

Urticaria and Angioedema

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can persist for years to decades. The causes of urticaria and angioedema are varied and may be immunologic, nonimmunologic, or idiopathic. This article reviews the literature and provides primary care physicians with up-to-date information of the epidemiology, basic pathophysiology, diagnosis, and management of this common and often debilitating condition. Additionally, clinical manifestations of acute and chronic urticaria, hereditary and acquired angioedema, as well as the physical urticarias will be discussed. *Mt Sinai J Med* 78:784–802, 2011. © 2011 Mount Sinai School of Medicine

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Urticaria and angioedema frequently occur together. The appearance of pruritic, erythematous, cutaneous elevations that blanch with pressure, indicating the presence of dilated blood vessels and edema, is characteristic of urticaria. Angioedema is caused by similar pathologic alterations but occurs in the dermis and subcutaneous tissue. Thus, an area involved with angioedema has swelling as the prominent manifestation and the appearance of the skin itself may be normal. Because angioedema occurs in deeper skin layers where there are fewer mast cells and sensory nerve endings, the lesions are nonpruritic and may be associated with pain or burning. Urticaria may occur anywhere on the body, whereas angioedema

ABSTRACT

Urticaria and angioedema are common disorders that can severely impair the quality of a patient's life and can be extremely difficult to treat. Symptoms

Because angioedema occurs in deeper skin layers where there are fewer mast cells and sensory nerve endings, the lesions are nonpruritic and may be associated with pain or burning.

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frequently involves the face, tongue, genitalia, or extremities. Angioedema does not usually occur in dependent areas and is often asymmetric in distribution. Primary care physicians frequently encounter

patients with urticaria, occasionally with angioedema and sometimes with angioedema alone. Differential diagnosis and treatment can be challenging for physician and patient alike.

EPIDEMIOLOGY

Urticaria has significant morbidity and involves heavy use of healthcare services. Acute urticaria is extremely common, affecting up to 10%–20% of the population; 0.1–1% of these patients have chronic urticaria. An estimated 50% of chronic urticaria is autoimmune in nature.^{1,2} One study in Spain describes the percentage of urticaria/angioedema patients with work absences as higher than all allergy sufferers.³

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DEFINITION

Urticaria is characterized by pruritic, evanescent, erythematous papules and plaques with central swelling of various sizes (with or without surrounding erythema) and well-defined borders. The skin returns to normal appearance usually within 1–24 hours. Individual lesions can range in size from <1 cm in diameter to affecting an entire anatomical region without leaving residual hypo- or hyperpigmentation, or residual ecchymosis.

Angioedema is defined as an abrupt swelling of the lower dermis and subcutaneous tissue, with occasional pain rather than pruritus, commonly involving the mucous membranes, with skin returning to normal appearance, usually within 72 hours. Acute urticaria and angioedema are defined by their duration (<6 weeks) compared with chronic urticaria and angioedema.⁴ The most common identifiable causes of acute urticaria are infections, medications, foods, and insect-bite reactions.⁵ Chronic urticaria is an umbrella term encompassing physical urticarias, chronic idiopathic urticaria, and urticarial vasculitis. It is important to distinguish physical urticarias, as treatment differs from idiopathic chronic urticaria or urticarial vasculitis. Table 1 summarizes the classification of urticaria and angioedema.

Table 1. *Characterization of Urticaria and Angioedema.*

Spontaneous urticaria
Acute urticaria
Chronic urticaria
Physical urticaria
Cold contact urticaria
Delayed pressure urticaria
Heat contact urticaria
Solar urticaria
Dermographia
Vibratory urticaria/angioedema
Other urticaria types
Aquagenic
Cholinergic
Contact urticaria
Urticarial vasculitis
Angioedema
Allergic(IgE-mediated mast cell/basophil degranulation)
Nonallergic (mast cell/basophil degranulation)
Bradykinin mediated
Leukotriene mediated
Unclear (idiopathic, etc.)

Abbreviations: IgE, immunoglobulin E.
Adopted from Khalaf *et al.*, 2008, and Zuberbier *et al.*, 2009.^{122,123}

ACUTE URTICARIA

Acute urticaria is most commonly caused by infections, medications, or foods. It is commonly self-limited. When caused by drug allergies, urticaria may appear minutes to days after drug administration. Later reactions, typically starting 7–14 days after the drug exposure, are more likely manifestations of serum sickness associated with fever, lymphadenopathy, morbilliform or urticarial eruptions, angioedema, and arthralgias that can last up to 7 weeks. Among antibiotics, β -lactams are the most common cause of acute urticaria. Other medications that commonly cause urticaria or angioedema include analgesics, radiocontrast media, sedatives, sulfonamides, and diuretics; however, all medications can potentially cause urticaria or angioedema. Once the drug is eliminated, the urticaria gradually resolves. No standard testing (with the exception of penicillin) exists to diagnose drug-induced urticaria or angioedema. Thus, elimination is the best method to determine the causative agent. Once symptoms resolve, medications are reintroduced one at a time over a course of several weeks, with the assistance of an allergy specialist, to determine the etiologic agent. If the medication is absolutely necessary, an alternative class should be sought.⁶

Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause episodic urticaria; however, this is thought to be nonimmunologic. Nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthetase

via acetylation.⁷ Patients who are aspirin-sensitive commonly do not tolerate other NSAIDs.

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Food allergy can cause acute urticaria or angioedema. Percutaneous skin testing is routinely performed to evaluate food allergies. Because intradermal skin testing to food has been shown to cause a high percentage of false-positive reactions, it is not used. Percutaneous skin tests to foods have a good

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Percutaneous skin tests to foods have a good negative predictive value. Skin testing (or in vitro test for specific immunoglobulin E) is exceedingly helpful for uncovering the etiology of acute urticaria to foods, venom, and medications. However, there must be a strong correlation between the clinical history and a positive skin test before food avoidance is considered.

negative predictive value. Skin testing (or in vitro test for specific immunoglobulin E [IgE]) is exceedingly helpful for uncovering the etiology of acute urticaria to foods, venom, and medications. However, there must be a strong correlation between the clinical history and a positive skin test before food avoidance is considered. The food allergy should be confirmed

with monitored oral food challenge if there is no contraindication. The involvement of an allergist who is experienced with food allergy is invaluable in these situations. However, skin testing for aeroallergens and foods has no role in chronic urticaria.⁸

Infectious diseases may manifest as acute urticaria. This is especially true in viral illnesses, such as upper respiratory infections, hepatitis, or infectious mononucleosis. Urticaria is associated with parasitic infections that accompany eosinophilia.

ANGIOEDEMA

Acute Angioedema

Localized, sudden, transient, and often recurrent swelling of the skin, subcutaneous tissues, or submucosa that usually resolves within 72 hours, occurring for <6 weeks, is referred to as acute angioedema. It results from interstitial edema from mediators affecting capillary and venule permeability. Lesions tend to be large, asymmetric, pale, nonpruritic, painful, or burning in nature, and occur anywhere on the body, but more frequently in highly vascular areas (lips, oropharynx, and periorbital regions). Fifty to sixty percent of cases are accompanied by urticaria.⁹ The main causes of angioedema without urticaria are idiopathic, complement C1 esterase inhibitor deficiency (hereditary and acquired) factor XII mutation, external agents (foods, drugs, or environmental allergen), and angiotensin-converting enzyme inhibitor medications.¹⁰ Aspirin and other NSAIDs may produce angioedema because of their blockade of cyclooxygenase, increasing leukotriene production.¹¹

Allergic Angioedema

Allergic angioedema (IgE-mediated) is diagnosed when history suggests a relationship between the onset of swelling and exposure to allergens including stinging insects, foods, latex, medications, or aeroallergens. Angioedema commonly is associated with anaphylaxis.¹²

Angiotensin-Converting Enzyme Inhibitor–Induced Angioedema

Angioedema can occur second to therapy with ACE inhibitors. This can occur anytime from days to years after initiation of this medication group.¹³ Black Americans have an incidence of ACE inhibitor–induced angioedema that is 4×–5×

higher than that of white Americans. Other risk factors include cigarette smoking, female gender, and atopy.^{14–16}

Differential Diagnosis

Several conditions may cause swelling and are mistakenly labeled as angioedema. Patients with right ventricular heart, renal, or hepatic failure may develop dependent edema that can on occasion be misinterpreted as angioedema. A central obstruction of the superior vena cava can result in upper extremity edema when supine or prone that resolves with change in position.^{12,17} Some infections can also present with swelling, including parasitic infections or cellulitis, but these are generally associated with fevers and erythema (some parasitic infections such as gnathostomiasis do not cause fever). Infiltrating disorders such as hyperthyroidism with proptosis or hypothyroidism with myxedema resulting from accumulation of mucin within the dermis, as well as macroglossia in systemic amyloidosis, can all mistakenly be diagnosed as angioedema. Melkersson-Rosenthal syndrome is characterized by persistent swelling of the lips from noncaseating granulomatous infiltration. It is associated with orofacial edema, facial nerve palsy, and a fissured tongue.^{12,18}

Hereditary Angioedema

Hereditary angioedema (HAE) is a rare disorder with 3 known forms (types I, II, and III). Types I and II demonstrate quantitative and/or functional C1 esterase inhibitor (C1-INH) deficiency and are transmitted in an autosomal dominant fashion. Type III has normal complement levels and may be caused by mutations in the factor XII gene.^{19,20} C1 esterase inhibitor regulates vascular permeability and inhibits components of the complement (C1r and C1s), contact (factor XII and kallikrein), coagulation (factor XI and thrombin), and fibrinolytic (tissue-type plasminogen activator and fibrinolysin) systems, and thus regulates the generation of bradykinin.^{19,21} Bradykinin, a nonapeptide hormone, dilates peripheral blood vessels and increases capillary permeability. The regulation of bradykinin is crucial in halting the development and progression of angioedema.²² Type I HAE is characterized by impaired synthesis of active C1-INH with increased turnover, and has inadequate plasma concentrations of C1-INH. Type II HAE has dysfunctional C1-INH with normal quantity.^{19,23} The different types of HAE are phenotypically similar.

Hereditary angioedema patients have sporadic attacks of swelling involving any part of the body,

including visceral involvement. Swelling is not life-threatening unless the airway is involved, leading to asphyxiation and death. Visceral involvement causes severe nausea, vomiting, and/or diarrhea with severe pain, and undiagnosed patients often endure unnecessary abdominal surgery because of their clinical symptoms.²⁴ The angioedema is not associated with urticaria. Attacks can last 1–3 days, and are self-limited; but a large amount of variability exists, with some attacks lasting up to 9 days.²⁴ Triggering events may include stress, infection, trauma or pressure, or attacks may occur spontaneously, but they are often preceded by a prodrome of tingling or an erythematous, nonpruritic, serpentine rash (erythema marginatum). The disease most frequently manifests in childhood but can begin at any age. Serum levels of C4 are almost always low, and may be undetectable during an attack. If low levels of C4 are detected, both functional and quantitative C1-INH levels should be sought because low levels will confirm the diagnosis. Eighty-five percent of patients have low levels of C1-INH (Type 1) and 15% of patients have normal or elevated levels of a poorly functioning protein (Type 2).²⁴

Therapy is divided into chronic long-term therapy, short-term prophylactic therapy, and treatment of acute attacks. Nanofiltered human C1-INH was recently approved by the US Food and Drug Administration and is indicated for routine prophylaxis against angioedema attacks in adolescents and adult patients with HAE. Attenuated androgens, such as danazol, have been widely evaluated in chronic long-term therapy for HAE. The mechanism of action for these medications involves increased synthesis of C1-INH by the liver. Side effects include virilization, headaches, liver damage, and dyslipidemia.²⁴ Epsilon aminocaproic acid (EACA) has also been reported to be effective therapy in HAE.^{25,26} It is thought that plasmin acting on C2 may generate peptides stimulating angioedema; therefore, utilizing a plasmin inhibitor may prevent the generation of these peptides.²⁷ Tranexamic acid has also been used for prophylaxis in this disease, but is not approved for use in the United States.²⁸

Short-term prophylaxis may be indicated prior to dental procedures or in motor vehicle accidents if the attack has not begun. This would be performed with fresh frozen plasma (usually 2 units prior to a surgery to prevent attacks). It is thought that fresh frozen plasma replaces the C1 inhibitor that is missing. Of note, high-molecular-weight kininogen found in the fresh frozen plasma has the potential to exacerbate an ongoing attack, thus this therapy should be given in advance of symptom onset.²⁴ There are case reports of patients with HAE who

have had successful short-term prophylaxis with intravenous C1-INH and icatibant.^{29,30} A recent report from the Seventh International C1-INH Deficiency Workshop revealed that preprocedural nanofiltered C1-INH protein prevents angioedema in all but 2% of adult and pediatric cases involved.³¹

Kallikrein inhibitors (ecallantide) or recombinant C1-INH are presently available for HAE attack therapy. Ecallantide is a plasma kallikrein inhibitor developed for the treatment of acute HAE attacks.³² Treatment with purified C1-INH effectively aborts episodes of swelling acutely.¹⁹ Icatibant, which is in phase III US clinical trials, is a selective bradykinin B2 receptor antagonist with an affinity for the B2 receptor that inhibits bradykinin-induced vasodilatation in humans.³³ Also in clinical trials is a recombinant C1-INH that is purified from the milk of transgenic rabbits.

Acquired Angioedema

Acquired angioedema (AAE) is associated with C1-INH deficiency. The exact mechanism has not been fully elucidated; however, production of bradykinin plays a crucial role in the attacks of angioedema. A recent review of the literature found 146 reported cases of AAE.³⁴ Functional C1-INH levels can range from undetectable to 30% of normal.^{34,35}

Acquired angioedema can be associated with increased catabolism of C1-INH protein and with anti-C1-INH autoantibodies. Patients with lymphoma, connective tissue disorders, cryoglobulinemia, or carcinoma may have depressed C1-INH levels. Diagnosis is confirmed via low C4 and low C1-INH quantitative and qualitative values. Consumption of C1q by immune complexes yields a low C1q level, which distinguishes this condition from HAE. Therapy includes treatment of the associated diseases and prevention or reversal of the angioedema. Treatment of the underlying disease can induce clinical remission of angioedema symptoms. Attenuated androgens and antifibrinolytic therapy have been shown to have efficacy in AAE.³⁶ Reports of therapy with fresh frozen plasma, as well as with replacement C1-INH, icatibant, or ecallantide are limited; however, most patients treated for acute attacks appear to be responsive.^{36–39}

Idiopathic Angioedema

Idiopathic angioedema consists of recurrent angioedema without urticaria, when no exogenous agent or underlying abnormality is found. The swelling can

affect lips, tongue, pharynx, cheeks, eyes, extremities, or genitalia; however, the airway is not typically affected. Therapy is usually high-dose antihistamines and corticosteroids.

PHYSICAL URTICARIAS

Physically induced urticarias are a unique subgroup of chronic urticaria in which patients develop urticaria in response to environmental stimuli. Common triggers include exercise, temperature changes, cold, heat, pressure, sunlight, vibration, and water. Systemic symptoms have occurred during severe episodes. Physical urticarias are responsible for 20%–30% of all cases of chronic urticaria. With the exception of delayed pressure urticaria, lesions last <2 hours and appear in the site of the stimuli. History may suggest a physical stimulus, such as trauma, pressure, exercise, cold, heat, and water-induced lesions. Biopsy is not required for the diagnosis, but when performed it may support or rule out other diagnoses.

Dermatographism

Dermatographism (also referred to as dermographism or urticaria factitia) literally means “to write on the skin.” Patients with this condition develop the rapid onset of a cutaneous wheal and flare after experiencing skin pressure. It is the most common of the physical urticarias and is often an incidental finding in the evaluation of other skin conditions, most commonly atopic dermatitis, chronic idiopathic urticaria, and the other physical urticarias. Dermatographism is elicited by stroking the skin, causing a characteristic symptomatic urticarial lesion within 15 minutes. Patients with dermatographism can be diagnosed in an office setting by stroking the skin with a firm object, such as a tongue blade. The H1 (nonsedating) antihistamines have been shown to be effective in dermatographism and are the initial drug of choice.

Cholinergic Urticaria

Cholinergic urticaria, or generalized heat urticaria, refers to hives that are precipitated by an increase in core body temperature. Triggers include exercise, strong emotions, and bathing in hot water. It is believed to account for ~5% of all cases of chronic urticaria and ~30% of all cases of physical urticaria. Cholinergic urticaria typically appears as numerous punctate wheals (1–3 mm) surrounded by large flares, which may be associated with a tingling, itching, or burning sensation of the skin. The lesions

typically begin on the trunk and spread distally to involve the face and extremities, although lesions may begin anywhere on the body. The underlying mechanism is unknown but thought to involve an abnormal cutaneous response in the presence of cholinergic agents.⁴⁰ Confirmation is done by provocation testing. Identification and avoidance of known triggers is the mainstay of therapy. Medications that are effective are predominantly oral first- or second-generation antihistamines.⁴¹

Cold Urticaria

Cold urticaria is characterized by the rapid onset of pruritus, erythema, and edema after exposure to cold stimuli. It is usually superficial and rarely associated with angioedema. Symptoms occur while outdoors on a cold day, standing in front of air conditioners, or when holding cold objects. Total body exposure (swimming) can result in massive mediator release, resulting in hypotension. These patients should be counseled to never swim alone. The diagnosis is based on history-taking and the ice cube test,⁴² which entails placing an ice cube on the patient's forearm for 4 minutes. A large hive mimicking the shape of the ice will form (Figure 1). Underlying disease must be evaluated, such as cryoglobulinemia, cold agglutinin disease, cryofibrinogenemia, and paroxysmal cold hemoglobinuria (the Donath-Landsteiner antibody associated with secondary syphilis).⁴³ The disease generally responds to second-generation antihistamines, and there are reports that cyproheptadine (8–16 mg daily in divided doses) is effective.⁴⁴ The use of leukotriene receptor antagonists in cold urticaria remains controversial.^{45,46} Attempts to desensitize patients using ice baths have been

reported; however, highly sensitive patients could have anaphylactoid symptoms.⁴⁷

Delayed Pressure Urticaria

Delayed pressure urticaria involves urticaria spontaneously occurring with a pressure stimulus. Delayed pressure urticarial lesions typically develop 1–12 hours after sustaining pressure to the skin. This form of urticaria may be present in up to 40% of patients with chronic idiopathic urticaria (CIU; see below) and poses a greater burden in quality of life.⁴⁸ Therapy with antihistamines is rarely effective and patients often require corticosteroids.⁴⁹

Solar Urticaria

Solar urticaria is an uncommon condition characterized by development of urticaria within minutes after brief exposure to light. Urticaria only affects sun-exposed areas and resolves within 1–3 hours. Systemic symptoms may occur when large areas of the body are exposed to sunlight. Therapy includes antihistamines, sun avoidance, protective clothing, and sunscreen lotions containing zinc or titanium oxide.⁵⁰

Aquagenic Urticaria

Aquagenic urticaria occurs after contact with water at any temperature. This is very uncommon, and other forms of physical urticaria must be excluded. Diagnosis can be made by applying a compress of water to the skin when all other causes of urticaria have been ruled out.^{51,52}



Fig 1. Ice cube test for cold urticaria.

CHRONIC IDIOPATHIC URTICARIA

Chronic idiopathic urticaria is characterized by episodes of short-lived, recurrent, pruritic wheals that are well circumscribed, raised, and erythematous. Approximately 50% of patients with CIU also experience concurrent angioedema. The duration of the disease varies among individuals, with a mean duration of 3–5 years.⁵³ A small proportion of patients can have CIU for >20 years.⁵⁴ The diagnosis is largely one of exclusion.

At least 2 subgroups of patients with CIU exist. One subgroup has circulating serum immunoglobulin G autoantibodies targeting the high-affinity IgE receptor FCER1 on dermal mast cells and basophils, evoking release of histamine and other mediators,

resulting in urticaria and angioedema. This suggests an autoimmune basis accounting for up to 30%–50% of patients with chronic urticaria, referred to as chronic autoimmune urticaria.⁵⁵ This disease has increased incidence of antithyroid antibodies (antimicrosomal and antithyroglobulin antibodies), and may be associated with Hashimoto thyroiditis.^{56–58} Likewise, hypothyroidism is associated with increased incidence of chronic urticaria. The incidence of antithyroid antibodies in chronic urticaria ranges between 15% and 24%.^{59,60} These patients are often poorly responsive to conventional therapy for urticaria and may have more chronic disease.

The primary medical doctor should be mindful that urticaria may be a manifestation of underlying systemic illness, such as collagen vascular disease or

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carcinoma. Systemic vasculitides may be associated with urticarial vasculitis, diagnosed via skin biopsy. These conditions generally have elevated erythrocyte sedimentation rate (ESR), sometimes with complement activation.

Urticarial Vasculitis

In a small percentage of patients with chronic urticaria, there is an underlying small-vessel vasculitis. Urticarial vasculitis can cause significant morbidity and is often a manifestation of a serious illness. Successful diagnosis and treatment requires careful assessment over time for underlying diseases such as systemic lupus erythematosus, Sjögren syndrome, infections such as hepatitis B and C, Lyme disease, and infectious mononucleosis. Medications including ACE inhibitors, cimetidine, diltiazem, penicillins, sulfonamides, and thiazides, as well as lymphoproliferative diseases such as mixed cryoglobulinemia and immunoglobulin M gammopathy, may be associated with urticarial vasculitis.⁶¹ Most cases are idiopathic.

Urticarial vasculitis is an important diagnosis to make and requires confirmation by biopsy. Histopathology reveals endothelial cell damage, leukocytoclastic vasculitis, and fibrin deposition. Immunofluorescence reveals deposition of Ig and complement. Screening includes serum complement levels; ESR; liver function tests; urinalysis; antinuclear antibody test; antigens for Ro/SSA and La/SSB; hepatitis, *Borrelia*, or Epstein-Barr virus serology; immunoglobulins; protein electrophoresis; and

cryoglobulins based on clinical history. Patients with hypocomplementemic urticarial vasculitis syndrome are more likely to have an associated connective-tissue disease and systemic symptoms than patients with normal complement levels. These patients may also have IgG antibodies to the collagen-like domain of C1q.⁶²

The lesions of urticarial vasculitis typically last 3–7 days and are often painful or burning, leaving residual bruising or hyperpigmentation of the skin. Forty percent of patients with urticarial vasculitis have associated angioedema.⁶³ Patients may have systemic signs including arthralgias, respiratory symptoms, fevers, and abdominal discomfort. Treatment options include dapsone, colchicines, hydroxychloroquine, NSAIDs, systemic corticosteroids, azathioprine, cyclophosphamide, cyclosporine, and anakinra, but should be dictated by the severity of the disease and degree of internal-organ involvement.⁶⁴

PATHOGENESIS

The pathogenesis of urticaria and angioedema involves dermal edema from vascular dilation and leakage of fluid into the skin in response to mast-cell degranulation. Histamine, a preformed mediator, produces a short-lived urticaria. The major noncytotoxic mechanism by which histamine is released requires the combination of an antigen with IgE antibody bound to basophils or tissue mast cells.⁶⁵ However, the spectrum and pattern of urticaria and angioedema indicate that other molecules contribute to this disease. A variety of mediators with vasoactive properties are released. Histamine is released from preformed granules as a consequence of this antigen-antibody reaction and is capable of eliciting the classic triple response consisting of vasodilation (erythema), increased vascular permeability (edema), and an axon reflex that increases the extent of the reaction, particularly the erythema. The axon reflex appears to result from the release of substance P from nonadrenergic, noncholinergic type C cutaneous fibers by antidromic conduction. Substance P acts as a potent vasodilator and stimulates cutaneous mast cells to release histamine and thereby augments the reaction.⁶⁶

Additionally, various lipid-derived vasoactive factors are liberated. Of the arachidonic acid metabolites, prostaglandin D₂ is a vasodilator, and leukotrienes C and D (previously called “slow-reacting substance of anaphylaxis”) can increase vascular permeability; these may be synergistic in the skin. Almost any stimulus causing cutaneous mast-cell degranulation would cause the release of

each of these chemicals. Platelet-activating factor is also released from mast cells. It is a lipid metabolite that can increase vascular permeability when injected directly into skin. Platelet-activating factor is released during challenge of patients with cold urticaria, but it has not been examined in other types of urticaria or angioedema.⁶⁷

A second pathway leading to the noncytotoxic release of histamine from basophils or mast cells involves the complement cascade. Three fragments of complement components, termed C3a, C4a, and C5a, act as anaphylatoxins. They interact directly with the cell surface in the absence of antibody to trigger histamine release. C5a acts as a chemotactic factor and can attract neutrophils, eosinophils, or mononuclear cells to a site of inflammation, whereas C3a has selective chemotactic activity for eosinophils.⁶⁸

Hageman factor (HF, factor XII) autoactivates when binding to initiating surfaces. Activated Hageman factor (HFa) digests surface-bound Hageman factor, which then initiates coagulation and fibrinolysis, and converts prekallikrein to kallikrein.⁶⁹ Kallikrein goes on to digest high-molecular-weight kininogen, yielding bradykinin, a potent vasoactive peptide. Bradykinin then causes vasodilation and increased vascular permeability.

The major causes of urticaria and angioedema include drug reactions, foods, contact with antigens, transfusion reactions, infections, insects, collagen vascular disease, malignancy, physical urticarias, mastocytosis, chronic autoimmune urticaria and angioedema, chronic idiopathic urticaria and angioedema, and idiopathic angioedema (Table 1).

Recent studies elucidate the role of the tissue factor pathway of blood coagulation in patients with chronic urticaria and angioedema. This suggests that the extrinsic pathway of the coagulation cascade is activated in chronic urticaria and may lead to thrombin generation.⁷⁰ Elevated plasma levels of prothrombin fragment F₁₊₂ have been detected in chronic urticaria patients, thought to be the result of the activation of the tissue factor pathway of the coagulation cascade. Studies have shown elevated fragment F₁₊₂ and D-dimer plasma levels in patients with severe exacerbations of chronic urticaria, suggesting that the coagulation cascade may be activated, up to the production of fibrin, as a result of the generation of thrombin.⁷¹ Additionally, increased markers of inflammation, such as matrix metalloproteinase-9 and C-reactive protein, have been found in increased amounts in plasma of patients with chronic urticaria, correlating with clinical severity. This suggests that there is an ongoing inflammatory process independent of circulating histamine-releasing factors.⁷²

APPROACH TO THE PATIENT

The diagnostic evaluation of urticaria and angioedema includes a comprehensive and detailed history and physical examination, supplemented with limited laboratory testing. History should detail exposure to drugs, foods, physical triggers, infection (especially viral hepatitis), occupational exposures, and insect stings or bites. Tests that may be indicated include a

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complete blood count with differential, urinalysis, ESR, liver function tests, antinuclear antibody test, antithyroglobulin and antimicrosomal antibodies, chronic urticaria index, stool for ova and parasites (in patients with marked eosinophilia), skin testing (for acute urticaria/angioedema with possible food or venom triggers), and skin biopsy with immunofluorescence when indicated. The Chronic Urticaria Index (IBT Laboratories, Lenexa, KS) is a commercially available, though unvalidated, in vitro basophil histamine release assay in which a patient's serum is mixed with donor basophils and the released histamine levels are measured through a quantitative enzyme immunoassay.¹⁶ A Chronic Urticaria Index value of ≥ 10 indicates that the patient has either an autoimmune basis for their urticaria (antibodies for IgE, FcεRI, or anti-FcεRII) or an alternate histamine-releasing factor.⁷³ Testing should be tailored to the patient's history (Table 2).

DIFFERENTIAL DIAGNOSIS

Many diseases present with erythematous, edematous, pruritic plaques, which can be mistaken for urticaria. Usually these lesions are chronic and may have associated clinical features that aid in differentiating them from urticaria.⁷⁴ Some diseases present with urticaria as one of the cutaneous manifestations but are not acute or chronic urticaria and

Table 2. *Diagnostic Evaluation in Patients With Urticaria and Angioedema.*¹²⁴

Food and drug reactions	Eliminate offending agent; skin test (if possible) and challenge with suspected foods or medications
Collagen vascular disease	Skin biopsy with immunofluorescence; complement levels (C3, C4, CH50)
Malignancy with angioedema	Complement levels; C1 INH levels, C1q
Cold urticaria*	Ice cube test
Solar urticaria*	Exposure to defined wavelength of light, porphyrin levels (red cell protoporphyrin, fecal protoporphyrin, and coproporphyrin)
Dermographism*	Stroking with firm pressure
Pressure urticaria*	Application of pressure for defined time and intensity
Vibratory angioedema*	Vibration with laboratory vortex for 4 minutes
Aquagenic urticaria*	Challenge with tap water at various temperatures
Urticaria pigmentosa	Skin biopsy, test for dermographism
Hereditary angioedema	C4, C2, C1-INH quantitative and qualitative
Idiopathic/autoimmune urticaria	Skin biopsy with immunofluorescence; antithyroglobulin and antimicrosomal antibodies

Abbreviations: C, complement; C1-INH, complement 1 esterase inhibitor.

Adopted from Kaplan AP.¹²⁴

*For a more complete diagnostic evaluation of physical urticaria, please see Magerl *et al.*¹²¹

angioedema. Others manifest with fixed urticarial lesions with features such as lack of itch, duration longer than 24 hours, vesicles or blistering, with an inconsistent histopathologic appearance.

Allergic contact dermatitis may present with urticaria and angioedema and be intermittent, relapsing, or chronic. Patients may exhibit swollen, itchy eyelids. In these patients there is persistent edema, and when the swelling does subside, peeling occurs, which is never seen in CIU. The diagnosis of allergic contact dermatitis is confirmed with patch testing.

Dermatomyositis can present with eyelid edema associated with erythema and telangiectasia, with pruritus. The facial rash may be mistaken for CIU. Dermatomyositis also presents with Gottron's papules and nail-fold telangiectasia in addition to systemic involvement, which is not seen with CIU.

Cryopyrin-mediated autoinflammatory disorders includes familial cold autoinflammatory syndrome, Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous articular syndrome. These are rare autoinflammatory diseases associated with recurrent urticaria. These diseases are caused by

a mutation in the gene encoding for cryopyrin. Common features include nonpruritic, urticarial rash from birth that is persistent, urticarial, and migratory, associated with fever. In familial cold autoinflammatory syndrome and MWS, patients have episodic inflammatory rash, arthralgias and fever, as well as conjunctivitis, sensorineural hearing loss, and secondary amyloidosis (in MWS and chronic infantile neurologic cutaneous articular syndrome). These patients have recurrent episodes consisting of urticarial skin lesions accompanied by fever, arthralgia, arthritis, and malaise.⁷⁵

Schnitzler syndrome is characterized by a chronic urticarial rash, fever, arthralgias or arthritis, bone pain, lymphadenopathy, and IgM gammopathy. Most patients are labeled as having antihistamine-unresponsive chronic idiopathic urticaria. The urticarial lesions can last up to 36 hours and tend to appear in crops, with nonpruritic wheals. Biopsy reveals dermal neutrophilia without vasculitis. Direct immunofluorescence (DIF) is usually negative but may show IgM deposition around blood vessels or along the dermoepidermal junction. Fifteen percent of patients progress to lymphoproliferative disorder.⁷⁶ An IgG autoantibody against interleukin-1 α was found in the sera of patients with Schnitzler syndrome more frequently than in controls.⁶⁵ Sustained response has been achieved with recombinant interleukin-1 receptor antagonist anakinra.⁷⁷

Erythema multiforme minor is often preceded by prodromal symptoms of malaise fever, sore throat, muscle aches, and arthralgia followed by cutaneous responses that are rarely urticarial in nature. Lesions are fixed with a burn or sting sensation. Recurrent erythema multiforme, erythematous, targetoid lesions symmetrically involving the extremities in crops, with swelling and crusting at the mucocutaneous junctions, can also be mistaken for CIU. The lesions leave residual pigmentation and desquamation. A skin biopsy reveals mononuclear cell interface dermatitis with exocytosis of CD8+ cells into the epidermis and satellite-cell necrosis.⁵⁵

Cutaneous lupus erythematosus⁷⁸ is subdivided into 3 distinct patterns: acute cutaneous lupus erythematosus, chronic cutaneous lupus erythematosus,⁷⁸ and subacute cutaneous lupus erythematosus. Of the 3 patterns, the subacute can present with urticarial-like lesions that burn more than itch. The lesions are nonscarring and appear mainly on sun-exposed areas. The lesions last for days to weeks and may have a fine scale at the periphery. Biopsy reveals a sparse dermal infiltrate of mononuclear cells, dermal mucin deposition, and vasculopathy of basal cells. Direct immunofluorescence demonstrates granular deposition of IgG and complement along a thickened

basement membrane zone. Therapy with topical and systemic corticosteroids, immunosuppressives, and antimalarials is effective.⁷⁴

Fixed drug eruptions present initially as red and edematous lesions; however, they almost always blister and leave a residual pigmentation, which is not seen in CIU. Fixed drug eruptions can occur with systemic administration of medications. The lesions occur in the same area with each exposure to the medication. The lesions initially appear as erythematous macules that can become edematous and hyperpigmented. Causative agents include tetracyclines, sulfamethoxazole, barbiturates, NSAIDs, and antihistamines. The lesions persist for days and are nonpruritic. The biopsy reveals a dense infiltrate of CD8+ T lymphocytes with occasional bullae formation. Treatment includes avoiding the offending agent.

Cutaneous mastocytosis is the most common and benign form of mastocytosis. Multiple variants exist, including urticaria pigmentosa, diffuse mastocytosis, and mastocytomas. Urticaria pigmentosa mimics CIU, but may have a reddish-brown or pale color and exhibit Darier sign (ability to elicit urticaria by stroking the lesion). The lesions tend to be 1–2 cm in diameter and spare the face, scalp, palms, and soles. Therapy is aimed at relieving symptoms and includes antihistamines, topical corticosteroids, and phototherapy.⁷⁹

Familial Mediterranean fever has an autosomal-recessive pattern of inheritance with a predilection for Sephardic Jews, Arabs, and Armenians. Most patients present with recurrent, self-limited attacks of fever, tendency to pleurisy, peritonitis, and synovitis. Rash includes a distinctive erysipelas-like lesions on the lower extremities, and rarely urticarial and vasculitis lesions. Nearly 25% of these patients progress to renal amyloidosis, which is commonly fatal. Symptom control may be attained with colchicine.⁸⁰

Sweet syndrome, or acute febrile neutrophilic dermatosis, is classically associated with respiratory or gastrointestinal infection, or after vaccination. It predominantly affects women. The disease is characterized by the acute onset of fever, leukocytosis, and plaques that appear similarly to urticaria but are more persistent, lasting weeks to months, and that heal with scarring. The lesions classically begin as erythematous papules that coalesce to form tender, irregularly shaped urticarial plaques with pronounced edema. Patients may have systemic symptoms as arthralgias, malaise, headache, and myalgia. There is a densely neutrophilic infiltrate in the upper dermis. Treatments consist of systemic steroids, colchicine, dapsone, or cyclosporine.⁷⁴

Bullous pemphigoid is an autoimmune subepidermal blistering disease of older individuals.

Immunoglobulin G autoantibodies are directed against components of hemidesmosome adhesion complexes. Blister formations occur at the base of the epidermis, yielding tense vesicles or blisters. Patients with bullous pemphigoid can rarely present with multiple, erythematous, urticarial plaques without blistering, accompanied by pruritus which can be mistaken as CIU. Biopsy reveals superficial infiltrate of lymphocytes and histiocytes with eosinophils. The DIF reveals immunoreactants (C3 with or without IgG) in a linear pattern at the basement membrane. Majority of patients have indirect immunofluorescence revealing circulating IgG against the basement membrane. Treatment ranges from topical corticosteroids, oral tetracyclines, or niacin to high-dose systemic corticosteroids with immunosuppressive agents like azathioprine, mycophenolate mofetil, methotrexate, or cyclophosphamide.⁸¹

Reticular erythematous mucinosis is a rare disorder affecting middle-aged women that appears as areas of erythema on chest and back, which can mimic urticarial lesions. Cycles of exacerbations and remissions are common, and up to 30% experience pruritus.⁸² Biopsy reveals perivascular and perifollicular mononuclear infiltrate with increased dermal mucin. The DIF is normal. Treatment consists of topical calcineurin antagonists, hydroxychloroquine, and laser therapy.

TREATMENT

Treatment of patients with urticaria involves reducing symptoms with the least-invasive effective therapy.

Treatment of patients with urticaria involves reducing symptoms with the least-invasive effective therapy. Primary measures include identifying and avoiding or eradicating triggers. Nonspecific aggravating factors, such as stress, alcohol, heat (showers/exercise), pressure (tight clothing, bra straps, shoes), anxiety/stress, and medications (NSAIDs) have the potential to worsen urticaria, and should be minimized.

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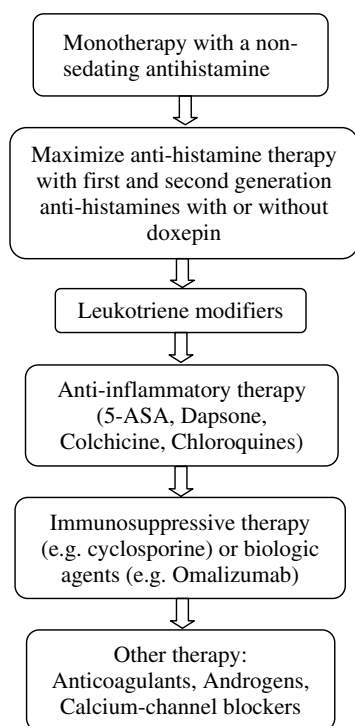


Fig 2. Stepwise therapeutic approach for chronic urticaria. **Abbreviations:** ASA, acetylsalicylic acid (aspirin).

such as stress, alcohol, heat (showers/exercise), pressure (tight clothing, bra straps, shoes), anxiety/stress, and medications (NSAIDs) have the potential to worsen urticaria, and should be minimized. Cooling antipruritic lotions (1% menthol in aqueous cream and calamine lotion) may soothe urticaria. Reassurance and education is also an important intervention.

The mainstay of pharmacologic therapy consists primarily of scheduled use of first- and second-generation H1 antihistamines, or concomitant therapy with H1 and H2 receptor blockers (Figure 2).⁸³ The sedating antihistamines remain useful first-line agents for many patients. Combination of several

The mainstay of pharmacologic therapy consists primarily of scheduled use of first- and second-generation H1 antihistamines, or concomitant therapy with H1 and H2 receptor blockers.

antihistamines and often at higher doses is widely practiced, but may not achieve adequate control in up to 50% of patients with chronic urticaria.⁸⁴ Some nonselective antihistamines have other useful

receptor properties that may extend additional efficacy in certain cases, including doxepin, cyproheptadine, and ketotifen.^{85–88} Management of chronic urticaria can prove to be challenging given its refractory nature. Alternative therapy may include leukotriene receptor antagonists, corticosteroids, and immunomodulatory agents. For patients with an unremitting and extremely severe disease unresponsive to standard therapy, plasmapheresis and immunosuppressive drugs have been successfully attempted.^{85,89}

Nonsedating second-generation antihistamines should be considered as first-line symptomatic treatment for chronic urticaria. These newer-generation antihistamines can be differentiated in terms of their selectivity for the H1-receptor and their ability to cross the blood-brain barrier. These include cetirizine, fexofenadine, loratadine, levocetirizine, and desloratadine. Depending on the different pharmacokinetics and H1 receptor affinity of each drug, different concentrations in skin can be expected. The dosage should be increased up to 4-fold if required before switching to second-line therapies.⁹⁰

Fexofenadine is a nonsedating, long-acting specific peripheral histamine H1 receptor antagonist that has been shown to be effective and safe for the symptomatic relief of CIU. Several double-blind, randomized controlled trials in both adults and children (aged >12 years) support this assertion.^{91–97} The effective dose of fexofenadine is 60 mg twice daily. For children aged 6–11 years, the recommended dose is 30 mg twice daily. The most beneficial once-daily dose of fexofenadine hydrochloride is 180 mg. The clinical efficacy of this dose was examined in a large clinical, placebo-controlled trial in the United States. Patients in the treatment group experienced significantly greater improvements in mean daily number of wheals and pruritus compared with placebo.⁹⁸

Desloratadine is a nonsedating H1 receptor antagonist. The efficacy and safety of 5 mg once daily was evaluated in 190 patients with CIU. Desloratadine was superior to placebo in controlling pruritus and total symptoms after the first dose and maintained throughout the 6 weeks of the study. Measures of sleep, daily activity, and therapeutic response were significantly improved.^{99–101}

Levocetirizine is the active R-isomer of cetirizine and demonstrates twice the affinity for the H1 receptor compared with the parent compound. It has been shown to be more active than currently marketed antihistamines.^{102,103} Two randomized, double-blind and controlled multicenter trials evaluated levocetirizine. The first was a 4-week study comparing efficacy and safety of 2.5 mg, 5 mg, and 10 mg once daily in 258 patients with chronic

urticaria. There was a statistically significant linear dose-response relationship between the 3 dosages, with benefit increasing with increasing dose.¹⁰² The second study compared the efficacy of 5 mg levocetirizine to placebo in 166 patients with chronic urticaria. Levocetirizine was superior to placebo in reducing the mean total symptoms score, the number of daily episodes, and number of wheals, as well as overall severity of symptoms and quality of life.¹⁰⁴

A multicenter, randomized, double-blind study compared levocetirizine 5 mg and desloratadine 5 mg undergoing 4 weeks of therapy in 886 patients with symptomatic CIU. The outcome measure included the pruritus severity score after 1 week of treatment and mean score over 4 weeks, number and size of wheals, mean CIU composite score (sum of scores for pruritus severity and numbers of wheals), quality of life, and satisfaction with treatment. Levocetirizine led to a significantly greater decrease in pruritus severity scores than desloratadine, as well as decreased pruritus duration and mean CIU scores with increased satisfaction.¹⁰⁵

Alternative agents are often required in a subset of patients with chronic urticaria with severe disease who are intolerant to or in whom high-dose combination antihistamines have failed. These include leukotriene modifiers, dapsone, sulfasalazine, hydroxychloroquine, colchicine, calcineurin inhibitors, and mycophenolate. These are classified as second-line agents in a recent review based on criteria including safety, convenience, efficacy, and cost.^{85,89}

Combination therapy with H1 and H2 antihistamines has been studied; however, the evidence is difficult to interpret due to the small sample size, different H1 antihistamine that was evaluated, and the dose of the H2 antihistamine that was employed. A combination of an H1 antihistamine (ciproheptadine) and an H2 antihistamine (cimetidine) was evaluated in 8 patients with chronic urticaria. Fifty percent of the patients responded with $\geq 90\%$ improvement within 10 days. The remaining 50% showed no benefit. Side effects of the medications were minimal.¹⁰⁶

Another review evaluated 40 patients in a double-blind study receiving either chlorpheniramine + cimetidine 400 mg daily (21 patients) or chlorpheniramine + placebo (19 patients) for 8 weeks. Results found a statistically significant difference between the average response in the 2 treatments after 4 and 8 weeks of treatment ($P < 0.05$ and $P < 0.01$, respectively). No significant side effects related to treatment were noted.¹⁰⁷

A double-blind, parallel group study in 16 patients found synergy between H1 and H2 antagonists (hydroxyzine 25 mg or cetirizine 10 mg with cimetidine 600 mg every 12 hours) for 10 days. When hydroxyzine was administered with cimetidine, the partial hydroxyzine area under the curve increased significantly ($P < 0.05$). When hydroxyzine was given with cimetidine, wheal and flare suppression increased compared with when hydroxyzine was given alone, but the differences were not statistically significant ($P > 0.05$). When cetirizine was administered with cimetidine, the pharmacokinetics of cetirizine did not change significantly, and no enhancement of wheal and flare suppression was observed.¹⁰⁸

Leukotrienes play an important role in the pathophysiologic mechanisms of allergic inflammation; thus, leukotriene modifiers montelukast, zafirlukast, and zileutin have been used (monotherapy or in combination with antihistamines) to treat urticaria.

The results of several studies have indicated a positive therapeutic effect of these medications in chronic urticaria, especially the urticaria-angioedema exacerbated by acetylsalicylic acid and by other NSAIDs, cold urticaria, chronic autoimmune urticaria, steroid-dependent urticaria, delayed-pressure urticaria, CIU, and dermatographism, and reveal good safety data compared with other alternative steroid-sparing medications.^{46,109,110} A double-blind, placebo-controlled trial demonstrated superiority of montelukast over cetirizine or placebo in patients with chronic urticaria and acetylsalicylic acid intolerance.¹¹¹

Another randomized, double-blind, placebo-controlled study on patients with chronic urticaria demonstrated that the combination of desloratadine and montelukast was superior, compared with placebo and desloratadine alone.¹¹²

Despite these promising results, one randomized, placebo-controlled trial evaluated 46 patients and found that in comparison with placebo, treatment with zafirlukast resulted in no significant positive effect at a dose of 20 mg b.i.d. in patients with chronic urticaria.¹¹³

Corticosteroids are a widely accepted alternative agent in the treatment of refractory chronic urticaria, regardless of their many adverse side effects. Low-dose oral corticosteroids on a daily or alternate-day schedule are occasionally used for patients who fail antihistamine therapy.¹¹⁴ Steroids should be reserved for patients who fail antihistamines or are more severe in nature. Though effective, steroids do not result in remission or alter the disease course.⁸⁵ The long-term use of oral corticosteroids includes

Table 3. *Alternative Agents for the Treatment of Chronic Urticaria.*

Medication	Onset of Efficacy	Time to Relapse	Likelihood of Remission	Side Effects	Monitoring
Leukotriene modifiers: montelukast, zafirlukast, zileuton	1–7 days	Days	Unlikely	Headache, GI complaints	Zileuton: Baseline LFTs, then monthly for first 3 months, then every 3 months for the first year, then periodically
Sulfones: dapsone	Days to weeks	Days	Yes	Anemia, peripheral neuropathy, rash, GI complaints; less likely: methemoglobinemia, blood dyscrasias, dapsone hypersensitivity syndrome. Contraindications: patients with hemoglobin M or low levels of G6PD or methemoglobin reductase	Baseline G6PD level, renal function, UA, LFTs, CBC Follow-up: CBC 1–2 weeks after initiation, then periodically
5-Aminosalicylic acid: sulfasalazine, olsalazine	Days to weeks	Days	Possible	Dose related. Headache, GI complaints, oligospermia; rare: rash, photosensitivity, proteinuria, cytopenias, cyanosis, hepatotoxicity	Baseline: G6PD, CBC, LFTs, renal function. Follow-up: CBC monthly for 3 months, then periodically
Chloroquines: hydroxychloroquine	1–3 months	Unknown	Uncertain	GI complaints; rare: retinal and other ocular reactions, myopathy. Caution: Children, and patients with porphyria, psoriasis, low levels of G6PD	Baseline: CBC, renal function, LFTs, eye examination if prolonged therapy or high dose. Follow-up: periodic eye examination
Colchicine	Days to 1 month	Days	Uncertain	GI complaints, stomatitis, marrow depression, rash, peripheral neuropathy, alopecia	Baseline: CBC, renal function, LFTs. Follow-up: CBC periodically
Calcineurin inhibitors: cyclosporine, tacrolimus	2 days to weeks	1 day to weeks	Yes	GI complaints, headache, tremor, renal dysfunction, hypertension, hyperlipoproteinemia, hirsutism, gingival hyperplasia, leukopenia, neuropathy; rare: infection and neoplasia (dose-dependent secondary to immune suppression)	Baseline: blood pressure, renal function, electrolytes, lipoproteins, LFTs. Follow-up: Blood pressure, renal function, electrolytes monthly for 3 months, then periodically. Drug level every 3 weeks (cyclosporine <300 µg/mL, tacrolimus <20 µg/mL)
Mycophenolate	Weeks	Unknown	Yes	GI complaints; less likely: leukopenia, anemia, dose-dependent immune suppression–related infections	Baseline: CBC, LFTs. Follow-up: CBC

(continued overleaf)

Table 3. (Continued).

Medication	Onset of Efficacy	Time to Relapse	Likelihood of Remission	Side Effects	Monitoring
Corticosteroids	Days to 1 week	Variable	No	Mood alteration, fat and water weight gain, hypertension, hyperglycemia, hyperlipoproteinemia, cataracts, increased intraocular pressure, headache, GI complaints, dermal atrophy, osteopenia, infections. Caution: Children, preexisting psychiatric disorders, diabetes	Baseline: glucose, mental status examination, blood pressure, lipoproteins. Follow-up: same
Third-line agents Androgens: danazol	1 day to 2 weeks	Days	Possible	Virilization, vasomotor symptoms, weight gain, hypertension, hyperlipoproteinemia, cardiotoxicity; rare: hepatotoxicity, polycythemia, photosensitivity, hemorrhagic cystitis. Caution: females, children, thrombotic complications, porphyria	Baseline: LFTs, lipoproteins, CBC, UA; consider liver and spleen ultrasound. Follow-up: same, every 6 months
Antifolate antimetabolites: methotrexate	Days to 2 weeks	2–3 weeks	Possible	GI complaints, stomatitis, marrow suppression, rash, hepatotoxicity, alopecia, infections. Caution: pregnancy	Baseline: CBC, renal function, LFTs Follow-up: CBC and LFTs monthly, renal function
Immunoglobulin (IVIG)	Days to weeks	Days to months	Yes	Flushing, myalgias, headache, fever, backache, nausea, chest tightness, wheeze; rare: aseptic meningitis, anaphylaxis	Baseline: CBC, LFTs, viral hepatitis panels; consider IgA level
Phototherapy	Days to weeks	Days to months	Yes	Photoaging, cutaneous neoplasia, pruritus, dyspigmentation, nausea, headache, fatigue. Caution: photosensitivity disorder, porphyria, coadministration of methotrexate or hydroxychloroquine	Baseline: skin examination, eye protection. Follow-up: same.
Anticoagulants: warfarin, heparin	Days	Days	Unlikely	Hemorrhagic complications, osteoporosis; rare: skin necrosis, cholesterol embolization, hepatotoxicity, heparin-induced thrombocytopenia. Caution: pregnancy	Baseline: INR for warfarin. Follow-up: same

(continued overleaf)

Table 3. (Continued).

Medication	Onset of Efficacy	Time to Relapse	Likelihood of Remission	Side Effects	Monitoring
Nitrogen mustard (alkylating agents): cyclophosphamide	Months	Unknown	Yes	GI complaints, malaise, alopecia, marrow suppression, stomatitis. Rarely: rash, cystitis, delayed neoplasia, immune deficiency, infertility	Baseline: CBC, renal function, UA, LFTs. Follow-up: CBC, UA. Cumulative dose <50 g
Dihydropyridine CCB: nifedipine	1 week	Days	No	Hypotension, peripheral edema; rare: flushing, lightheadedness, GI complaints	Baseline: blood pressure. Follow-up: same
Gold salts: aurothiomalate	Weeks	Unknown	Maybe	GI complaints, photosensitivity, stomatitis, rash, metallic taste, renal dysfunction, anemia	Baseline: CBC, renal function, UA. Follow-up: CBC, renal function every 1–4 weeks
Plasmapheresis	Days to weeks	Days to months	Maybe	Fatigue, GI complaints, fever, electrolyte disturbances; rare: humoral immune deficiency, anaphylaxis	Baseline: venous access, CBC, electrolytes, LFTs, coagulation parameters. Follow-up: hemodynamics, cardiac monitoring, electrolytes

Abbreviations: CBC, complete blood count; CCB, calcium channel blocker; GI, gastrointestinal; IgA; immunoglobulin A; INR, international normalized ratio; IVIG, intravenous immunoglobulin; LFT, liver function tests; UA, urinalysis. Adopted from Morgan *et al.*^{85,89}

the risk of severe side effects such as bone loss, increased fasting blood sugar, hypertension, adrenal suppression, cataracts, and growth suppression in children.¹¹⁵

Steroids should be reserved for patients who fail antihistamines or are more severe in nature. Though effective, steroids do not result in remission or alter the disease course. The long-term use of oral corticosteroids includes the risk of severe side effects such as bone loss, increased fasting blood sugar, hypertension, adrenal suppression, cataracts, and growth suppression in children.

Additional agents that are less favored included immunosuppressives or “steroid-sparing” therapies classified as third-line agents (androgens, methotrexate, intravenous Ig, phototherapy, anticoagulants, cyclophosphamide, calcium channel blockers, and plasmapheresis) (Tables 3 and 4).

Recent studies evaluate therapy with omalizumab for cold induced urticaria, CIU, chronic autoimmune urticaria, and idiopathic angioedema.^{116–120} Omalizumab is a recombinant humanized monoclonal antibody that selectively binds IgE. Omalizumab inhibits the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils and reduces the number of FcεRI receptors on basophils in atopic patients. It is hypothesized that patients with chronic autoimmune urticaria will express less FcεRI to prevent IgG antibody-mediated cross-linking of adjacent α subunits and thereby prevent cellular activation.¹¹⁷ In a study of 12 patients with chronic autoimmune urticaria refractory to antihistamine therapy, 7 achieved complete remission when treated with omalizumab. Case reports reveal efficacy of omalizumab therapy in cold-induced urticaria. Further randomized, double-blinded, placebo-controlled trials are necessary to assess the efficacy of this medication.

CONCLUSION

Urticaria and angioedema are commonly encountered by the primary care physician, who institutes initial therapy. A comprehensive history and physical

Table 4. *Alternative Therapy for Chronic Urticaria by Level of Evidence.*

Medication	Level of Evidence/ Strength of Recommendation*78,85,89
Leukotriene modifiers (Ib)	Ib/A
Monteleukast	
Zafirlukast	
Zileuton	
Calcineurin inhibitors	
Cyclosporine (Ib)	
Tacrolimus	
Androgens	
Danazol	Ib/B
Chloroquines	
Hydroxychloroquine (Ib)	
Dihydropyridine CCB	
Nifedipine (Ib)	Ib/C
Sulfones	
Dapsone (IIB)	IIB/B
Mycophenolate (IIB)	
Antifolate antimetabolites	
Methotrexate	
Immunoglobulin (IVIG) (IIB)	
Phototherapy (Ib)	
Anticoagulants (IIB)	IIB/C
Warfarin	
Heparin	
5-Aminosalicylic acid	
Sulfasalazine	
Olsalazine	
Plasmapheresis (III)	III/C
Colchicine (III)	
Nitrogen mustard (alkylating agents)	
Cyclophosphamide (III)	
Gold salts (III)	III/D
Aurothiomalate	
Corticosteroids ¹⁹	IV/D

Abbreviations: CCB, calcium channel blocker; IVIG, intravenous immunoglobulin.

Adopted from Shekelle *et al.*⁷⁸ and Morgan *et al.*^{85,89}

*Category of evidence: Ia, evidence from meta-analysis of randomized controlled studies; Ib, evidence from ≥ 1 randomized controlled trial; IIa, evidence from ≥ 1 controlled study, no randomization; IIB, evidence from ≥ 1 other type of experimental study; III, evidence from descriptive studies; IV, evidence from expert committee reports or opinions, or clinical experience. Strength of recommendation: A, directly based on category I evidence; B, directly based on category II evidence or extrapolated recommendation from category I evidence; C, directly based on category III evidence or extrapolated recommendation from category I or II evidence; D, directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence.

examination should be performed to delineate possible etiologies and guide therapy to provide the proper approach for each individual patient. The first-line therapy is to identify the causative agents, control symptoms with nonsedating antihistamines

that have a low side-effect profile, and encourage patient compliance in avoiding the causative agents. Adjunctive therapy with alternative medications may be added in refractory cases.

DISCLOSURES

Potential conflict of interest: Dr. Davis-Lorton: Speaks for Dyax, CSL Behring, and Shire Conducts research for Dyax and Shire.

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