

An approach to the patient with urticaria

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Summary

Patients with urticaria make up a large proportion of the referrals to allergy clinics. There are many causes of urticaria and it is the clinical history which is most important when attempting to identify potential causes; however, urticaria is very often idiopathic. In a small minority of patients urticaria may be a symptom of a serious underlying medical illness or the allergic symptoms may progress to cause systemic reactions, and it is important to identify these patients and to remember that severe urticaria is a distressing and disabling condition. This review will discuss classification, investigation and treatment of urticaria and will consider some of the more unusual types of urticaria that may be encountered in the out-patient clinic.

Keywords: anti-histamines, autoantibodies, urticaria, urticarial vasculitis, weals

Introduction

Urticaria (or 'hives' or 'nettle rash') consists of blanchable, erythematous, oedematous papules or 'weals' (Fig. 1). These weals vary in size from 1 mm to many centimetres – 'giant urticaria', and are usually intensely itchy. They are caused by vasoactive mediators, predominantly histamine, released from mast cells. In the vast majority of cases the weals are transient, lasting for only a few hours in any one place, but with new weals appearing in other places. This means that most urticarial rashes 'move' around the body – a useful pointer from the clinical history that the rash is urticarial. Urticaria is to be distinguished from 'angioedema', which is well-demarcated swelling, occurring within deep skin structures or in subcutaneous tissue (Fig. 2) and caused mainly by bradykinin production. Angioedema is not itchy, but may be painful. In about 50% of patients urticaria occurs alone; in about 40% of patients urticaria occurs with angioedema and in about 10% of patients angioedema occurs alone [1]. The aetiology of isolated angioedema is very often different from that of urticaria or urticaria with angioedema. The topic of isolated angioedema is to be reviewed in a further article in this series.

Urticaria is a common condition – it is estimated that lifetime incidence of urticaria is approximately 15%, with

females being affected more often than males. Both children and adults may develop urticaria, with the peak age of onset in adults being between 20 and 40 years. Urticaria is defined as 'acute' if it lasts for less than 6 weeks and 'chronic' if it lasts for more than 6 weeks. 'Episodic' urticaria, which occurs intermittently, but recurrently over months or years, is also recognized. Most urticarial reactions are acute and self-limiting; however, patients referred to allergy clinics usually have chronic urticaria or episodic urticaria. Histology shows oedema of the upper dermis, dilatation of blood vessels and lymphatics and a cellular infiltrate in the dermis. The nature of this cell infiltrate varies depending on the type of urticaria and the duration of the weal.

Classification

Urticaria may be classified on the basis of underlying aetiology (see Table 1) or by a clinical classification. In most cases of chronic urticaria it will not be possible to identify the underlying cause, i.e. the rash is idiopathic; however, when seeing a patient, it is helpful to use a clinical classification, as this guides history-taking and ensures that in any one individual all possible triggers for the urticaria are identified. In some patients several factors may cause/worsen the rash.



Fig. 1. Urticaria.

Immunoglobulin E (IgE)-mediated reactions – ‘contact urticaria’

Patients may become sensitized to a very wide range of allergens and produce specific IgE (SIgE) against these substances. Subsequent contact with the relevant allergen, either directly on the skin or through mucous membranes, may result in urticaria.

Acute urticaria caused by SIgE against food protein antigens is often identified easily by the patient, particularly as there may be oral symptoms as the food is eaten and as repeated exposure to the foodstuff may lead to progressively more severe reactions, with angioedema and systemic symptoms [2,3]. However, it may be more difficult to identify the causative antigen if this is a contaminant in the food, such as a mould [4] or storage mite [5], or if there is an unexpected ingredient in the foodstuff and a detailed list of ingredients is lacking.

Insect venoms, animal danders and/or saliva, penicillin, protease enzymes in biological detergents [6] and latex pro-

teins are other common causes of IgE-mediated urticaria, which again are often identified by the patient. Patients who are latex-protein allergic may also react to a wide variety of foods [7] (Table 2) because of cross-reactivity between the latex protein antigens and food antigens or, if they are highly sensitized, they may develop symptoms after eating foodstuffs which have been handled by workers wearing latex gloves [8].

Non-IgE-mediated food-related urticaria

It has been suggested that natural salicylates in foods and food additives (‘E’ numbers), including colourings (azo and non-azo dyes), preservatives (sulphites, nitrates and nitrites), antioxidants [butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)] and aspartame (an artificial sweetener), may cause urticaria [9,10], particularly in patients who develop acute allergic symptoms after taking aspirin (acetylsalicylic acid) or non-steroidal anti-inflammatory drugs (NSAIDs); however, randomized controlled trials are lacking [11]. Skin prick testing and SIgE tests to the foods are negative, as the reaction is not IgE-mediated.

In some patients, foods such as egg white, shellfish and strawberries seem to trigger direct histamine release from mast cells and episodes of urticaria are related to ingestion of these foods. Again, skin prick testing and SIgE tests to the foods are negative, as the reaction is not IgE-mediated.

An unusual, but well-recognized non-IgE-mediated, food-related cause of urticaria is histamine poisoning, which occurs if food containing a very high content of histamine is eaten. The best-known example is ‘scombroid poisoning’ which is due to ingestion of scombroid fish (spiny-finned fish of the mackerel genus), such as tuna, mackerel and swordfish, which has not been stored properly and in which bacteria have decarboxylated histidine to produce histamine.



Fig. 2. Angioedema.

Table 1. Aetiological classification of urticaria.

Aetiology	Mechanism	
Idiopathic	Unknown	Investigations: normal
Immunological		
Autoimmune	IgG autoantibodies to IgE Receptor or IgE on mast cells	ASST usually positive Other autoantibodies may be present, e.g. anti-thyroid antibodies
IgE/contact	Contact with allergen cross-links SIgE on mast cells	Often identified by clinical history SIgE and/or SPT positive
Immune complex	Infection-related Urticarial vasculitis	Serology according to clinical history Usually idiopathic; but also connective tissue disease, infection, drugs
Non-immunological		
Physical urticaria	Physical factors trigger histamine release from mast cells	Often identified by clinical history or, possibly, challenge testing
Drug treatment	Sensitivity to COX-inhibitors Direct mast cell histamine release	Urticaria with aspirin, NSAIDs Opiates, radio-contrast media
Dietary pseudo-allergens	Sensitivity to natural salicylates, colourings, preservatives	
Medical conditions:		
Urticaria pigmentosa	Increased mast cell load	
Cryopyrin-associated Periodic syndrome (CAPS)	Mutation in CIAS1 gene	

COX: cyclo-oxygenase; NSAID: non-steroidal anti-inflammatory drug.

(Ingestion of spoiled non-scombroid fish including herring, sardines and anchovies may also cause histamine poisoning.) Symptoms usually begin within 1 h of ingestion of the fish and patients develop urticaria and gastrointestinal symptoms. In severe cases there may be bronchospasm and hypotension [12,13].

Physical urticaria

Physical factors such as cold, heat, sweating, exercise, pressure, sunlight, water and vibration may all trigger urticarial reactions. The weals of physical urticarias tend to be short-lived (less than an hour), apart from those of delayed pressure urticaria, which develop over a few hours and may take up to 2 days to disappear. International standards for diagnosing physical urticarias have been proposed [14].

Cold urticaria is usually idiopathic, but it may occur in patients with cold-dependent antibodies, such as cryoglobu-

lins or cold agglutinins [15] and there is a very rare familial form of cold-induced urticaria which is dominantly inherited [16]. Patients develop itching, erythema and urticaria affecting that part of the body which has been exposed to cold. Symptoms may worsen as the exposed area is warmed. Total immersion in cold water can cause severe symptoms with hypotension and patients should be warned that swimming in cold water can be dangerous. Local heat-induced urticaria is rare [17]. Some unfortunate patients may develop urticaria on exposure to both heat and cold [18]. Generalized heat-induced urticaria or 'cholinergic' urticaria is caused by exercise, sweating and hot showers or baths. The term 'cholinergic' is used because sweat glands are innervated by cholinergic nerve fibres. The urticarial lesions are often small and intensely itchy. Very severe cholinergic urticaria may cause hypotension and therefore there may be some overlap with the clinical syndrome of exercise-induced anaphylaxis [19,20].

In some patients pressure on the skin may cause histamine release and a 'weal and flare' response, a condition known as dermographism (Fig. 3). There may also be a delayed response to pressure, with urticaria and/or angioedema developing several hours after a pressure stimulus [21].

Solar urticaria is a rare disorder in which urticaria develops on areas of the body which are exposed to sunlight. Itching and urticaria may develop within a few minutes and may progress to angioedema. The symptoms usually resolve in a few hours. (Polymorphic light eruption may also cause an itchy rash on sun-exposed skin, but this rash is papular or eczematous; usually starts 6–8 h after sun exposure and lasts

Table 2. Foods which may cross-react with latex proteins.

High frequency of cross-reactivity			
Avocado	Banana	Chestnut	
Moderate frequency of cross-reactivity			
Apple	Carrot	Celery	Kiwi
Melon	Papaya	Potato	Tomato
Low frequency of cross-reactivity			
Apricot	Cherry	Fig	Grape
Hazelnut	Mango	Nectarine	Passion Fruit
Peach	Peanut	Pear	Plum
Pineapple	Soybean	Strawberry	Walnut



Fig. 3. Dermographism.

for several days.) Very rarely, patients may develop 'aquagenic' urticaria where their skin has been in contact with water (irrespective of its temperature) or urticaria in response to vibration.

Frequently, more than one type of physical urticaria may occur in a patient and it may be difficult for the individual to avoid the triggering stimulus/stimuli. The physical urticarias may, therefore, be difficult to treat and may be long-lasting.

Drug-related urticaria

Many different drugs may cause urticaria. The cyclo-oxygenase (COX)-inhibitor drugs such as aspirin [22] and NSAIDs [23] are a common cause. Opiates, including codeine, may trigger direct histamine release from mast cells [24]. Many different over-the-counter analgesics contain aspirin, NSAIDs and/or codeine and it is therefore important to be specific as to exactly which painkillers patients may or may not be able to take. These reactions are not IgE-mediated and specific IgE testing for aspirin, NSAIDs and opiates is not indicated. Evidence of oxidative damage, as shown by increased protein carbonylation and lipid peroxidation, and of increased anti-oxidant enzyme activity has been found in patients who develop non-IgE-mediated drug-related urticaria [25]; however, it is not known if this oxidative stress is the cause or the effect of the reaction. [Drugs such as angiotensin converting enzyme inhibitors (ACEI) and statins cause isolated angioedema much more commonly than urticaria]. Radio-contrast media and plasma substitutes may also cause urticarial reactions.

Infection-related urticaria

A wide variety of different infections, including hepatitis [26], infectious mononucleosis [27], *Helicobacter pylori* infection [28], dental infections, sinusitis and urinary tract

infections, have all been implicated as causing urticaria. However, in adults seen in the clinic, the overall incidence of infection-related urticaria is low. In contrast, children commonly develop urticaria as a result of viral respiratory infections. This urticaria may be severe and may be associated with episodes of angioedema, but it usually resolves over a few weeks. Worldwide, parasitic infections are a common cause of urticaria and there is nearly always an associated eosinophilia.

Urticaria related to medical conditions

Diseases such as systemic lupus erythematosus (SLE) and Sjögren's syndrome may be associated with chronic urticaria, a cryoglobulin-related urticaria or urticarial vasculitis (see below). There is an increased incidence of autoimmune thyroid disease in patients with chronic urticaria, particularly those with histamine-releasing autoantibodies – 'autoimmune urticaria' (see below) [29,30]. Patients are usually clinically euthyroid, but both hypothyroidism and hyperthyroidism [31] may present with urticaria. Although there are case reports of urticaria associated with malignancy, a study of more than 1000 patients showed no association between chronic urticaria and malignancy [32]. In contrast, urticarial vasculitis may sometimes occur in patients with lymphoproliferative disease (see below).

Hormone-related urticaria

Occasionally women notice that their urticaria seems to fluctuate in severity in relation to their menstrual cycle, and there is a rare cyclical form of urticaria, known as autoimmune progesterone urticaria, which occurs 7–10 days premenstrually [33]. In pregnancy urticaria will often improve, but there is a distinct clinical condition known as polymorphic eruption of pregnancy or 'pruritic urticarial papules and plaques of pregnancy' (PUPPP) [34], in which the rash starts as itchy, urticarial papules and plaques in striae on the abdomen and thighs and then spreads to affect the whole trunk and limbs. It usually begins in the third trimester and is most common in first pregnancies or the first multiple pregnancy. *In vitro* fertilization, with the increased chance of multiple pregnancies, has increased the incidence of this condition. Treatment is with emollients, anti-histamines, topical steroids and occasionally, in severe cases, oral steroids. The rash usually resolves within days of delivery and generally does not recur. There is no adverse effect on the fetus. Urticaria occurring only during pregnancy and recurring during subsequent pregnancies has been reported [35].

Stress-related urticaria

Acute urticaria may develop in relation to a particular stressful event and it is recognized that financial, personal or professional stress may all worsen chronic urticaria. The condition itself may be very debilitating and it reduces quality of life [36].

Urticaria related to histamine-releasing autoantibodies (autoimmune urticaria)

Approximately 50% of adults [37] and children [38,39] with chronic urticaria have histamine-releasing autoantibodies. These are IgG autoantibodies directed against the α subunit of the IgE receptor on mast cells (and basophils) or, more rarely, against IgE bound to mast cells (or basophils). These autoantibodies cause mast cell degranulation via activation of the classical complement pathway [40,41]. They may be demonstrable by the autologous serum skin test (ASST), in which intradermal injection of autologous serum causes a weal and flare response [42]; however, the ASST is not performed routinely in clinic and clinically, therefore, these patients are very often classified as having idiopathic urticaria. Patients with autoimmune urticaria frequently have associated angioedema and the urticaria tends to run a more chronic course.

Investigations

The most important part of the investigation of a patient with urticaria is to take a detailed history [43]. This should include structured questions about the many possible clinical causes of urticaria (see above); the frequency, timing and duration of attacks; whether the patient has developed more severe allergic symptoms such as angioedema or wheezing in association with the urticaria; and whether there are any symptoms suggestive of an underlying medical condition such as a connective tissue disease and/or urticarial vasculitis. Photographs may be helpful in confirming the diagnosis and patients may have compiled a symptom diary, which is sometimes useful when trying to identify possible triggers for the rash.

Clinical examination may reveal urticaria, dermographism or angioedema or signs of a connective tissue disease or urticarial vasculitis, but it is often normal. Similarly, investigations are very often normal, particularly if there is a long history of urticaria, with no obvious triggering factors and if the patient is clinically well. Recent guidelines from the British Association of Dermatologists [44] and the British Society of Allergy and Clinical Immunology [45] suggest that investigations are not needed in all patients; however, individual patients may be reassured by a series of normal results. Depending on the clinical history, tests may include: full blood count (FBC) and differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), routine biochemistry, glucose, thyroid function, thyroid autoantibodies, anti-nuclear antibody (ANA), immunoglobulins and protein electrophoresis, complement C3 and C4, cryoglobulins, SIgE tests, serology for infections, stool sample for ova, cysts and parasites and urine analysis (for evidence of infection or renal vasculitis). Further investigations may, of course, be required if the initial screening tests are abnormal. For example, the presence of a normochromic, normocytic

anaemia, lymphopaenia and strongly positive ANA would prompt further investigations for SLE.

Skin prick testing may be helpful to determine if an individual is atopic and if there are any specific contact antigens, such as foods or latex, which are likely to be triggers for the urticaria. Patients often expect 'allergy testing' and, once again, may be reassured by negative skin test results. However, there are two potential problems when skin prick testing patients with urticaria. First, patients need to stop anti-histamine treatment (usually for 3 days) prior to having the skin testing and during this time urticarial symptoms may become very severe and may even progress to systemic reactions requiring hospital treatment. Secondly, patients with urticaria may exhibit some degree of dermographism, which can make interpretation of skin tests very difficult. SIgE testing is the alternative to skin prick testing, although it is much more costly [46].

Challenge testing for physical urticarias may be appropriate [14]. For example, cold urticaria may be induced by applying ice to the forearm for a few minutes and then allowing the skin to re-warm, and dermographism may be induced by scratching the skin lightly. A skin biopsy should be taken, ideally from a 'new' lesion, if urticarial vasculitis is suspected (see below). The ASST is not performed routinely. It is less sensitive and specific than *in vitro* basophil histamine release assays [47] for the detection of histamine-releasing autoantibodies, but again these are not available routinely.

Treatment

General measures

Initially it is helpful to explain to patients what urticaria is and that very often it is not due to 'an allergy'. They may be reassured that in nearly all cases there is no serious underlying medical problem causing the rash; that safe, effective treatments are available and that the long-term prognosis is usually good. A patient information leaflet, such as that available from the British Association of Dermatologists [48], is helpful.

Next, if any obvious triggering factors have been identified from the history these should be eliminated, wherever possible. For example, specific food triggers should be excluded from the diet; treatment with aspirin, NSAIDs and codeine should be stopped; physical triggers such as cold and heat should be avoided whenever possible; and clinical thyroid disease or underlying infection treated. Anti-pruritic, cooling skin lotions such as calamine lotion or 1% menthol in aqueous cream may help to relieve itching.

Drug treatments

Anti-histamines. The initial medical treatment for urticaria is a standard dose of a second-generation H1 anti-histamine.

These drugs penetrate the blood–brain barrier to only a slight extent and so cause fewer central nervous system side effects than the older first-generation anti-histamines, although symptoms such as sedation and psychomotor impairment may still occur. Seven such anti-histamines are licensed for use in the United Kingdom: Cetirizine, desloratidine, fexofenadine, levocetirizine, loratidine and mizolastine, which are all given once a day, and acrivastine which is given three times a day, and may therefore be less effective and convenient to use. Cetirizine and levocetirizine [49] and loratidine [50] may have clinically useful ‘anti-inflammatory’ properties at therapeutic doses. Cetirizine may cause drowsiness in some patients and mizolastine is contra-indicated in patients with cardiac disease; prolonged Q-T interval; or severe liver disease. Dose reductions may be needed if there is renal impairment. Clinical response and tolerability may be better with one second-generation H1 anti-histamine than another, so if symptoms are not well controlled or the patient notices side effects with the first drug chosen, a second drug should be tried. Often, symptom control is improved if the dose of anti-histamine is increased to twice daily. This is above the licensed recommended dose; however, ‘off-label’ dosages are recommended widely [44,45,51]. A night-time dose of one of the older first-generation, sedating H1 anti-histamines, such as chlorphenamine or hydroxyzine, may help patients to sleep. Empirically, anti-histamine treatment is usually prescribed for 3–6 months (or longer if the patient has angioedema associated with the urticaria) and is tailed off gradually. Episodic urticaria may be treated with stat doses of anti-histamines as required.

If the urticaria remains unresponsive to high-dose H1 anti-histamines, H2 anti-histamine treatment, at standard dosage, may be added. This is an off-licence use of these drugs, but there is evidence that combined H1 and H2 anti-histamine treatment gives better symptom control than H1 anti-histamine treatment alone [52,53]. Unlike cimetidine, ranitidine does not inhibit oxidative hepatic drug metabolism and so has less potential to cause drug interactions.

Leukotriene receptor antagonists (LTRA). An alternative second-line treatment to H2 anti-histamines in patients who still have severe urticaria despite high-dose H1 anti-histamine treatment, is an LTRA such as montelukast or zafirlukast. LTRA treatment may be particularly effective if the patient is sensitive to aspirin or has a positive ASST [54]; however, urticaria does not always improve with LTRA and, very occasionally, patients notice worsening of the rash [55] – in which case they should stop the treatment. LTRA alone are not used for urticaria.

Corticosteroids. In patients with very severe acute urticaria, associated possibly with angioedema or systemic symptoms, a short course of oral steroids is indicated. Dose and duration of the treatment is determined by the patient’s weight

and clinical response. Prolonged courses of oral steroids for chronic urticaria should be avoided whenever possible, and if long-term steroid treatment is considered necessary, the patient should be followed-up regularly and prescribed prophylactic treatment against steroid-induced osteoporosis at an early stage [56]. Oral steroids may be needed for urticarial vasculitis (see below) or severe delayed pressure urticaria.

Dietary interventions

An objective trial of a low salicylate diet may be indicated in patients who give a clear history of having developed more severe urticaria, or even angioedema or bronchospasm, after taking aspirin or NSAIDs and, particularly, if the patient also responds to LTRA treatment [57]. It is important to explain to the patient that the diet should not become more troublesome than the urticarial symptoms themselves and it may be simpler for patients to take a regular dose of an anti-histamine, rather than continue on a strict exclusion diet.

In children, an objective trial of a low E numbers diet may be helpful, especially if the clinical history suggests that episodes of urticaria may be related to ingestion of foods which are high in E numbers.

Patients with severe urticaria unresponsive to standard treatments

In a very small number of patients, severe, debilitating urticaria, associated possibly with airway angioedema, bronchospasm and hypotension, persists despite treatment with high-dose H1 anti-histamines; H2 anti-histamines and/or LTRA; corticosteroids; and, perhaps, dietary interventions. These patients usually have autoimmune urticaria and cyclosporin treatment has proved effective in about 65% of such patients in a randomized double-blind study [58]. Longer courses of cyclosporin may give a lengthier clinical response [59]; however, the optimum dose and length of treatment have not yet been established. Tacrolimus [60] and mycophenolate mofetil [61] have also been effective in open-label studies. Results of intravenous immunoglobulin treatment in small numbers of patients have been variable [62,63]. The current recommendation from the clinical guidelines for the use of intravenous immunoglobulin [64] is that intravenous immunoglobulin should not be used unless all other therapies have failed. If patients require immunomodulating therapies, referral to a specialist centre is recommended.

Urticaria in children

In children, urticaria is more often acute than chronic. Acute urticaria is caused frequently by IgE-mediated allergic reactions to foods or by acute infections, usually viral respiratory tract infections. ‘Papular urticaria’ occurs more often in chil-

dren than in adults, and is due usually to insect bites. There is an immediate IgE-mediated weal and flare reaction, but lesions can develop into intensely itchy, indurated papules which may take several weeks to resolve.

Chronic urticaria is estimated to affect between 0.1–3% of children in the United Kingdom [1]. Physical factors, such as pressure and cold, are the most common identifiable trigger and children with chronic urticaria usually also have angioedema. Approximately 30% of children with chronic urticaria have a positive ASST [39] and approximately 4% have positive thyroid peroxidase antibodies. It is suggested that thyroid function be monitored in children with chronic urticaria and positive thyroid autoantibodies, even though it has not been well established that treatment of clinical thyroid disease, if it develops, will improve the urticaria [65]. It has also been reported that children with severe chronic urticaria have a higher incidence of coeliac disease than controls [66].

Treating children with urticaria

As with adults, any potential triggering factors should be identified and, if possible, avoided. Non-sedating H1 anti-histamines are the first-line medical treatment. All these drugs are licensed for children over 12. Age restrictions and dosage vary for the different drugs in younger children. Cetirizine, desloratidine, levocetirizine and loratidine are all available as syrups, with desloratidine being licensed for the youngest age group (1–5 years). In children under 1 year, only the sedating H1 anti-histamines chlorphenamine and hydroxyzine are licensed. High-dose treatment, or a combination of two different non-sedating H1 anti-histamines, or a combination of a non-sedating H1 anti-histamine in the morning, with a sedating H1 anti-histamine at night may be needed. If symptoms are still not well controlled, an H2 receptor antagonist and/or a LTRA may be tried. Montelukast is licensed for prophylaxis of asthma in children from 6 months of age and is available as granules and as a chewable tablet for younger children as well as in a standard tablet format. Zafirlukast is licensed for prophylaxis of asthma in children from 12 years of age and is available only in a standard tablet format. Finally, if high-dose H1 anti-histamines, H2 receptor antagonists and LTRA are ineffective, oral steroids may be needed; however, even oral steroids may be ineffective if the child has severe physical urticaria. Referral to a specialist centre is suggested if the child has very severe symptoms.

Pregnancy and breast feeding

Pregnancy

Whenever possible, drug treatment should be avoided during pregnancy. Fortunately, chronic urticaria often improves in pregnancy; however, if symptoms are very severe

and treatment is considered absolutely necessary, either chlorphenamine or loratidine may be prescribed. Data from several thousand women who had taken either chlorphenamine or loratidine in pregnancy, including data from several hundred who took anti-histamines during the first trimester [67,68], showed no increase in the incidence of fetal malformations. The lowest dose which controls symptoms should be used and the possibility of adverse effects should be discussed and documented. There is less clinical experience with cetirizine and therefore cetirizine is not recommended in pregnancy. Hydroxyzine is the only anti-histamine which is specifically contraindicated in pregnancy in the summary of product characteristics.

Breast feeding

Significant amounts of most anti-histamines are secreted in breast milk, but cetirizine and loratidine are secreted at lower levels and therefore these drugs are recommended if anti-histamine treatment is necessary in a woman who is breast feeding. The lowest possible cumulative dose should be used. Chlorphenamine has been reported to cause poor feeding and drowsiness and should be avoided.

Prognosis

A prospective study published in 2004 found that chronic urticaria lasted longer in patients who had associated angioedema; severe urticaria; a positive ASST; or positive thyroid autoantibodies [69]. In this study chronic urticaria lasted for > 1 year in more than 70% of patients and for 5 years (the end of the study period) in 14% of patients. A retrospective study [70] found that 44% of patients seen in a dermatology clinic with either acute or chronic urticaria had a good response to H1 anti-histamine treatment. Patients with physical urticaria responded less well than patients with other types of urticaria and had a more prolonged clinical course.

In children, chronic urticaria usually resolves, with about 25% having disease remission within 3 years of presentation [38].

Unusual types of urticaria

Urticarial vasculitis

In a small percentage of patients with chronic urticaria, perhaps about 2% [71], there is an underlying small vessel vasculitis. It is important to diagnose these patients because they may have an associated systemic illness which can lead to severe complications and because the treatment of urticarial vasculitis differs from that of ordinary chronic urticaria. Clinically, the lesions of urticarial vasculitis are longer-lasting (3–7 days) than those of ordinary chronic urticaria. They are often painful or 'burning' and they may

leave residual bruising or hyperpigmentation of the skin. Approximately 40% of patients with urticarial vasculitis will have associated angioedema. Urticarial vasculitis may occur at any age, but the median age of incidence is 43 years. Women are affected twice as often as men. Two categories of urticarial vasculitis are recognized – hypocomplementaemic and normocomplementaemic [72]. Patients with hypocomplementaemic urticarial vasculitis syndrome (HUVS) are more likely to have an associated connective tissue disease and systemic symptoms than patients with normal complement levels [73] and may have IgG antibodies to the collagen-like domain of C1q [74]. There may be associated fever, arthralgia (50%), gastrointestinal involvement with abdominal pain, nausea, vomiting and diarrhoea (20%); pulmonary disease with dyspnoea or pulmonary effusions (20%); and glomerulonephritis with haematuria and proteinuria (5–10%). Progressive renal disease is rare, unless the urticarial vasculitis is associated with SLE. Other rare manifestations include eye involvement, lymphadenopathy, splenomegaly and pericardial effusions.

Diagnosis is by skin biopsy, taken ideally from a 'new' lesion (within 12 h of appearance), which shows a small vessel leucocytoclastic vasculitis involving post-capillary venules, with endothelial cell swelling, a neutrophil cell infiltrate, extravasation of red blood cells and fibrinoid deposits in and around blood vessels [75]. The condition is thought to be mediated via a type III/immune complex hypersensitivity reaction, in which antigen/antibody complexes deposit in vessel walls. This results in complement activation, neutrophil chemotaxis and infiltration and the release of proteolytic neutrophil enzymes, such as collagenases and elastases, which cause tissue damage. Immunofluorescence shows deposition of immunoglobulin and complement.

In most cases urticarial vasculitis is idiopathic, but it may be associated with connective tissue diseases such as SLE or Sjögren's syndrome; infections such as hepatitis B and C, Lyme disease and infectious mononucleosis; treatment with drugs, including ACEI, cimetidine, diltiazem, penicillins, sulphonamides and thiazides; and lymphoproliferative diseases such as mixed cryoglobulinaemia and IgM gammopathy. A specific syndrome of urticarial vasculitis and IgM gammopathy with fever, bone pain and arthralgia or arthritis – 'Schnitzler's syndrome' – was first described in 1972 [76,77].

The clinical history should indicate if a vasculitic process is likely, with the lesions lasting for several days, instead of hours, and being painful or burning, instead of itchy. Patients should be asked about drug treatment and joint, gastrointestinal and pulmonary symptoms. Examination may show purpura or hyperpigmentation at the sites of earlier lesions and, possibly, signs of an associated underlying disease such as SLE. Investigations which may be relevant include skin biopsy to confirm the diagnosis; FBC and ESR; renal and liver function tests; urine analysis; complement C3 and C4 levels and anti-C1q antibodies; ANA and extractable nuclear antigens (ENA) (often positive for Ro/SS-A and

La/SS-B if the patient has Sjögren's syndrome); hepatitis, Borrelia or Epstein–Barr virus serology; immunoglobulins and protein electrophoresis and cryoglobulins and chest X-ray (CXR) and pulmonary function tests if symptoms suggest lung involvement. [Anti-neutrophil cytoplasmic antibodies (ANCA) are rarely found in urticarial vasculitis and if ANCA testing is positive an alternative diagnosis such as Wegener's granulomatosis or microscopic polyangiitis should be considered.]

Treatment of urticarial vasculitis differs from that of ordinary chronic urticaria and depends upon whether there is systemic involvement and/or an underlying medical condition. If the disease is limited to the skin, anti-histamines and NSAIDs usually relieve symptoms, although occasionally NSAID treatment may make the urticaria worse. If anti-histamines and NSAIDs are ineffective, colchicine, dapsone or hydroxychloroquine may be tried. Oral steroids may be required if there is systemic involvement. There are case reports of patients responding to rituximab [73] and mycophenolate mofetil [78]. The clinical course is variable and depends upon whether there is associated hypocomplementaemia and/or systemic involvement. In most patients urticarial vasculitis remains confined to the skin, but it may persist for years.

Urticaria pigmentosa

Mastocytosis is a disease in which there is mast cell hyperplasia affecting the skin, gastrointestinal tract, bone marrow, liver, spleen and lymph nodes. Clinical features include urticaria, pruritus, flushing, nausea, vomiting, abdominal pain, diarrhoea and headache. Patients may be prone to severe anaphylactoid reactions after exposure to certain medications [79] and severe anaphylactic reactions after exposure to antigens to which they are sensitized, such as insect venom [80], because of the increased tissue load of mast cells. Mastocytosis is classified into cutaneous and systemic variants and urticaria pigmentosa is the most common form of cutaneous mastocytosis, occurring in approximately 85% of children and 95% of adults in whom mastocytosis is limited to the skin. Systemic mastocytosis varies from an indolent condition, where there is no associated haematological disease, to an aggressive mast cell leukaemia. The lesions of urticaria pigmentosa are variable in colour, macular or maculopapular and are usually symmetrical in distribution, with sparing of the extremities and face. The diagnosis of urticaria pigmentosa is made by skin biopsy, which shows a significant increase in dermal mast cells [81]. Patients have symptoms of pruritus and dermographism and pressure on affected skin causes erythema and urtication – 'Darier's sign'. Children usually present before the age of 2 years and urticaria pigmentosa may be present at birth. They tend to have fewer, larger skin lesions than adults and they may also develop bullae, which do not occur in adults. Treatment is with H1 and H2 anti-histamines and ketotifen [82] (an anti-

histamine with mast cell-stabilizing properties), methoxsalen with long-wave ultraviolet radiation (psoralen plus ultraviolet A₁) [83] and topical steroids [84] may all be used to alleviate urticaria and pruritus. It is rare for children to develop systemic mastocytosis and urticaria pigmentosa resolves completely in about 50% of children. In contrast, urticaria pigmentosa in adults usually persists and about 50% of patients may go on to develop systemic mastocytosis. The prognosis in adults is, therefore, highly variable.

Cryopyrin-associated periodic syndromes (CAPS)

Mutations in the CIAS1 gene, which codes for cryopyrin, cause autoinflammatory syndromes, one of which is Muckle-Wells syndrome [85], also known as urticaria-deafness-amyloidosis (UDA). It is a rare, autosomal dominant condition which presents with spontaneous urticaria, sensorineural deafness, episodic fevers and arthralgia and it may progress to renal amyloid.

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