

Chronic urticaria

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Chronic urticaria has a spectrum of clinical presentations and causes. About 50% of patients with “idiopathic” disease have histamine-releasing autoantibodies in their blood. The term *autoimmune urticaria* is increasingly being accepted for this subgroup of patients, in whom immunosuppressive therapies may be appropriate if conventional approaches to management are unsuccessful. This article reviews the classification, causes, and management of chronic urticaria in light of recent advances in the understanding of its etiology. (J Am Acad Dermatol 2002;46:645-57.)

Learning objective: At the conclusion of this learning activity, participants should have up-to-date knowledge of the classification, assessment, and management of chronic urticaria and understand where the concept of autoimmune urticaria fits into existing frameworks.

Urticaria is characterized by short-lived swellings of the skin, mouth, and genitalia due to transient leakage of plasma from small blood vessels into the surrounding connective tissue. Superficial swellings of the dermis are called wheals (Fig 1). The wheals are usually itchy and often pale in the center when they develop because of intense edema, before maturing into pink superficial plaques that resolve over hours without a mark unless the skin is damaged by scratching. The surrounding flare is due to an axon reflex. Deeper swellings of the dermis and subcutaneous and submucosal tissues are called angioedema (Fig 2). They may be painful rather than pruritic and take longer to resolve. Wheals and angioedema often coexist in urticaria but may occur alone.

THE SPECTRUM OF URTICARIA

The diverse presentation of urticaria, ranging from occasional localized wheals to widespread recurrent whealing with angioedema, emphasizes the importance of recognizing clinical patterns for a better understanding of its assessment, management, and prognosis. The simple clinical classification in



Fig 1. Superficial swellings of the dermis are called wheals. They are usually pale in the center with a red surrounding flare when they erupt and become pink as they mature.

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Funding sources: None.

Conflict of interest: None.

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0190-9622/2002/\$35.00 + 0 16/2/122759

doi:10.1067/mjd.2002.122759

Table I distinguishes urticarias provoked by physical stimuli, skin contact, or small vessel vasculitis from all other presentations, which are grouped under the



Fig 2. Deeper swellings of the skin and submucosa called angioedema are less well defined and do not necessarily show any difference in color from unaffected skin.

umbrella term “ordinary” urticaria. The groups are not mutually exclusive since physical and ordinary urticaria may coexist but do provide a framework for clinical use and defining groups for studies. It is useful to separate angioedema occurring without wheals from other presentations of urticaria because its etiology and management may be different, such as in C1-esterase inhibitor deficiency.

Any pattern of recurrent urticaria occurring at least twice a week for 6 weeks is called chronic. All chronic urticaria implicitly goes through an acute stage (<6 weeks' duration). The term *chronic urticaria* makes no assumption about its cause, although it is sometimes used loosely as an abbreviation for chronic “idiopathic” (unexplained) disease. This is unsatisfactory because many cases of ordinary urticaria, previously regarded as idiopathic, can now be ascribed to autoimmunity. Approximately 50% of cases nevertheless remain unexplained after evaluation for autoimmune urticaria. Reactions to food additives and illness, including chronic infection, probably account for only a small proportion of these (Fig 3).

Table I. Clinical classification of urticaria/angioedema

Ordinary urticaria (recurrent or episodic urticaria not in the categories below)
Physical urticaria (defined by the triggering stimulus)
Adrenergic urticaria
Aquagenic urticaria
Cholinergic urticaria
Cold urticaria
Delayed pressure urticaria
Dermographism
Exercise-induced anaphylaxis
Localized heat urticaria
Solar urticaria
Vibratory angioedema
Contact urticaria (induced by biologic or chemical skin contact)
Urticarial vasculitis (defined by vasculitis as shown by skin biopsy specimen)
Angioedema (without wheals)

DIAGNOSIS

The diagnosis of urticaria is primarily clinical. A thorough history is essential. Using a questionnaire, Kozel et al¹ found that an extensive panel of screening investigations added little to the diagnosis of chronic urticaria or the detection of underlying disorders. The timing of onset and duration of individual wheals may be very helpful in arriving at an initial diagnosis (Fig 4). *Urticaria* is typically here today, gone tomorrow, whereas *urticarial rashes*, such as urticarial vasculitis and some drug reactions, usually last several days. Physical urticarias usually appear within 10 minutes of the trigger stimulus and clear within an hour, except delayed pressure urticaria that characteristically arises several hours after sustained pressure and lasts at least a day. Contact urticaria arises within 10 to 30 minutes of exposure to the contactant and settles over about 2 hours. The wheals of ordinary urticaria usually fade after 2 to 24 hours. Urticarial vasculitis is often included in classifications of urticaria because the lesions may be morphologically indistinguishable but should, more correctly, be regarded as a pattern of small vessel vasculitis. It is defined by the presence of small blood vessel damage on histologic examination of lesional skin. Wheals usually last several days, may bruise, and tend to burn rather than itch.

Morphology of the wheals can be informative in the physical urticarias, such as the linear lesions of dermatographism or the small papular wheals of cholinergic urticaria and aquagenic urticaria. The distribution may suggest a cause, such as the predilection for the palms, soles, and lower back in delayed pressure urticaria or the restriction to light-exposed skin in solar urticaria. The size of individual wheals or angioedema in ordinary urticaria does not usually

Chronic Urticaria - a heterogeneous disorder

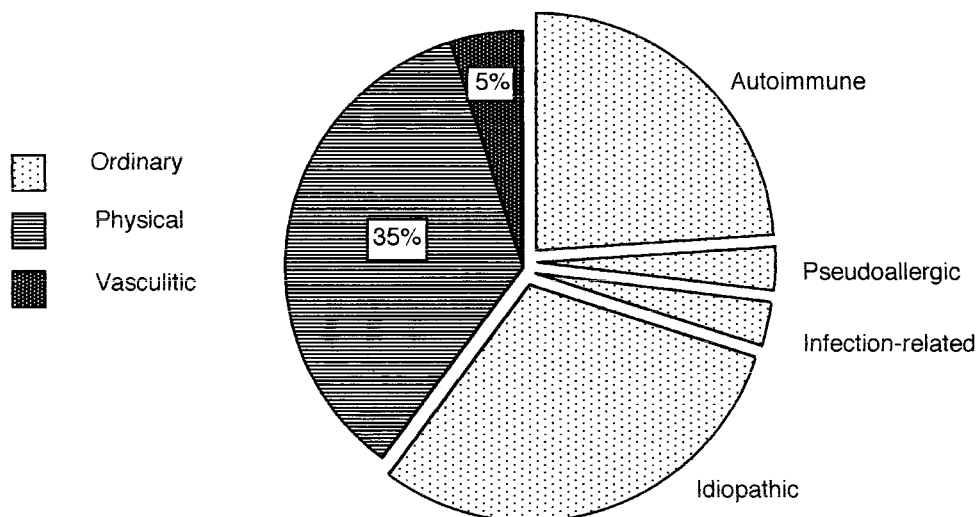


Fig 3. Frequency chart of the different clinical patterns of urticaria shows relative proportion of patients with ordinary urticaria having a definable origin or idiopathic disease.

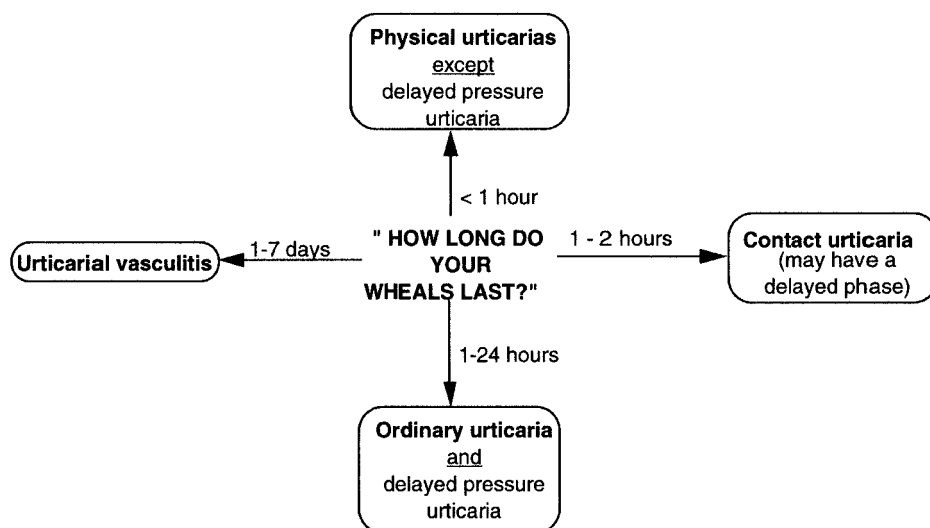


Fig 4. Duration of wheals may be helpful in initial diagnosis of urticaria.

help understand its origin, but may reflect disease activity or the response to therapy. General examination for associated systemic disease, such as thyroid dysfunction and other autoimmune disorders, should not be overlooked.

PATHOGENESIS

The importance of histamine as a mediator of urticaria has been recognized for many years. Degranulation of mast cells with release of histamine is central to the development of wheals and angioedema. There is lack of agreement about mast cell

numbers in chronic urticaria, which appear to be increased with conventional stains² but normal with tryptase.³ However, there is agreement that their mediator content may be released more easily, as evidenced by an enhanced whealing tendency to intradermal codeine⁴ and increased histamine release by the nonimmunologic stimulus, compound 48/80, in chronic "idiopathic" urticaria.⁵ The reason for this enhanced releasability is not clear. A range of nonimmunologic and immunologic mast cell-degranulating stimuli have been described including opiates, neu-

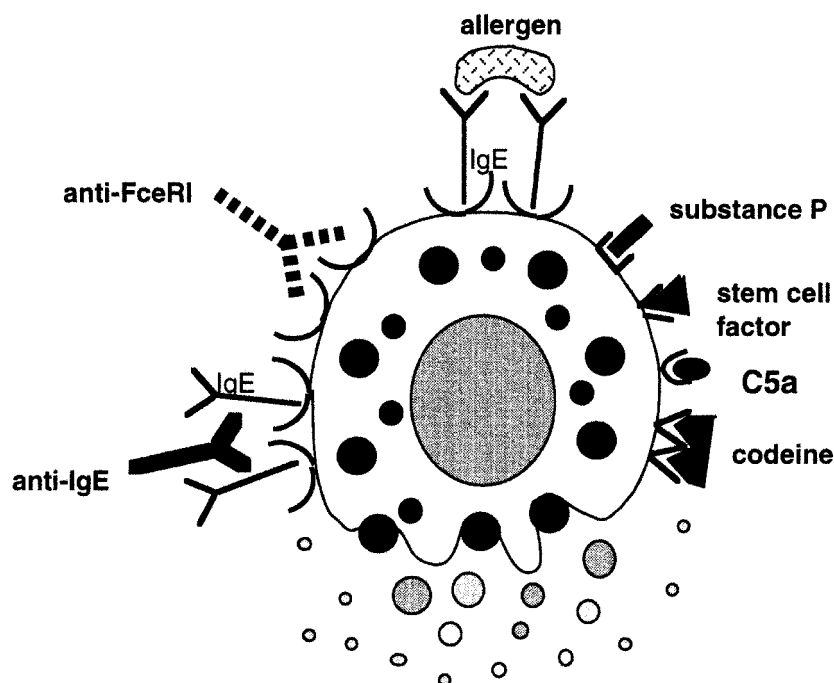


Fig 5. Several immunologic and nonimmunologic stimuli of mast cell degranulation are recognized *in vitro*. Of those illustrated, only allergen-specific IgE interactions, anti-IgE and anti-FcεRI antibodies and C5a appear to have a definite physiologic role *in vivo*.

ropeptides, stem cell factor (c-kit ligand), C3a and C5a anaphylatoxins, allergen binding of specific immunoglobulin E (IgE) and autoantibodies that cross-link cell-bound IgE or high-affinity IgE receptors (FcεRI) (Fig 5). There is little evidence that nonimmunologic stimuli have a physiologic role in chronic urticaria. C5a may augment autoantibody-induced histamine release from skin mast cells. Immediate hypersensitivity reactions involving the binding of allergen to specific IgE on mast cells are a well-recognized cause of some cases of acute urticaria but do not seem to be important in the pathogenesis of chronic recurrent disease. It is still unclear what event, or events, initiate degranulation in the skin or the control mechanisms that prevent degranulation of mast cells in other tissues. Local factors including heat and pressure may encourage vasopermeability and vasodilatation that could facilitate extravascular leakage of relatively large proteins, including autoantibodies, into the dermis at sufficient concentration to induce degranulation. Peripheral blood basophils probably play no part in the initial phase of wheal formation but may amplify and sustain urticarial lesions by migrating into them from the circulation, as seen in late-phase reactions.⁶

A range of proinflammatory mediators, cytokines, proteases, and heparin is released from mast cells at the time of degranulation (Fig 6). Histamine is the most important preformed mediator. Newly synthesized leukotrienes (LTC₄, D₄, and E₄), platelet-acti-

vating factor, and prostaglandin D₂ may contribute to the subsequent inflammatory events. The possible contribution of mast cell-derived cytokines and chemokines in urticaria has been reviewed recently.⁷ Endothelial cell immunoreactivity to tumor necrosis factor α (TNF-α) is increased in urticaria and may thereby promote the inflammatory response by up-regulation of vascular adhesion molecules.

Although histamine-releasing autoantibodies have been demonstrated in up to half of patients with chronic ordinary urticaria presenting to specialist hospital clinics, many cases remain unexplained (idiopathic). Pseudoallergic reactions to food additives and natural dietary salicylates may be important in some, although this remains controversial.⁹ The underlying mechanisms for pseudoallergic reactions remain unproven but may involve diversion of arachidonic acid metabolism from prostaglandin formation to leukotrienes. A possible association between *Helicobacter pylori* gastritis and chronic urticaria currently remains to be confirmed by double-blinded studies of eradication therapy. An indirect role for *H pylori* by evoking autoantibody production through molecular mimicry has recently been proposed.¹⁰

The reason for cutaneous mast cell degranulation after specific physical triggers in the physical urticarias is unknown, although passive transfer studies have demonstrated an immunoglobulin serum fac-

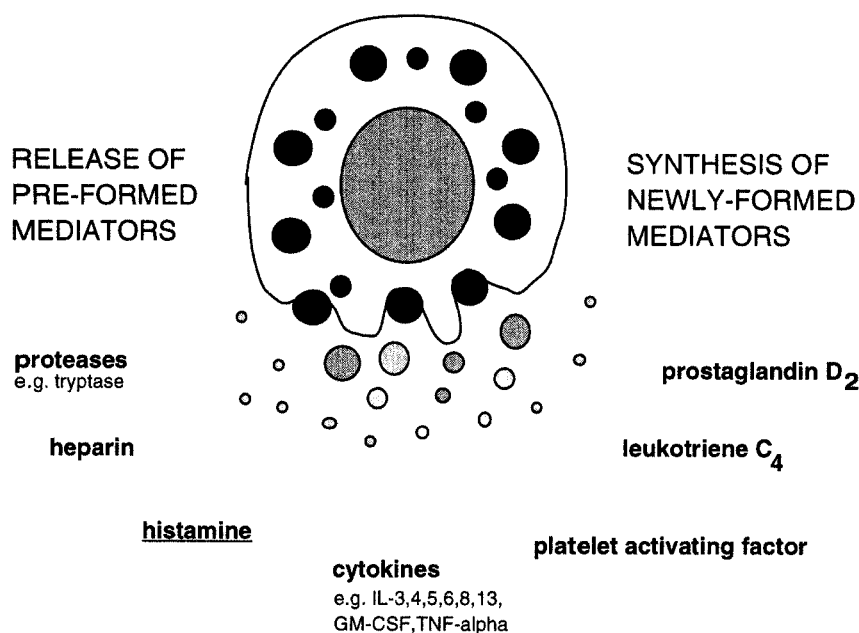


Fig 6. Consequences of degranulation include release of preformed histamine, heparin, proteases, and cytokines and newly generated arachidonic acid metabolites.

tor in some cases of dermographism, cholinergic, cold, and solar urticaria. Histamine-releasing autoantibodies were not found in symptomatic dermographism¹¹ or cholinergic urticaria (personal communication, R. A. S., 2001). Systematic screening of other patterns of physical urticaria for histamine-releasing activity has not been undertaken. Gruber et al¹² detected functional anti-IgE in the IgM fraction of one cold urticaria serum, but the significance of this finding as a cause of cold urticaria has not been evaluated.

AUTOIMMUNE URTICARIA

The concept of autoimmune urticaria has evolved over the past decade as evidence for histamine-releasing autoantibodies and their relationship to disease activity has accrued.¹³ Malmros¹⁴ in 1946 observed that serum from some patients with urticaria could induce an immediate wheal-and-flare response on reinjection into their skin. He described a wheal at the site of injection within 15 minutes in 53 of 956 patients (5.5%) with diverse medical conditions, including urticaria, but did not draw specific conclusions about the nature of the serum factor. A detailed clinical, immunologic, and histologic study of 12 patients with chronic "idiopathic" urticaria in 1986 showed a wheal-and-flare response to intradermally injected autologous serum in 7 patients, which resembled spontaneous urticarial lesions in appearance, histologic characteristics, and time course.¹⁵ The response was not seen in healthy subjects. Although there was no support for the original

hypothesis that the skin reaction was due to circulating immune complexes, it was found that the presence of the serum factor related to overall disease activity and might therefore be relevant to its pathogenesis. The autologous serum skin test (ASST) response was not abolished by heating serum at 56°C for 30 minutes to inactivate IgE and was demonstrable by using heparinized plasma.¹⁶ It was concentration but not volume dependent and could be transferred passively to a healthy volunteer.¹³ Pretreatment with antihistamines or the mast cell-degranulating chemical compound 48/80 substantially reduced the response, suggesting that it was histamine and mast cell dependent.¹³ However, it should be noted that vasoactive factors generated during clotting may contribute to the ASST response on a background of intrinsic mast cell releasability in chronic urticaria, and it should not be regarded as a specific test for circulating functional autoantibodies.

Evidence for histamine-releasing autoantibodies

Initial studies of ASST-positive chronic urticaria sera on basophils from an atopic donor showed substantial histamine-releasing activity with properties suggestive of an IgG anti-IgE autoantibody.¹¹ Other sera released histamine from a healthy basophil donor with very low levels of IgE. These basophils failed to respond to anti-IgE, which suggests that the release mechanism was independent of cell-bound IgE. Further detailed study of 4 of these sera

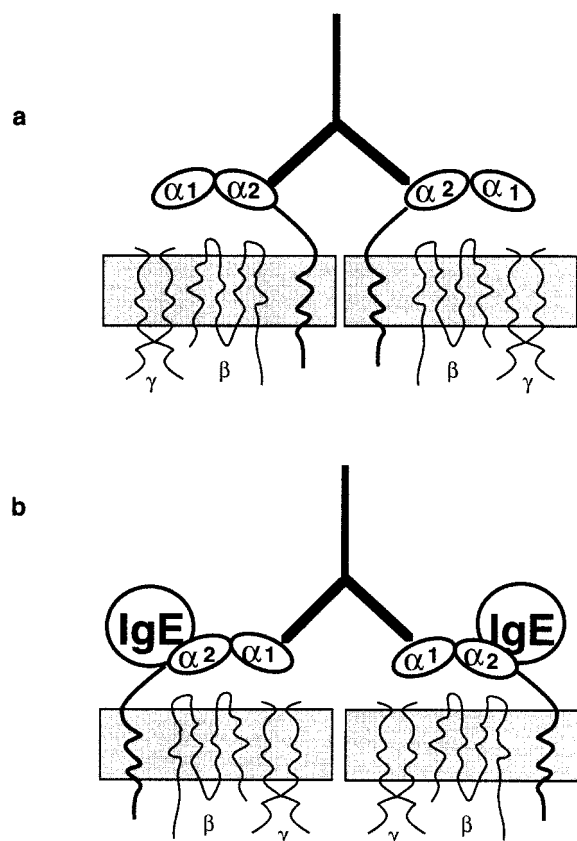


Fig 7. a, Autoantibodies that compete for the IgE binding site on the α_2 domain of FcεRI are competitive. **b,** Autoantibodies that bind to the α_1 domain of FcεRI in the presence of IgE are noncompetitive.

and IgG purified from them showed that they contained functional autoantibodies directed against the α -subunit of the high-affinity IgE receptor (FcεRI α) on basophils and mast cells.¹⁷ Binding of the autoantibody was inhibited by the presence of receptor-bound IgE. Thus the antibody competed with IgE for the binding site on the α -chain (Fig 7, *a*). When a larger number of chronic urticaria sera were studied, it was evident that many were able to bind FcεRI α in the presence of cell-bound IgE.¹⁸ These autoantibodies are known as noncompetitive (Fig 7, *b*).

These early results have now been confirmed and extended by other workers.¹⁹⁻²² Sabroe et al²³ found evidence of functional autoantibodies in 31% of 107 patients with chronic urticaria. The majority of these had predominant anti-FcεRI α activity. Zweiman et al¹⁹ reported basophil histamine-releasing activity in 30% of 70 chronic urticaria sera. Tong et al²⁰ reported basophil release of histamine with sera of 52% of 50 patients with chronic urticaria. They also assayed their sera on a rat basophil leukemia cell line transfected with the FcεRI α subunit and found positive release in 76% of them. Ferrer, Kinét, and

Kaplan²¹ found that 48% of 68 chronic urticaria sera released histamine from basophils.

Autoantibody assays

The studies referred to in the preceding paragraphs used functional assays on basophils from healthy volunteers. Skin mast cells have been used as target cells in a few studies but are more difficult to obtain and require a different source for each experiment. Ferrer, Kinét, and Kaplan²¹ found that basophil histamine release correlated well with release from enzymatically dispersed mast cells. Chronic urticaria sera with the highest histamine release on basophils also induced histamine release from mast cells in foreskin slices, but there was no response to sera from control subjects.¹⁸

Immunoassays measure total levels of functional and nonfunctional autoantibodies in sera rather than their biologic ability to affect a target cell. Anti-IgE autoantibodies detected by immunoassay were found in chronic urticaria and cold urticaria sera by Gruber et al¹² in 1988, but only one of the cold urticaria sera had functional histamine-releasing activity. Ferrer, Kinét, and Kaplan²¹ found anti-FcεRI α autoantibodies by Western blotting in a higher proportion of chronic urticaria sera than released histamine from basophils. Fiebiger et al²² developed an enzyme-linked immunosorbent assay for anti-FcεRI α autoantibodies, which allowed large numbers of sera to be screened. They found anti-FcεRI α autoantibodies in 38% of 281 patients with chronic urticaria and in the sera of 39% of patients with pemphigus vulgaris, 36% with dermatomyositis, 20% with systemic lupus erythematosus (SLE), and 13% with bullous pemphigoid. Only anti-FcεRI α -positive sera from patients with chronic urticaria were able to induce histamine release from basophils. Ninety-one percent of the releasing sera were of IgG1 or IgG3 subclass, whereas the nonreleasing sera in the other autoimmune conditions were mainly IgG2 or IgG4 in this series. These findings need confirmation because it may well be significant that IgG1 or IgG3 are very effective at fixing complement, whereas IgG2 or IgG4 are less so.

Role of complement

A role for complement in autoantibody-mediated histamine release is further suggested by the demonstration that decompensation of urticaria sera by heating caused loss of functional activity on basophils in some but not all sera.²² The loss could be reproduced by using a C5a inhibitory peptide. More recently, Ferrer, Nakazawa, and Kaplan²⁴ have confirmed the dependence of chronic urticaria serum-induced histamine release on the presence of complement by using dispersed human skin mast cells.

IgG derived from chronic urticaria sera with histamine-releasing activity did not release histamine from mast cells unless normal serum-containing complement was added. Addition of C2- or C5-deficient sera did not, however, restore histamine-releasing activity. These data suggest that cross-linking of the FcεRI by IgG activates complement, which then augments or causes histamine release from mast cells. Fiebiger et al²² argue that the restriction of urticarial lesions to the skin in patients with autoantibodies could be explained by expression of the C5a receptor by cutaneous mast cells but not by those in lung or intestinal mucosa. However, complement deposition in urticarial wheals, such as occurs in urticarial vasculitis, is not seen in biopsy specimens, and direct proof of the involvement of complement *in vivo* is still lacking.

Association with autoimmunity

Leznoff and Sussman²⁵ reported that 14% of 624 patients with chronic "idiopathic" urticaria had evidence of thyroid autoimmunity compared with an expected prevalence of 6% in the general population. Autoimmune conditions (thyroid disease, vitiligo, insulin-dependent diabetes, rheumatoid arthritis, and pernicious anemia) were associated more frequently with chronic urticaria patients having functional autoantibodies than in those without autoantibodies.²³ A strong association has recently been shown between *in vitro* basophil histamine-releasing activity and HLA-DR4 and its associated allele DQ8 in chronic urticaria patients with a positive ASST response.²⁶ A less striking but still highly significant association with HLA-DR4 was seen in patients with a positive ASST response but no demonstrable basophil histamine-releasing activity. Those with a negative ASST were no different than controls.

Diagnosis of autoimmune urticaria

The basophil histamine release assay is currently the "gold standard" for detecting functional autoantibodies in serum of patients with chronic urticaria. However, this bioassay is difficult to standardize because it requires fresh basophils from healthy donors and is time consuming. It is likely to remain confined to research centers. Western blotting and other nonfunctional assays, including enzyme-linked immunosorbent assay and flow cytometry using chimeric cell lines expressing the human FcεRIα, may be useful for screening sera in the future but need to be validated. The ASST (Fig 8) is currently the best *in vivo* clinical test for detection of *in vitro* basophil histamine-releasing activity. The ASST has a sensitivity of approximately 70% and a specificity of 80% when read as a pink serum-in-



Fig 8. Positive ASST comprises a pink wheal response larger than an adjacent control skin test with normal saline. Note similarity to a spontaneous wheal in the antecubital fossa.

duced wheal 1.5 mm or greater than an adjacent normal saline control injection at 30 minutes,²⁷ although experience is required to obtain reproducible results. The finding that peripheral blood basophils are reduced or absent in patients with chronic urticaria with histamine-releasing autoantibodies^{28,29} may prove to be a helpful clinical marker of autoimmune urticaria once rapid and reliable methods for measuring small numbers of circulating basophils are available.

Clinical presentation of autoimmune urticaria

The clinical presentation of patients with or without autoantibodies is surprisingly similar, although those with autoantibodies tend to have more severe disease.²³ Histologic examination of spontaneous wheal biopsy specimens showed significantly greater numbers of neutrophils, activated eosinophils, and lymphocytes in lesions of less than 4 hours (Fig 9) or more than 12 hours old when compared with uninvolved skin. There was no important difference between patients with and with-

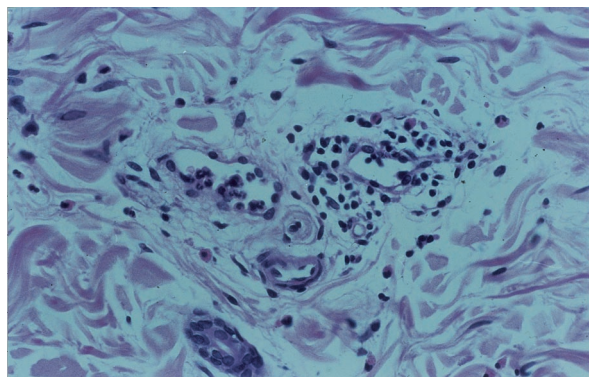


Fig 9. Photomicrograph of early spontaneous wheal shows perivascular lymphocytes and intraluminal and perivascular neutrophils with perivascular and interstitial eosinophils.

out autoantibodies.³⁰ The neutrophilic pattern of urticaria described in some urticaria biopsy specimens³¹ was not evident. The lack of a clear clinical and histologic separation between chronic ordinary urticaria patients with and without autoantibodies indicates that the occurrence of skin mast cell degranulation may be more important in determining clinical presentation than its cause. Nevertheless, it is possible that more patients would show functional autoantibodies than currently recognized if more sensitive assays for their detection become available.

PHYSICAL URTICARIAS

The physical urticarias are characterized by the predominant physical stimulus that elicits them. It is quite common for one form of physical urticaria to overlap with another, such as dermatographism and cholinergic urticaria. Physical urticarias can also co-exist with ordinary urticaria. For instance, up to 40% of patients with chronic ordinary urticaria have delayed pressure urticaria.³² They may present with wheals or angioedema and, very rarely, anaphylaxis. Apart from confirming the diagnosis with physical challenge tests, investigations should not be undertaken routinely. Consensus guidelines for these tests have been published.³³

Symptomatic dermatographism

The typical lesion is a red, itchy, linear wheal appearing within minutes of light stroking of the skin, as opposed to the linear asymptomatic reddening commonly seen in healthy people after scratching or the blanching response seen in atopic eczema known as white dermatographism. It can be reproduced easily on upper back skin by stroking the tip of a blunt instrument at different pressures but may be reduced if the patient is taking antihistamines. The condition can occur at any age without any

recognizable trigger and lasts around 2 to 3 years but may be longer. Mucosal involvement and angioedema do not occur. There are no recognized systemic associations (such as atopy or autoimmunity).

Cholinergic urticaria

Cholinergic urticaria presents with multiple transient papular wheals 2 to 3 mm in diameter surrounded by a pink flare most commonly extending from the neck to the thighs but any region of the body can be affected. It occurs mainly in adolescents and young adults. It is caused by a rise in core temperature due to exercise, overheating, or stress. Angioedema is an uncommon but well-recognized feature. The cholinergic sympathetic innervation of sweat glands is involved (hence the name) because the rash can be blocked by topical anticholinergic drugs, but how this leads to urticaria is unclear. Wheezing may complicate more severe attacks. Exercise-induced anaphylaxis may resemble cholinergic urticaria in some cases. The syndrome is characterized by pruritus, whealing, and angioedema that may progress to respiratory obstruction or cardiovascular collapse. It has been linked with ingestion of specific foods or a heavy food load before exercise.³⁴

Delayed pressure urticaria

The onset of urticaria is delayed from 2 to 6 hours after pressure is applied perpendicularly to the skin. The swellings tend to be deeper and more painful than those of ordinary urticaria and last 24 hours or more. Patients may feel unwell with a low-grade pyrexia and experience arthralgia. Anaphylaxis has been recorded after pressure testing,³⁵ and large extensive swellings of delayed pressure urticaria resemble angioedema. The cause is unknown, but increased levels of interleukin 6 (IL-6) have been found in suction blister fluid over induced lesions.³⁶ Histologic examination of delayed pressure urticaria shows some resemblance to the delayed phase reaction of an immediate hypersensitivity response in that there are abundant neutrophils and eosinophils but no evidence of vasculitis. This may explain the poor response to antihistamines of these patients. Oral corticosteroids are often necessary for disease control.

Cold urticaria

This physical urticaria presents with the rapid onset of confluent or papular wheals on the face, neck, or hands after cold exposure followed by rewarming of the skin. Angioedema or anaphylaxis may also occur when it is severe. It usually arises at the site of localized cooling (such as application of ice to the skin) or, less commonly, results from

lowering of the body temperature, which leads to a more generalized rash. Almost all acquired cold urticarias are idiopathic (essential) and associated with short-lived whealing. A few may be secondary to an associated cryoglobulin, cold agglutinin, or cryofibrinogen, in which case the wheals may last 24 hours or more. This finding should, in turn, lead to investigation for an underlying cause, such as hepatitis C or B infection, lymphoreticular disease, or infectious mononucleosis.

URTICARIAL VASCULITIS

Patients with this form of small vessel vasculitis may present with both urticaria and arthritis. They are at risk of kidney, lung, eye, or central nervous system involvement. Normocomplementemic urticarial vasculitis is usually idiopathic, but hypocomplementemic urticarial vasculitis may be associated with underlying SLE, Sjögren's syndrome, or cryoglobulinemia (which itself is closely linked with hepatitis B or C virus infection). Primary urticarial vasculitis can occasionally evolve into SLE.³⁷ Immune complexes are thought to lodge in small blood vessels with activation of complement, mast cell degranulation, infiltration by acute inflammatory cells, fibrin deposition, and blood vessel damage. The diagnosis must be confirmed by skin biopsy. The clinical features, course, and prognosis have been reviewed.³⁸

INVESTIGATIONS

Investigations for chronic urticaria should be guided by the clinical presentation. Blood tests are unnecessary for mild ordinary urticaria responding to antihistamines. A complete blood cell count can be used as a baseline screening investigation in more severe disease. Blood eosinophilia should prompt stool examination for parasitic infestations, although this is a rare cause of chronic urticaria in developed countries. The erythrocyte sedimentation rate may be raised in urticarial vasculitis or Schnitzler's syndrome (recurrent urticaria, bone pain, fever, high erythrocyte sedimentation rate, and IgM paraproteinemia). A search for thyroid autoantibodies is appropriate for all chronic ordinary urticaria not responding to first-line therapies with antihistamines, especially when autoimmune urticaria is suspected. Dietary exclusion and double-blind, placebo-controlled oral challenge may reveal food additives as a cause of chronic urticaria in a few patients. Skin biopsy is essential to confirm urticarial vasculitis but does not distinguish between other clinical patterns of urticaria.

MANAGEMENT

Many pharmacologic and nonpharmacologic interventions are available (Fig 10). None is universally successful, and the choice should be tailored to individual patients. Management should be directed at the cause of chronic urticaria in the rare instance that one can be found. Aggravating factors that may be identified from the history (eg, heat, tight clothing, stress, alcohol) and trigger stimuli for physical urticaria should be avoided if possible. Providing clear information and advice on preventive measures, such as covering exposed skin of patients with cold urticaria, and symptomatic measures, such as taking cool showers for cholinergic urticaria or rewarming in a hot bath for attacks of cold urticaria, can be helpful. Simple cooling lotions, such as 0.5% to 1.0% menthol in aqueous cream, are often welcomed.

Avoidance of aspirin and other nonsteroidal anti-inflammatory drugs in favor of acetaminophen as an analgesic should usually be recommended because these drugs aggravate chronic urticaria in about 30% of patients.³⁹ Patients taking low-dose aspirin for its antithrombotic properties can usually continue regular treatment, although nonaspirin alternatives, such as clopidogrel, are available. Pseudoallergic reactions to nonsteroidal anti-inflammatory drugs as a cause of acute urticaria undoubtedly occur and are most easily recognized when they present acutely with angioedema or anaphylactoid reactions. It is good practice to recommend avoidance of codeine and other opiates in view of the enhanced skin test reactions to codeine found in chronic urticaria.⁴ It is common to see exacerbations of chronic urticaria at the time of minor viral infections, and it may be difficult to differentiate between a flare caused by the illness and a flare caused by medication taken for it. Angiotensin-converting enzyme inhibitors should usually be avoided in urticaria since angioedema and, rarely, urticaria are recognized adverse effects. Angioedema may present months after the onset of therapy.⁴⁰

Avoidance of dietary pseudoallergens, including food colors, preservatives, and natural salicylates, has been practiced for many years. The benefits of this approach for chronic ordinary disease are controversial, and there is general agreement that dietary measures have no role in most forms of chronic urticaria unless proven by double-blind, placebo-controlled challenge. Only 19% of 47 diet responders in a recent open prospective study of a low pseudoallergen diet in chronic "idiopathic" urticaria had confirmed reactions to double-blind, placebo-controlled challenges with individual pseudoallergens.⁹

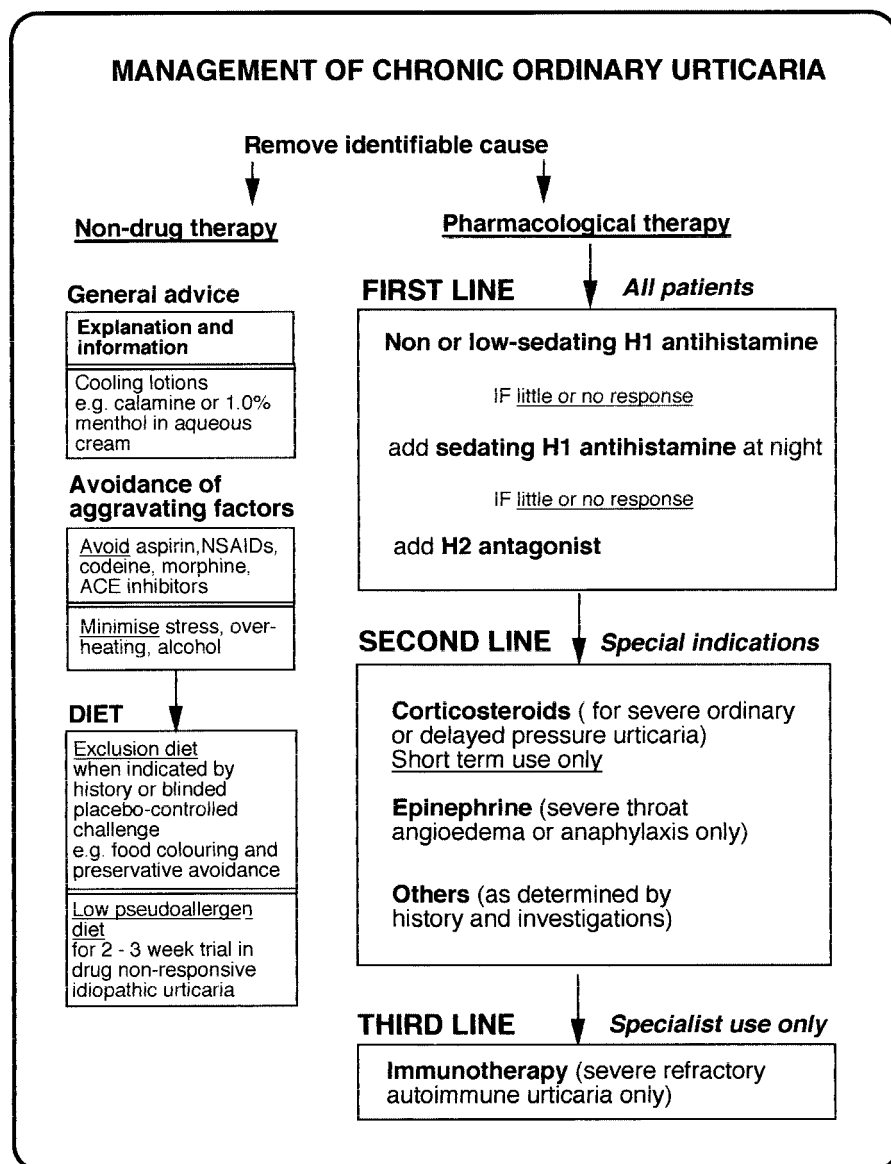


Fig 10. Management summary for chronic urticaria.

First-line drug therapies

Oral antihistamines are the mainstay of drug treatment for chronic urticaria. They reduce itch, whealing, or both. A recent retrospective survey found that 44% of 390 patients attending a hospital clinic with urticaria reported a good response to H₁-receptor antagonists and 15% had partial relief of symptoms.⁴¹ All patients with symptomatic chronic urticaria should be offered a choice of at least 2 nonsedating or minimally sedating antihistamines. All the currently available antihistamines detailed in Table II have been shown to be effective for chronic "idiopathic" urticaria and are probably of similar efficacy, although it is a common experience for patients to prefer one over

Table II. Nonsedating and minimally sedating antihistamines for urticaria

Generic name	Trade name	Daily dose (mg)	Special features
Cetirizine	Zyrtec	10	Minimally sedating
Fexofenadine	Allegra	180	
Loratadine	Claritin	10	
Desloratadine	Clarinex	5	

another. They should be taken regularly for best disease control, although some patients prefer to take antihistamines shortly before periods when they anticipate exacerbations of physical urticaria.

It is becoming common practice in Europe to exceed the licensed dose in severely affected patients. Additional benefit after achieving full blockade of cutaneous H₁ receptors may occur from stabilizing mast cells, inhibitory effects on adhesion molecule expression, and eosinophil chemotaxis.^{42,43} Clinically important drug interactions involving antihistamines are rare since the worldwide withdrawal of terfenadine and astemizole, although concurrent use of hepatic cytochrome inhibitors and drugs known to prolong the QT interval, such as class I and III antiarrhythmics, should be avoided with mizolastine (available in Europe but not the United States). The use of antihistamines in pregnancy and childhood should be guided by current information from the manufacturers. If possible, it is best to avoid all antihistamines in pregnancy, especially during the first trimester, although none has been shown to be teratogenic in humans. If an antihistamine must be prescribed during pregnancy, the consensus is that chlorpheniramine is among the safest. It is nonmutagenic.⁴⁴

Addition of a sedating antihistamine at night, such as chlorpheniramine, hydroxyzine, or diphenhydramine, can be helpful when sleep is disturbed by itching that occurs predominantly in the evening and at night.²³ The use of a sedating antihistamine as monotherapy for chronic urticaria is less desirable because of impairment of cognitive function, including driving performance⁴⁵ and concentration. The tricyclic antidepressant doxepin has potent antihistaminic effects but should not be taken with cimetidine, which can cause clinically significant fluctuations in drug levels through an action on the hepatic cytochrome P-450 enzyme pathway. Neither should it be taken with sympathomimetics (including epinephrine). Combining H₁ and H₂ receptor antagonists has a sound theoretic basis because cutaneous H₂ receptors influence vasodilation and vasopermeability but not itch or flare.⁴⁶ Double-blinded studies of chlorpheniramine with cimetidine⁴⁷ and terfenadine with ranitidine⁴⁸ have demonstrated a small benefit for chronic "idiopathic" urticaria although, in practice, such combinations can prove clinically unimpressive.

Second-line drug therapies

Oral corticosteroids may occasionally be required in short reducing courses for severe exacerbations of chronic urticaria that have not responded to full-dose antihistamines. Delayed pressure urticaria and urticarial vasculitis respond poorly, if at all, to antihistamines. Oral corticosteroids may be justifiable for severe disease, although fairly high doses (≥ 30 mg prednisolone daily) may be required. Long-term administration of corticosteroids should be avoided

if possible by introducing steroid-sparing therapies (see "Other interventions"), although the evidence for their use is often limited to small uncontrolled studies or anecdotal reports. Low-dose alternate-day corticosteroids may be appropriate when applied carefully.⁴⁹

Epinephrine aerosol inhalers directed onto the affected mucosa may offer limited benefit for angioedema of the lips and mouth. Intramuscular epinephrine may have to be used rarely for laryngeal edema accompanying exacerbations of chronic urticaria, although it is not considered to be effective for hereditary angioedema.

Other interventions. Numerous other therapies have been reported for antihistamine-unresponsive chronic urticaria, although the quality of evidence for the intervention is often poor because of the small numbers studied. It is sometimes possible to target a specific subgroup of urticaria with a novel approach after first- and second-line therapies have failed. For instance, thyroxine has been used in euthyroid patients with positive thyroid autoantibodies,⁵⁰ *H pylori* eradication therapies in chronic urticaria,⁵¹ nifedipine for chronic urticaria,⁵² sulfasalazine in delayed pressure urticaria,⁵³ and leukotriene receptor antagonists in aspirin-sensitive urticaria.⁵⁴ Colchicine,⁵⁵ hydroxychloroquine,⁵⁶ dapsone,⁵⁷ and indomethacin⁵⁸ have been used, apparently successfully, in urticarial vasculitis.

Third-line (immunosuppressive) therapies

Immunosuppressive therapy is becoming a realistic option in some patients in whom chronic urticaria proves to have an autoimmune basis but only when the disease is pursuing a severe disabling and recalcitrant course. With the exception of cyclosporine, evidence from randomized controlled studies is still lacking. An open study of plasmapheresis for 8 patients with severe chronic autoimmune urticaria showed benefit in 6.⁵⁹ Two of the patients had complete clearing for 3 to 8 weeks but relapsed as serum histamine-releasing activity recovered. Intravenous immunoglobulin (2 g over 5 days) was beneficial for 9 of 10 patients with severe autoimmune urticaria.⁶⁰ Two were still clear after 3 years. Several studies of cyclosporine have shown benefit at doses ranging between 2.5 and 5 mg/kg per day.⁶¹⁻⁶⁴ In our own randomized study cyclosporine at 4 mg/kg per day for 4 weeks was superior to placebo.⁶⁵ The overall number of responding patients who received randomized and/or open-label cyclosporine for up to 8 weeks was 65%. Twenty-six percent of the responders were still clear 6 months after starting therapy. Posttreatment serum histamine-releasing activity fell significantly in this study, but there may be other explanations for the very rapid improvement in itch

and wheal numbers (within 36 hours) seen in some patients, such as inhibition of histamine release from cutaneous mast cells.⁶⁶ It is possible that other immunosuppressive therapies, such as azathioprine, methotrexate, or mycophenolate mofetil, may be useful for autoimmune urticaria. Protocols need to be developed to define optimal treatment regimens.

Future treatment modalities

Epitope mapping of the α -chain of the high-affinity IgE receptor should lead to development of structure-based peptides, which could be humanized and used for selective immunotherapy in autoimmune urticaria. Other therapeutic options might include DNA plasmid vaccination to induce tolerance to the α -chain. Trials of recently developed therapeutic antibodies, such as humanized monoclonal anti-IgE, anti-TNF- α , and anti-IL-5 could be considered.

We thank Mr David Francis for reviewing the manuscript.

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Answers to CME examination

Identification N. 802-105

May 2002 issue of the Journal of the American Academy of Dermatology

Questions 1-30, Grattan CEH, Sabroe RA, Greaves MW. *J Am Acad Dermatol* 2002;46:645-57.

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|------|-------|-------|-------|
| 1. c | 9. a | 17. e | 25. b |
| 2. b | 10. b | 18. b | 26. e |
| 3. d | 11. e | 19. e | 27. a |
| 4. c | 12. a | 20. a | 28. c |
| 5. c | 13. d | 21. c | 29. b |
| 6. e | 14. d | 22. b | 30. c |
| 7. d | 15. c | 23. c | |
| 8. b | 16. c | 24. b | |

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CME examination

Identification No. 802-105

Instructions for Category I CME credit appear in the front advertising section. See last page of Contents for page number.

Questions 1-30, Grattan CEH, Sabroe RA, Greaves MW. *J Am Acad Dermatol* 2002;46:645-57.

Directions for questions 1-30: Give single best response.

1. What defines urticaria as being chronic?
 - a. Being associated with angioedema
 - b. Having an obvious cause
 - c. Duration of at least 6 weeks of continuous activity
 - d. Association with systemic symptoms
 - e. Occurrence of at least 3 separate episodes
2. A 25-year-old woman presents with almost daily wheals lasting from 3 to 12 hours for 3 months, which started after antibiotic treatment of a urinary tract infection. Which of the following is the most likely diagnosis?
 - a. Urticarial drug eruption
 - b. Chronic ordinary urticaria
 - c. Symptomatic dermatographism
 - d. Urticarial vasculitis
 - e. Acute urticaria
3. In a 20-year-old patient working at a delicatessen counter, widespread urticaria with fainting develops within minutes of food being collected for display from cold storage. Which of the following is the most likely diagnosis?
 - a. Allergic urticaria
 - b. Contact urticaria
 - c. Symptomatic dermatographism
 - d. Cold urticaria
 - e. Cholinergic urticaria
4. Urticarial wheals characteristically
 - a. affect the mouth and other mucous membranes
 - b. have a circular outline
 - c. itch rather than burn
 - d. burn rather than itch
 - e. are deep and poorly defined
5. Angioedema characteristically
 - a. never affects the larynx
 - b. is confined to the throat
 - c. may affect any part of the skin
 - d. presents with itchy red swellings
 - e. is a cause of expiratory wheeze
6. Which of the following is a feature of cold urticaria?
 - a. Wheals may occur anywhere except the head and neck.
 - b. Wheals burn rather than itch.
 - c. Wheals typically last more than 2 hours.
 - d. Angioedema does not occur if wheals are present.
 - e. There is a risk of anaphylaxis.
7. Which of the following exposures is most likely to aggravate chronic idiopathic urticaria?
 - a. Dietary intake of nitrites
 - b. Skin contact with latex
 - c. Retained soap powder in washing
 - d. Aspirin
 - e. Acetaminophen
8. Which of the following features is typical of chronic ordinary urticaria?
 - a. Bruising within wheals
 - b. Wheal duration of 2 to 24 hours
 - c. Angioedema without wheals
 - d. Wheals at least 2 cm in diameter
 - e. Pyrexia
9. Which of the following clinical features suggests a diagnosis of delayed pressure urticaria?
 - a. Urticaria on the palms and soles
 - b. Wheals arising within minutes of pressure
 - c. Linear wheals after scratching
 - d. A good response to antihistamines
 - e. Angioedema of the tongue
10. Which of the following clinical features would be most typical of cholinergic urticaria?
 - a. Occurrence on rewarming of the body after cold exposure
 - b. Occurrence on overheating of the body
 - c. Urticaria initiated by a heavy food load
 - d. Urticaria initiated by alcohol
 - e. A good response to β -blockers
11. A patient presents with a 6-month history of daily wheals. Which of the following systemic symptoms would be most typical of urticarial vasculitis?
 - a. Dyspepsia
 - b. Malaise
 - c. Headache

- d. Transient abdominal colic
 - e. Joint pain
12. Which of the following is the most frequent cause of chronic ordinary urticaria in a developed country?
- a. Histamine-releasing autoantibodies
 - b. Untreated dental abscesses
 - c. Food allergy
 - d. Natural salicylates in the diet
 - e. Intestinal parasites
13. Which of the following conditions is most likely to be associated with chronic ordinary urticaria?
- a. Multinodular goiter
 - b. Infectious mononucleosis
 - c. Previous *Helicobacter pylori* gastritis
 - d. Autoimmune thyroid disease
 - e. Latent hepatitis C infection
14. Which of the following blood abnormalities is often present in chronic autoimmune urticaria?
- a. Lymphopenia
 - b. Eosinophilia
 - c. Neutropenia
 - d. Basopenia
 - e. Monocytosis
15. What proportion of patients with chronic ordinary urticaria has functional autoantibodies that release histamine from basophils or cutaneous mast cells?
- a. 0%
 - b. 1%-25%
 - c. 26%-50%
 - d. 51%-75%
 - e. 76%-100%
16. Which of the following investigations is most likely to confirm suspected urticarial vasculitis?
- a. Antineutrophil cytoplasmic antibodies
 - b. Erythrocyte sedimentation rate
 - c. Lesional skin biopsy
 - d. C4 component of complement in serum
 - e. C1-esterase inhibitor assay
17. Which of the following histologic features of a lesional skin biopsy specimen characterizes chronic autoimmune urticaria?
- a. Leukocytoclasia
 - b. Endothelial cell disruption
 - c. Lymphocytic vasculitis
 - d. Eosinophils
 - e. None of these
18. The autologous serum skin test response in urticaria
- a. is a definitive test for an autoimmune subset of ordinary urticaria
 - b. is reduced by taking antihistamines
 - c. was first described in the 1960s
 - d. is positive in physical urticaria
 - e. involves the passive transfer of serum from a patient to a healthy volunteer
19. Which of the following tests is most specific for detecting functional autoantibodies in patients with chronic autoimmune urticaria?
- a. Western blot
 - b. Enzyme-linked immunosorbent assay
 - c. HLA phenotyping
 - d. Flow cytometry for CD4⁺ cells in peripheral blood
 - e. Basophil histamine release assay
20. What is the most likely laboratory finding in essential cold urticaria?
- a. No abnormality
 - b. Cold agglutinins
 - c. Cryoglobulins
 - d. Positive Paul-Bunnell
 - e. Positive hepatitis B surface antigen
21. The most characteristic laboratory abnormality of Schnitzler's syndrome is
- a. hypergammaglobulinemia
 - b. reduced renal function
 - c. IgM paraproteinemia
 - d. positive antinuclear factor
 - e. thyroid autoantibodies
22. Which feature of urticarial vasculitis is the most likely to indicate a poor prognosis?
- a. Arthralgia
 - b. Hypocomplementemia
 - c. Raised erythrocyte sedimentation rate at presentation
 - d. Headaches
 - e. Lack of response to antihistamines
23. If antihistamines are taken as the sole treatment for chronic urticaria, the proportion of patients expected to benefit would be about
- a. 0%-10%
 - b. 20%-30%
 - c. 50%-60%
 - d. 80%-90%
 - e. 100%
24. The addition of an H₂ antagonist to an H₁ antagonist for the management of chronic urticaria might
- a. help itch but not wheal numbers or severity
 - b. reduce wheal numbers and severity but not itch
 - c. stabilize mast cells
 - d. discourage the development of tolerance to the H₁ antagonist
 - e. lead to better enteral absorption of the H₁ antagonist
25. Which of the following drug combinations for chronic urticaria would be inadvisable?
- a. Fexofenadine with ranitidine
 - b. Doxepin with cimetidine
 - c. Loratadine with prednisolone
 - d. Cyclosporine with cetirizine
 - e. Chlorpheniramine with cimetidine

26. Which of the following antihypertensive medications should usually be avoided in chronic ordinary urticaria with angioedema?
- Calcium channel blockers
 - Thiazide diuretics
 - Loop diuretics
 - Cardioselective β -blockers
 - Angiotensin-converting enzyme inhibitors
27. If oral analgesics must be used for mild to moderate pain in chronic urticaria, which of the following should be preferred?
- Acetaminophen
 - Codeine
 - Diclofenac
 - Ibuprofen
 - Aspirin
28. For which of the following situations would intramuscular epinephrine be most appropriate?
- Severe whealing on the trunk
 - Angioedema of the lips
 - Collapse because of cold urticaria
 - Angioedema of the eyelids
 - Painful delayed pressure urticaria of the foot
29. In which form of physical urticaria are systemic steroids often necessary for control of disabling symptoms?
- Cold urticaria
 - Delayed pressure urticaria
 - Vibratory angioedema
 - Cholinergic urticaria
 - Symptomatic dermographism
30. Which of the following therapies has been confirmed to be effective by double-blind randomized controlled study for autoimmune chronic urticaria?
- Doxepin
 - Plasmapheresis
 - Cyclosporine
 - Intravenous immunoglobulins
 - Leukotriene receptor antagonists

AMERICAN BOARD OF DERMATOLOGY EXAMINATION DATES

In 2002, the Certifying Examination of the American Board of Dermatopathology (ABD) will be held at the Holiday Inn O'Hare International in Rosemont, Illinois on Oct 13 and 14, 2002.

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A certification process is being developed for the subspecialty of Pediatric Dermatology. The first examination will be administered in 2004. Further details about the examination will be available from the Board office early in 2003.

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