

Urticaria, angio-oedema and anaphylaxis

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Urticaria, angio-oedema and anaphylaxis are distinct clinical entities caused by transient plasma leakage from small blood vessels. When the affected vessels are superficial the result is a raised, itchy swelling of the skin known as a weal. Involvement of deeper vessels produces tender subcutaneous and submucosal swellings known as angio-oedema. Generalised plasma exudation leading to shock is a feature of anaphylaxis but also occurs in anaphylactoid reactions and the capillary leak syndrome.

Definitions

Urticaria is an eruption of transient superficial itchy weals, pale or pink in colour which may have a surrounding flare of redness. They may be few in number or numerous and widespread. Their size varies from a few millimetres to many centimetres. The hallmark of urticaria is its rapid fluctuation. Individual lesions come and go within 24 hours, but the eruption of fresh weals means that the whole attack may last much longer.

Key Points

Anaphylaxis is due to immunoglobulin E-mediated allergy

Allergy is an uncommon cause of urticaria and angio-oedema

The diagnosis of urticaria is based primarily on the history of weals with rapid fluctuation

Antihistamines are the first-line drug therapy for all urticarias except C1 esterase inhibitor deficiency

KEY WORDS: CPD, urticaria, angio-oedema, anaphylaxis

Urticarial lesions (ie areas of superficial swelling) are also seen in skin diseases other than urticaria (eg some drug reactions, bullous pemphigoid). In these conditions, the lesions do not show the rapid fluctuation which characterises urticaria. They will not be considered further in this article.

Angio-oedema implies deeper vascular leakage producing swellings predominantly affecting the subcutis. They tend to be large, pale and painful rather than red and itchy, and last longer than weals. Angio-oedema is a cause of distressing oropharyngeal swellings but may occur anywhere on the integument including the genitalia.

Anaphylaxis is defined by a life-threatening fall in blood pressure, difficulty with breathing or both. Other features, including widespread redness, itching and urticaria may occur (Table 1). True anaphylaxis is due to an allergic reaction involving allergen-specific immunoglobulin (Ig) E. Anaphylactoid reactions present similarly but do not involve IgE.

Classification of urticaria and angio-oedema

It is helpful to divide urticaria into different clinical categories for the purpose of management. Many acute cases are short-lived or episodic but recurrent urticaria that continues at least twice a week for over six weeks is defined as chronic.

The simplest working classification is to separate urticarias into four categories (Table 2):

- ordinary
- physical
- vasculitic urticaria (urticarial vasculitis)
- contact urticaria.

Angio-oedema may be a feature of most patterns of urticaria and, for the most part, can be considered together with urticaria. However, it is worth considering angio-oedema separately when it occurs without weals (Table 3) because it may then be a presentation of C1 esterase inhibitor (C1 inh) deficiency or a drug reaction.

Ordinary urticaria

Ordinary urticaria is a useful collective term for all recurring urticarias that do not fall into the other three categories, in that they:

- do not have a predominantly physical trigger
- are not caused by underlying vasculitis
- are not caused by direct contact with the causative agent.

This heterogeneous group includes:

- the newly recognised 'autoimmune' urticaria
- urticaria due to dietary pseudoallergens, drugs and infections
- the remaining 'idiopathic' cases for which no cause can be identified.

Table 1. Features of anaphylaxis.

System	Clinical features
Cardiovascular*	Hypotension (loss of consciousness, collapse)
Respiratory*	Laryngeal oedema (inspiratory stridor) Bronchial spasm (expiratory wheeze)
Skin	Pruritus, erythema, urticaria
Nose	Rhinitis
Eye	Conjunctivitis
Gut	Abdominal pain
General	'Impending doom'

* One or both of these severe features must be present; other features are variable.

The common clinical feature of ordinary urticaria is that individual weals last less than 24 hours before disappearing completely without residual colour or texture change in the skin. The general health of the patient remains good but systemic symptoms such as lethargy, malaise and indigestion are quite common during severe attacks.

Physical urticaria

Physical urticaria is defined by the nature of the physical stimulus that reproducibly gives rise to urticaria. Weals typically fade within 30–60 minutes. The exception is delayed pressure urticaria when the weals take several hours to appear after sustained pressure and can last up to 48 hours. The morphology and distribution of the weals can also be helpful in identifying the trigger. Cold-induced urticaria, for instance, occurs on exposed skin or on immersion in cold water and may rarely progress to anaphy-

laxis. Cholinergic urticaria (due to a rise in core temperature) is mainly truncal. Delayed pressure urticaria predominates wherever there is sustained pressure (eg under belts or straps).

Vasculitic urticaria

In vasculitic urticaria there are urticaria-like lesions caused by underlying leukocytoclastic vasculitis. Subtle features which distinguish them from ordinary urticaria are pain, individual lesion duration longer than 24 hours and bruise-like discolouration or petechiae during resolution. This condition is usually idiopathic, but may be associated with systemic lupus erythematosus.

Contact urticaria

Contact urticaria occurs at the site of skin or mucosal contact with an agent that provokes increased vascular permeability. The cause can be either allergic

(eg allergy to natural rubber latex) or non-allergic. Certain chemicals in foods and cosmetics can cause localised urticaria without involving specific IgE. Affected individuals often make their own diagnosis and learn what to avoid because symptoms develop almost immediately after exposure.

Aetiology and pathogenesis

The release of histamine and other mediators from mast cells provokes vascular leakage responsible for the tissue swelling of urticaria and angio-oedema and the catastrophic vascular exudation of anaphylaxis. Mast cell activation may be allergic or non-allergic. The pathogenetic mechanisms responsible are shown in Table 4. There is poor correlation between patho-mechanism and clinical type. For instance, IgE-mediated allergy can present with localised contact urticaria, generalised urticarial weals or anaphylaxis depending on the type of exposure and the degree of hypersensitivity. No cause can be identified in 50% of acute urticaria. In the others, the commonest preceding event is an upper respiratory infection or a reaction (not necessarily an allergy) to a drug or food¹. Chronic urticaria is rarely, if ever, allergic in the sense of a defined environmental allergen being the cause, but 'pseudoallergic' reactions to dietary additives and natural salicylates may be important in some cases². Up to 50% of cases presenting with ordinary urticaria may be due to the recently recognised 'autoimmune' urticaria³. Underlying systemic disease (unless suspected on the patient's history) almost never emerges as the cause of ordinary urticaria even when long-standing.

Urticarial vasculitis results from immune complexes lodging in small blood vessels (type III hypersensitivity), generating C3a and C5a anaphylatoxins which are potent mast cell degranulators.

The angio-oedema of C1 inh deficiency is due to production of kinin-like peptides from C2. They cause vasopermeability without mast cell degranulation.

Anaphylactic reactions are always caused by type I IgE-mediated immediate hypersensitivity reactions.

Table 2. Clinical classification of urticaria, causes and triggers.

Clinical group of urticaria	Causes	Aggravating and trigger factors
Ordinary	usually unknown respiratory and other infections autoimmune drugs dietary intolerance	? aspirin ? dietary intolerance ? heat ? stress ? alcohol
Physical:		
• dermatographism	unknown	skin stroking
• cold urticaria		skin cooling
• cholinergic		rise in core temperature
• delayed pressure		sustained firm pressure
• (others)		
Contact	allergens (eg latex) chemicals (eg in toiletries)	direct contact
Vasculitic	usually unknown	

Table 3. Classification of angio-oedema.

With weals	Angio-oedema may occur in all forms of urticaria except dermatographism
Without weals	<ul style="list-style-type: none"> • idiopathic • drugs (ACEIs, NSAIDs) • C1 inh deficiency (hereditary and acquired)

ACEI = angiotensin-converting enzyme inhibitor; C1 inh = C1 esterase inhibitor;
NSAID = non-steroidal anti-inflammatory drug.

Diagnosis

The diagnosis of urticaria remains primarily clinical. A recent study showed that extensive routine investigations added little to a comprehensive history in the diagnosis of chronic urticaria⁴. Investigations should be guided by the clinical presentation (Table 5). They might include C4 assay as a screen for C1 inh deficiency in a patient with recurrent angio-oedema without weals or a lesional skin biopsy in a patient suspected of having urticarial vasculitis. Physical challenge tests can be useful for confirming suspected physical urticaria. Challenge capsules containing common dietary pseudoallergens can be of value in planning exclusion diets.

Management

Avoiding the cause of the urticaria is fundamental to preventing anaphylaxis but is often not possible in both urticaria and angio-oedema. It is nevertheless helpful to recognise trigger factors in physical urticarias and non-specific aggravating factors in ordinary urticaria such as stress, aspirin, overheating and alcohol. Cooling creams, such as 0.5% menthol in aqueous cream, are often soothing.

Despite advances in the range and scope of pharmacological treatments for urticaria, the emergency treatment of acute severe attacks still hinges on systemic antihistamines and steroids. Intramuscular adrenaline may be life-saving for anaphylaxis and the occasional attack of pharyngeal angio-oedema. Patients with known C1 inh deficiency presenting with angio-oedema of the mouth or bowel should be managed with an infusion of purified C1 inh or of fresh frozen plasma (3 units) if the inhibitor concentrate is not available.

Pharmacological management (Table 6)

The treatment of chronic urticaria is neither straightforward nor simple because the condition often lasts for years. Regular oral antihistamines should be given at full dose as first-line

Table 4. Aetiology and pathogenesis of urticaria and angio-oedema.

Unknown (idiopathic)	
Immunological	<ul style="list-style-type: none"> • Autoimmune (autoantibodies to high affinity IgE receptor or to IgE) • IgE-dependent (type I allergy) • Immune complex (type III allergy) • Complement-dependent (C1 inh deficiency)
Non-immunological	<ul style="list-style-type: none"> • Direct mast cell releasing agents (eg opiates) • NSAIDs and dietary pseudoallergens • ACEIs

ACEI = angiotensin-converting enzyme inhibitor; C1 inh = C1 esterase inhibitor; Ig = immunoglobulin; NSAID = non-steroidal anti-inflammatory drug.

Table 5. Relevant investigations.

Urticaria	FBC	ESR	C4	Skin biopsy	Challenge
Ordinary:					
• acute/episodic	—	—	—	—	—
• chronic	(✓)	(✓)	—	—	—
Physical	—	—	—	—	✓
Angio-oedema	—	—	✓	—	—
Contact	—	—	—	—	(✓)
Urticarial vasculitis	✓	✓	(✓)	✓	—

C4 = C4 component of complement as a marker for C1 esterase inhibitor deficiency and in hypocomplementaemic urticarial vasculitis; challenge = challenge with suspected stimulus; ESR = erythrocyte sedimentation rate; FBC = full blood count; () = discretionary investigations.

therapy for all patients. The non-sedating second-generation H₁ antagonists are the treatment of choice for most patients because 'classical' antihistamines often cause unacceptable daytime sedation or reduced ability to perform skilled tasks⁵. They are best given at night when itch and weals are often troublesome, with or without a regular non-sedating antihistamine by day. The addition of an H₂ antagonist, such as

ranitidine, can provide additional symptomatic control for some patients. The new third-generation antihistamine, desloratadine, has high affinity for the H₁ receptor and additional 'anti-allergic' effects *in vitro*, but it remains to be seen whether it controls urticaria better than older drugs.

Many second-line therapies are available for urticaria that is poorly controlled with antihistamines, but the

Table 6. Pharmacological management of urticaria and angio-oedema.

Level of therapy	Pharmacological treatment
First-line (all patients)	<ul style="list-style-type: none"> • Daily non-sedating antihistamine • Optional sedating (classical) antihistamine at night • Additional H₂ antagonist if poor response
Second-line (as determined by the clinical presentation)	<ul style="list-style-type: none"> • Prednisolone (short courses for severe urticaria or angio-oedema only) • Adrenaline (for anaphylaxis and severe pharyngeal angio-oedema) • Others (eg sulphonamides for delayed pressure urticaria)
Third-line (severe unresponsive urticaria only)	<ul style="list-style-type: none"> • Cyclosporin • Other immunosuppressive agents

evidence for their use is generally weak⁶. It is usually advisable to seek the help of a specialist urticaria clinic at this stage to define the urticarial subgroup. Some types may be more likely to respond to novel approaches, including the use of immunosuppressive drugs for patients with the most severe forms of autoimmune urticaria.

Prognosis

Many cases of urticaria are short-lived, lasting days or weeks. About 50% of patients with ordinary urticaria can be expected to have cleared by six months. The outlook for those with urticaria and angio-oedema is less encouraging since 50% will still have their condition five years later⁷. Urticarial vasculitis is likely to persist or recur over many years.

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Management of lower leg cellulitis

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Lower leg cellulitis is a common reason for urgent medical admission; it often results in prolonged hospitalisation and significant long-term morbidity^{1–5}.

Clinical features

Cellulitis is deeply situated inflammation of the skin and subcutaneous tissue, usually due to an infection. The distinction from erysipelas, which is more superficial and thus has more sharply demarcated margins, is somewhat artificial on the leg.

Typical lower leg cellulitis is characterised by progressive painful swelling and erythema (Fig 1) with pyrexia and general malaise which are often present before the localising signs. Blistering and ulceration may occur, usually if oedema is marked.

Bacteriology

Most patients with proximally spreading lower leg cellulitis have streptococcal infection^{1–5}. Group A streptococci are most important but groups C and G organisms are also common at this site. Staphylococcal cellulitis is usually more

localised but can mimic streptococcal disease. Other infections^{1,3} are much less common at this site but should be considered, particularly in the following situations:

- diabetes, immunosuppression or hepatic cirrhosis
- localised cellulitis
- penetrating injury or animal bite
- preceding ulceration
- recent foreign travel
- cellulitis at other body sites or in children.

Predisposing factors

Toeweb maceration is a common portal of entry for streptococci in lower leg cellulitis (Fig 2), while tinea pedis is a major factor in patients with recurrent episodes^{5,6}. Mycology cultures from macerated toeweb are important (note that athlete's foot fungi do not fluoresce and cannot be detected using Wood's light).

Lower leg oedema of any causation is a risk factor. Lymphoedema is especially important as a cause of recurrent episodes⁶ and is a situation in which streptococcal cellulitis can be particularly aggressive.

Other risk factors include obesity, recent surgery (especially venectomy for coronary artery bypass grafting) and preceding venous eczema or leg ulceration⁶. Blunt injury⁵ is reported sufficiently

Key Points

Most acute lower leg cellulitis is due to streptococcal infection

A diagnosis of bilateral lower leg cellulitis is likely to be incorrect

Antistreptolysin-O titre is extremely useful to confirm the cause of cellulitis but is unreliable in the first week

In resistant cases of streptococcal cellulitis, clindamycin is the best antibiotic choice

Treatment of associated tinea pedis and persistent oedema is critical to reduce the risk of recurrent episodes

KEY WORDS: CPD, cellulitis, erysipelas, necrotising fasciitis, streptococcal infection, lower leg