from ordinary urticaria without a skin biopsy. Individual weals usually last longer than 24 h, burn rather than itch and may leave residual discoloration as they subside.

Management of urticaria

Ordinary and physical urticaria

Management pathways for ordinary and physical urticarias are similar (Fig. 2) but not identical. In the physical urticarias, nonpharmacological interventions are limited to avoidance of the relevant trigger, stress, heat and alcohol. There is little evidence that

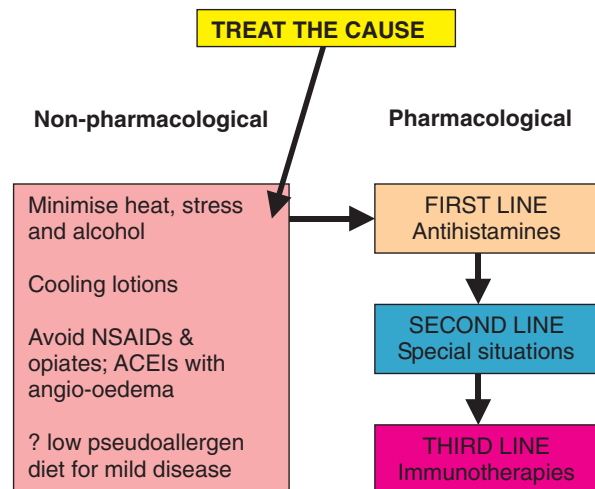


Figure 2 The management pathways of ordinary and physical urticarias are similar although, in the physical urticarias, there is little evidence of exacerbation with NSAIDs and immunosuppressive therapies are hardly ever appropriate. The management of angio-oedema without weals and urticarial vasculitis usually follows different pathways.

avoidance of drug and dietary pseudoallergens helps, unlike ordinary urticaria which is aggravated by aspirin in 25–30% of patients.³ Recent work suggests that the selective COX-2 inhibitor, rofecoxib, may be taken safely by chronic urticaria patients with proven aspirin intolerance⁴ and aspirin-induced urticaria.⁵ The evidence for avoiding opiates is less strong but it is common practice to recommend that codeine and other opiates should be avoided if possible. ACEIs are contraindicated by angio-oedema. They should be used with caution even when it is not a feature of urticaria. Urticaria has been reported as a side effect of angiotensin II receptor inhibitors but there is, as yet, no firm evidence of cross-reaction with ACEI-induced angio-oedema. Cooling lotions, such as 1% menthol in aqueous cream, can be soothing for many patients with very active urticaria. A low pseudoallergen diet, minimizing additives, natural salicylates and some foods containing as yet unidentified aromatic chemicals (found in tomatoes, peppers, spices and white wine) has been described by colleagues in Berlin⁶ and may be helpful for some antihistamine-responsive chronic ordinary urticaria patients but does not often improve control of severe disease. Pharmacological therapies for urticaria can be separated into first-, second- and third-line approaches which are normally used sequentially, depending on the response to previous treatments.

First-line drug therapies (antihistamines: to be used for all patients)

Commonly used antihistamines are shown in Table 1. All patients should be offered a choice of at least two nonsedating antihistamines at the manufacturers' recommended dose initially. They should be taken prophylactically and regularly as long as they help. Although individual patients may feel that an antihistamine has become less effective with time, there is no evidence of reduced effectiveness occurring with long-term use or cumulative toxicity. A sedating 'classical' antihistamine, such as diphenhydramine, chlorpheniramine or hydroxyzine, can be taken at night as well if there is insufficient relief of pruritus or urticarial activity with a nonsedating product. The addition of H₂ antihistamine, such as ranitidine, may improve urticaria control and often helps the acid indigestion that may be associated with severe ordinary urticaria. A trial of double or triple dose nonsedating antihistamine can be justified before moving onto second-line therapies as clinical experience suggests that a few patients who respond poorly to conventional doses can be controlled in this way. The rationale for doing this is to optimize 'antiallergic' effects of antihistamines at tissue concentrations above those required for full H₁ receptor binding,⁷ although it is not clear whether these can be achieved reliably *in vivo*.

The use of antihistamines in pregnancy and their capacity to interfere with subjective and objective measures of performance need special consideration. All antihistamines should be avoided in pregnancy as a rule, especially during the first trimester, but some clinicians may choose to prescribe chlorpheniramine or diphenhydramine because of their long use and apparent safety record. None of the second-generation antihistamines are recommended in pregnancy. Loratadine and hydroxyzine are contraindicated in their product datasheets. Classical antihistamines have been shown to increase sedation subjectively and impair cognitive and psychomotor functions objectively. Tolerance may develop to sedation but probably not to the impairments

Table 1 First-line treatment with antihistamines in ordinary and physical urticarias.

Classical (sedating) antihistamines	
chlorpheniramine	4 mg t.d.s.
diphenhydramine	10–25 mg t.d.s.
hydroxyzine	10–25 mg t.d.s.
Nonsedating antihistamines	
cetirizine	10 mg o.d. = levocetirizine 5 mg o.d.
fexofenadine	180 mg o.d.
loratadine	10 mg o.d. = desloratadine 5 mg o.d.

revealed by objective psychometric testing. It has to be asked whether any currently marketed antihistamines are completely devoid of centrally acting effects, especially when used at doses that exceed the manufacturers' recommendations.

Second-line drug therapies (used for specific indications)

Oral corticosteroids almost always control urticaria, provided the dose is right, and are undoubtedly the most versatile and useful second-line therapy. However, doses in excess of 0.5 mg/kg of prednisolone per day often have to be taken initially. This usually presents no problems with the short courses required for acute urticaria but the likelihood of unacceptable effects developing with continuous use for more than 6 weeks is very high. Patients with chronic urticaria (whether ordinary or physical) should therefore be monitored closely if long-term corticosteroids are essential and every effort should be made to find steroid-sparing therapies, including other second-line therapies. These may include the leukotriene receptor antagonist, montelukast, which has been reported favourably in aspirin-sensitive urticaria⁸ and delayed pressure urticaria⁹ in double-blinded studies when taken with an antihistamine. Sulphasalazine may be very helpful for otherwise corticosteroid-dependent 'pure' delayed pressure urticaria¹⁰ but its efficacy for this indication has not been confirmed by controlled studies. There have been reports of thyroxine suppressing disease activity in clinically euthyroid chronic urticaria patients with positive thyroid autoantibodies¹¹ but this beneficial effect is probably small and infrequent. Non-pharmacological second-line therapies that may have a role for some patients include cold desensitization for acquired cold contact urticaria¹² and ultraviolet B phototherapy¹³ or photochemotherapy (PUVA)¹⁴ for symptomatic dermatographism.

Third-line (immunosuppressive) therapies

Whilst immunotherapies for severe chronic ordinary urticaria are now accepted practice, there is still the problem of knowing which patients have autoimmune urticaria and are therefore most likely to respond. Laboratory tests for functional autoantibodies remain confined to research centres but the autologous serum skin test may be used in the clinic to screen for endogenous histamine releasing factors (including autoantibodies). The test involves injecting 50 µL of the patient's own serum into volar forearm skin and comparing the weal response at 30 min against a nearby control injection of normal saline.¹⁵ Although simple and safe to perform, it has the disadvantage of being time consuming and requires some familiarity

with the method for reproducible results. A background of other autoimmune diseases, such as autoimmune thyroiditis, pernicious anaemia or vitiligo may offer indirect support for an autoimmune aetiology in an individual patient.¹⁶ Detection of nonorgan-specific autoantibodies, including antinuclear antibody, should not be regarded as evidence of autoimmune urticaria. Because of this difficulty in confirming or refuting a diagnosis of autoimmune urticaria and the observation that some patients with no evidence of functional autoantibodies may respond nevertheless to immunotherapies, it is reasonable to offer a trial of immunotherapy to patients with severe disease unresponsive to medication other than oral corticosteroids, or patients who are steroid dependent. Nearly all of the trial evidence for immunotherapies relates to severe ordinary urticaria and they should only be considered for physical urticarias, such as solar and cold urticaria, in exceptional circumstances.

Cyclosporin A (ciclosporin). This has been the most thoroughly evaluated immunotherapy for refractory severe chronic urticaria to date. Its efficacy was confirmed in a randomized placebo controlled study using ciclosporin at 4 mg/kg/day for 4 weeks with cetirizine taken concurrently.¹⁷ Of those who did respond, only about 25% remained clear off treatment 5 months later. Taking ciclosporin at 5 mg/kg/day reducing to 3 mg/kg/day for 16 weeks resulted in more prolonged remissions than giving it for 8 weeks.¹⁸

Intravenous immunoglobulins (IVIG). Since an open study of IVIG appeared to benefit 9 of 10 chronic urticaria patients with a positive autologous serum skin test and induced long-term remission in two of the responders at 0.4 g/kg/day for 5 consecutive days,¹⁹ it has been a popular treatment for very difficult urticaria but is very expensive and optimal protocols of frequency and dose have yet to be developed.

Other immunotherapies. Anecdotal experience with methotrexate and azathioprine suggest that both these agents can be effective but are usually given in combination with oral steroids initially.

Angio-oedema without weals

The management of hereditary angio-oedema and acquired C1 esterase inhibitor deficiency is completely different from other forms of angio-oedema because kinins are the primary mediator of vasopermeability instead of histamine. The subject has been reviewed

recently.²⁰ Drug-induced angio-oedema due to ACEIs or NSAIDs responds to withdrawal of the medication. Treatment of idiopathic angio-oedema should follow the same pathway as for ordinary urticaria.

Urticarial vasculitis

Oral corticosteroids are nearly always required for disease control. Antihistamines are usually ineffective. A variety of steroid-sparing agents have been described including colchicine, azathioprine, hydroxychloroquine, dapsone and methotrexate²¹ but randomized placebo-controlled studies to support their use are not available. Patients with hypo-complementaemic urticarial vasculitis are more likely to develop significant renal disease or arthritis than those with normal circulating complement levels and management should then be directed at the primary clinical problem.

Learning points

- The term urticaria is better used to describe a disease process that encompasses the full spectrum of short-lived mucocutaneous swellings that may occur, rather than the narrower description for an eruption of weals.
- It is helpful for management purposes to classify urticaria clinically into six main patterns: ordinary urticaria, the physical urticarias, angio-oedema without weals, urticarial vasculitis, contact urticaria and urticarial syndromes.
- The management of ordinary and physical urticarias is similar, involving nonpharmacological measures and first-line antihistamines. Second-line drugs may be appropriate for specific indications (such as short courses of oral corticosteroids for severe exacerbations). Third-line immunotherapies should only be used for severe chronic ordinary urticaria in patients who would otherwise need corticosteroids or those who are steroid dependent.
- There is little evidence that physical urticarias are aggravated by drug and dietary pseudoallergens, unlike ordinary urticaria where 25–30% of patients are aggravated by aspirin. Selective COX-2 inhibitors, such as rofecoxib, may be safe in these patients.
- Angio-oedema without weals should be distinguished from angio-oedema with weals because it may be due to C1 esterase inhibitor deficiency or medications, including ACE inhibitors and NSAIDs.
- Urticarial vasculitis is distinguished from urticaria by showing leukocytoclastic vasculitis on lesional skin biopsy and often requires oral corticosteroids for disease control.

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