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Urticaria

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Urticaria with or without angioedema is frequently encountered in primary care medicine. Although many patients and physicians think that urticaria is evidence of an IgE-mediated allergic reaction, often the etiology of urticaria is unknown. This uncertainty frequently results in patients enduring unnecessary lifestyle changes or extensive testing. In more persistent cases, patients achieve control of their disease only with the use of more toxic medications, such as corticosteroids, and this can lead to a range of systemic complications. Acute urticaria is typically due to a hypersensitivity reaction while chronic urticaria has a more complex pathogenesis. Antihistamines remain the mainstay of symptomatic treatment for both.

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Urticaria with or without angioedema is frequently encountered in primary care medicine. If the urticaria is of short duration, it is usually not of major clinical concern. Conversely, if urticaria persists, it can become a difficult problem for both patients and physicians. Although many patients and physicians think that urticaria is evidence of an IgE-

mediated allergic reaction, often the etiology of urticaria is unknown. This uncertainty frequently results in patients enduring unnecessary lifestyle changes or extensive testing. In more persistent cases, patients achieve control of their disease only with the use of more toxic medications, such as corticosteroids, and this can lead to a range of systemic complications. Although this disease typically is associated with a good prognosis, patients with severe urticaria can suffer significant morbidity with a dramatic decline in their quality of life, productivity at work, and emotional well-being.

Definition

Urticaria, or hives, are pruritic, edematous, erythematous lesions that are typically round or oval. Pale raised centers called wheals are usually prominent in lesions and vary in size from a few millimeters to a few centimeters (Fig. 1). Approximately 40% of patients with urticaria experience angioedema, which affects deeper subdermal and/or submucosal sites and appears as brawny, nonpitting edema typically without well-defined margins and without erythema. Unlike other forms of edema, angioedema is usually not distributed in dependent areas of the body and may involve the lips, tongue, eyelids, and genitalia [1]. Angioedema in the absence of urticaria is rare and should alert the practitioner to alternative diagnoses, such as hereditary or acquired angioedema (see below).



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Fig. 1. Urticaria (hives).

Recurrent hives with or without angioedema lasting less than 6 weeks are considered to be acute and episodes lasting longer than 6 weeks are considered chronic [2]. This somewhat arbitrary distinction of 6 weeks becomes important in regards to potential mechanisms, approaches to evaluation, and options for treatment. Both urticaria and angioedema can peak within minutes to hours and last hours to days. In this article, the terms urticaria and urticaria with angioedema are used interchangeably.

Clinical manifestations

Cases

Case 1

A 58-year-old male with a history of hypertension, coronary heart disease, and gout comes to his primary care physician's office complaining of pruritis starting 5 days before and diffuse hives occurring 2 days before with new lesions continuing to occur. Each hive is intensely pruritic, lasts less than 24 hours, and leaves normal skin upon resolution. He denies any unusual food ingestions or changes in his environment (eg, soaps, shampoos). His medications include aspirin, 81 mg, once daily; hydrochlorothiazide, 25 mg, once daily; and extended-release metoprolol, 100 mg, once daily. He had an episode of gout the previous month with an elevated uric acid and was started on allopurinol approximately 6 days prior to his current visit.

Case 2

A 25-year-old female with urticaria and angioedema for the past 2 months reports that hives occur on her chest, abdomen, and extremities on a daily basis and have been unresponsive to fexofenadine, 180 mg, once daily; and diphenhydramine hydrochloride, 25 mg, once nightly. Each lesion lasts 24 to 36 hours, is very pruritic, and leaves residual hyperpigmentation that slowly resolves. She is unable to associate the hives with ingestion of medications or foods or to changes in temperature or environment. On one occasion, she experienced angioedema of the tongue associated with mild shortness of breath and now carries a self-injectable epinephrine device. Because of the intense pruritis, especially at night, and the sedation associated with the use of diphenhydramine, she has been unable to sleep or concentrate and is worried about successfully finishing her semester in graduate school.

Case 3

A 2-year-old girl is brought to the pediatrician's office for an episode of hives involving the upper body and face that lasted 1 day the week before. Her mother reports that she developed hives while at a picnic outside in the park with friends. The hives resolved in a few hours and there was no wheezing, shortness of breath, or swelling. The mother is unaware of all the food her daughter ate at the picnic but reports that seafood and peanut butter cookies were present and her daughter had not eaten these in the past.

Discussion of cases

The above three cases highlight the varying manifestations of urticaria and angioedema. Patients often report pruritis that is poorly localized before the onset of hives, as in case 1. The intensity of the pruritis varies and can progress to an unbearable intensity that may cause patients to go the emergency room. Hives can occur over a short period of time, such as in case 3, or last for days to months, as in the other two scenarios. Hives are limited to the skin in contrast to angioedema, which occurs in deeper sites. If angioedema occurs near the laryngeal, pharyngeal, or lingual areas, as in case 2, airway compromise may occur, which can be life-threatening. Patients with urticaria often have dramatic impairment in sleep due to either the pruritis or sedative effects of antihistamines. Furthermore, chronic urticaria often diminishes quality of life and, in extreme cases, can lead to loss of employment and social isolation [3]. A good example of the morbidity associated with this disease is the fatigue and emotional discomfort experienced by the patient in case 2. Finally, although chronic urticaria is occasionally caused by ingestants or topical exposures, usually the cause of the urticaria is unknown. In spite of this, many patients continue to believe that something in their diet or environment is causing the hives. Even if the hives can be characterized as physical or autoimmune in nature, our lack of understanding of mechanisms and lack of specific treatments are often frustrating for patients and physicians.

Epidemiology

An episode of urticaria with or without angioedema occurs in 15% to 25% of individuals at some time in life and is most often acute. Only 30% of these cases go on to become chronic [4]. Urticaria affects both genders and all races. Acute urticaria is more common in children and young adults and chronic urticaria is more common in adults, affecting women (~60%) more than men (~40%) [5] and [6].

Pathophysiology

Mast cells are the primary effector cells in urticaria and in most cases of angioedema. These cells are found in high numbers throughout the body and in many locations, such as the skin, subdermis, and mucosal surfaces. When mast cells are activated, there is a rapid release of histamine, leukotriene C4, and prostaglandin D2 [7] and [8]. The release of these mediators leads to vasodilatation and subcutaneous and intradermal leakage of plasma from postcapillary venules, which in turn lead to pruritis. There is also a more delayed (4–8 hour) secretion of inflammatory cytokines (tumor necrosis factor, interleukin 4, interleukin 5) that leads to an inflammatory infiltrate and longer-lasting

lesions. Angioedema can involve a similar mechanism but the extravasation of fluid is deeper in subdermal and/or submucosal sites. Chronic urticarial lesions are characterized by dense perivascular inflammatory infiltrate consisting of CD4- and CD8-positive T lymphocytes, eosinophils, basophils, and neutrophils [9], [10] and [11]. A minority of patients with chronic urticaria have urticarial vasculitis with lesions characterized by vascular destruction, fibrinoid necrosis, and immune complex deposition on microscopic examination (including immunofluorescence) [12].

Many cases of acute urticaria and angioedema are allergic or IgE-mediated reactions and tend to be self-limited. Typically, acute urticaria is a hypersensitivity reaction to foods, drugs, or insect stings (Box 1). They can also occur as an epiphenomena associated with inflammatory processes produced by viral illness, particularly in children. The most common culprit drugs include penicillins, sulfonamides, muscle relaxants, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs). For instance, in case 1 above, the patient's urticaria may be due to the initiation of allopurinol. In addition, his use of aspirin and metoprolol (non-IgE-mediated mechanism, see below) can exacerbate urticaria if he progresses into a more persistent form of the disease. The predominant foods that cause urticaria are milk, eggs, peanuts, tree nuts, finfish, and shellfish. These allergens lead to activation of mast cells by cross-linking IgE bound to the high-affinity receptor for IgE (FcεR1). In the pediatric case 3 above, the transient nature of the urticaria in the child may be due to ingestion of a food (eg, tree nuts or peanuts in the cookie, seafood) or to other causes (eg, insect bites, contact with pets). Sensitization to foods not previously eaten can occur in utero, during lactation, or from topical application (eg, lotions containing peanut products) [13]. Although uncommon, antioxidant food preservatives butylated hydroxyanisole and butylated hydroxytoluene have also been shown to exacerbate urticaria [14].

Box 1. Classification of urticaria

I. Acute urticaria/angioedema

A. Hypersensitivity reactions

- 1. Drug allergy
- 2. Food allergy
- 3. Insect allergy

B. Idiopathic

C. Pseudoallergic reactions

- 1. Drugs
- 2. Radiocontrast dye
- 3. Other foods

D. Toxic reaction

E. Contact urticaria

- 1. Latex
- 2. Animal saliva
- 3. Processing of foods or biologics

F. Immune complex

- 1. Serum sickness
- 2. Transfusion-related
- 3. Postviral

II. Chronic urticaria/angioedema

A. Autoimmune

B. Idiopathic

C. Physical

- 1. Dermographism

2. Cholinergic
3. Exercise-induced anaphylaxis
4. Delayed pressure
5. Solar
6. Cold
7. Vibratory
8. Aquagenic
- D. Presumed immune complex–induced
1. Thyroid disease
2. Urticarial vasculitis
3. Malignancy-associated
4. Collagen vascular disease–associated
- E. Hypersensitivity reactions
1. Drug allergy
2. Food allergy
- III. Rare syndromes
- A. Urticaria pigmentosa and systemic mastocytosis
- B. Cold inflammatory disorders

In contrast, other agents can cause acute urticaria and angioedema by an IgE-independent (pseudoallergic) mechanism. For instance, some drugs (eg, opioids, vancomycin, NSAIDs, beta-blockers), radiocontrast dye, viral infections (eg, hepatitis B, Epstein-Barr virus), or ingestion of fish contaminated by histamine-producing bacteria (eg, scombroid food poisoning) can produce urticaria by a non–IgE-mediated mechanism. NSAIDs can cause urticaria by either IgE-mediated or IgE-independent routes. In case 1 above, if cessation of allopurinol does not resolve the urticaria, the patient may have an IgE-independent cause of urticaria caused by his use of aspirin. Selective cyclooxygenase 2 inhibitors generally do not induce urticaria in patients who are sensitive to NSAIDs [15].

The two largest subgroups of patients with chronic urticaria are those with autoimmune urticaria and those with idiopathic urticaria with 35% to 40% of patients falling into each of these categories. The autoimmune subgroup is still being defined and some investigators consider cases with evidence of autoimmunity to still be idiopathic. Both groups have symptoms in the absence of specific physical triggers, allergen exposures, or coexistent disease. Patients with autoimmune urticaria are characterized by the presence of IgG antibodies that can cross-link Fc ϵ R1, whereas patients with idiopathic urticaria do not have evidence of autoimmunity [16]. In approximately 5% of patients with chronic urticaria and angioedema, symptoms may be related to ingestants (eg, foods, medicines, dietary supplements), contacts (eg, soaps, latex), infections (eg, multicellular parasites in endemic areas), hormonal changes, or systemic illness (eg, rheumatic disease, autoimmune thyroid disease, hepatitis) (see [Box 1](#)). There once was concern that chronic urticaria could be a manifestation of an occult neoplasm. Today, this is not a significant concern and most experts, in the absence of findings in history and physical examination, recommend only age and risk factor-appropriate cancer screening.

In approximately 20% of patients with chronic urticaria, a physical stimulus may be causal. The most common physical urticaria is dermographism (or dermatographism). With dermographism, wheals are created or “written” on the skin by stroking or scratching the skin. A linear response occurs on the skin after stroking because of reflex vasoconstriction. This linear response is followed by pruritis, erythema, and a linear wheal. In these patients, the primary stimulus may be dry skin. This leads to pruritis and scratching, which, in the dermographic individual, directly causes hives. Here, the best approach is to hydrate the skin or otherwise interrupt the initiating pruritis. Other physical stimuli include urticaria in response to heat, cold, sunlight, pressure, vibration, and water [17] and [18].

Some physical urticaria can have varying clinical manifestations [18]. Cholinergic urticaria occurs following exercise or exposure to heat and typically has a distinct clinical presentation involving diffuse erythema and elevated, pale monomorphic urticarial lesions that are a few millimeters in diameter. These lesions occur with rise of basal body temperature. In addition, patients with cholinergic urticaria can have more generalized cholinergic manifestations, such as wheezing, salivation, syncope, or lacrimation, although this is unusual [19]. Cold urticaria and solar urticaria usually manifest after exposure to a cold stimulus or sunlight and, in instances of massive total body exposure (eg, swimming, in the case of cold urticaria), hypotension or death can occur [20]. Delayed pressure urticaria usually manifests as angioedema 4 to 6 hours after pressure has been applied (eg, tight clothing, foot swelling after standing, buttock swelling after sitting) [21]. Although avoidance of inciting stimuli can prevent urticaria, this is frequently impossible and pharmacologic therapy is necessary.

Urticaria can rarely be a manifestation of a systemic illness. Atypical lesions or associated symptoms may justify a more extensive evaluation. For example, if the hives exhibit a burning quality more than pruritis, last longer than 24 hours, or do not blanch to local pressure, urticarial vasculitis or another dermatologic condition should be suspected [12].

Differential diagnosis

The differential diagnosis of urticaria includes the subgroups discussed above and in [Box 1](#). Other conditions that may easily be confused with urticaria include diffuse pruritis complicated by dermographism, flushing disorders, urticarial vasculitis, urticaria pigmentosa, systemic mastocytosis, exercise-induced anaphylaxis, exercise-induced food-

associated anaphylaxis, and idiopathic anaphylaxis. Patients who present with angioedema without urticaria are rare and this should lead to consideration of hereditary angioedema, acquired angioedema, angioedema associated with angiotensin-converting enzyme inhibitors, and primary vascular processes, such as the superior vena cava syndrome. Physical urticarias are usually easily identified by history, although occasionally there is some confusion. For example, solar urticaria must be distinguished from other types of light sensitivity (eg, from metabolic abnormalities or drug effects).

The following specific conditions may complicate or be confused with urticaria but often have atypical presentations. Urticarial vasculitis is suggested when the hives are more painful than pruritic, last longer than 24 hours, or leave a bruising or discoloration on the skin [12]. Systemic mastocytosis is a rare hyperplastic condition with increased numbers of atypical mast cells in the bone marrow, skin, and other organs. Patients can experience episodic flushing, urticaria pigmentosa, prominent gastrointestinal symptoms, anaphylaxis, or neuropsychiatric symptoms. Urticaria pigmentosa is characterized by distinctive pigmented cutaneous lesions containing nests of mast cells [22] and [23]. Hereditary angioedema, acquired angioedema, and angioedema associated with angiotensin-converting enzyme inhibitors are characterized by episodic swelling without urticaria and generally are not associated with pruritis.

Included in the differential for physical urticarias are several unusual systemic diseases. For instance, acquired cold urticaria must be distinguished from familial cold autoimmune syndrome, which is characterized by a cold-induced papular rash (not urticaria) and belongs to the group of hereditary periodic fever syndromes [24] and [25].

Diagnosis and evaluation

Acute

Patients are often able to identify a stimulus if the hives occur 5 to 30 minutes after ingestion of a food or drug. If the hives are short-lived or respond rapidly to over-the-counter antihistamines, patients do not typically seek medical care. Patients whose hives occur in the absence of an identifiable trigger and are recurrent in nature often come to the attention of physicians. The best initial approach to a patient with urticaria is a thorough history and physical (Fig. 2). History should include details of the hives in relation to medications (including herbals, supplements), foods, physical triggers, infections, occupational exposures, insect stings, and contact exposures as well as a complete review of systems. Physical examination should include at least examination of the skin, lymph nodes, eyes, joints, throat, neck, ears, lungs, heart, and abdomen to detect possible associated conditions [5]. Then, food supplements and drugs that are nonessential should be discontinued. Recently added drugs should be discontinued or replaced with a chemically unrelated agent. Often, no specific agent is found and the hives are treated symptomatically until they resolve spontaneously.



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Fig. 2. Evaluation of urticaria. BMP, basic metabolic panel; CBC, complete blood cell count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LFTS, liver function tests; UA, urinalysis.

Chronic

As for acute urticaria, evaluation of chronic urticaria begins with a detailed history and physical examination. Because patients often do not have lesions when they are seen in the office, it is also important to determine if the rash is indeed urticaria before embarking on an extensive evaluation. Not all dermatoses described by patients as hives are really urticaria [26]. The transient nature of the lesions is a good indication that the lesions are indeed urticaria and a photograph taken by the patient can be reassuring. Nonetheless, some skepticism is advised [26]. Key elements in the history are duration of the episodes, duration of individual lesions, nature of the lesions (eg, pruritic, painful), and presence of angioedema. In addition, a thorough medication history, including herbal remedies and supplements, should be taken. Some herbal products associated with urticaria include cranberry, echinacea, hypericum, willow, garlic, ginger, glucosamine, horseradish, phytoestrogen, propolis, royal jelly, and valerian [27] and [28]. In addition, topical use of herbal soaps may cause urticaria [29].

In approximately 95% of patients with chronic urticaria, neither the patient nor the physician can identify a specific ingestant or contactant causing hives. This is sometimes difficult for patients and physicians to accept. Therefore, an unnecessarily extensive, invasive, and expensive investigation is pursued without successfully identifying a specific culprit [30].

Included in a detailed physical examination should be exclusion of possible physical triggers. For instance, for cold-induced urticaria, an ice cube challenge should be done by placing an ice cube on the patient's skin for 5 minutes. Patients with cold-induced urticaria will develop hives upon rewarming of the skin [20]. Dermatographism can be tested by stroking the skin and observing for linear hives. Pressure-induced urticaria can be tested by applying pressure perpendicular to the skin (eg, a sandbag across the shoulder) and instructing the patient to observe for swelling 4 to 6 hours later. Aquagenic urticaria can be tested by applying water regardless of temperature to the skin. In addition, applying heat, vibration, and UV radiation may rule out other physical urticaria [18].

Although foods and drugs are uncommon causes of acute urticaria, many patients are not satisfied until these are ruled out. As in the evaluation of acute urticaria, patients must discontinue all unnecessary food supplements and drugs. Patients can then keep a food diary to identify suspect foods, which can then be eliminated. If patients are highly motivated, a trial of a very restrictive diet of lamb and rice can be implemented for 2 weeks while off all antihistamines. If the urticaria resolves, foods can be slowly reintroduced into the diet while monitoring for urticaria with the use of a food diary. This method rarely leads to identification of a specific trigger of chronic urticaria in adults.

Chronic infections have also been associated with urticaria. For example, *Helicobacter pylori* gastric infection, tinea pedis, cholecystitis, hepatitis, thyroiditis, sinus infections, and dental abscesses have been associated with urticaria. The association between antithyroid antibodies (antimicrosomal [peroxidase] and antithyroglobulin) that are most commonly seen in Hashimoto's thyroiditis and chronic urticaria is particularly strong, although urticaria occurs only in a few patients with Hashimoto's thyroiditis [31]. There are many reports, but no rigorous proof, that treatment of euthyroid urticaria patients who have antithyroid antibodies with l-thyroxine leads to resolution of the urticaria. In many of these cases, improvement of the urticaria appears to be coincidental. Nonetheless, some specialists do treat these patients with l-thyroxine [32].

In patients with chronic urticaria, some laboratory evaluation is warranted in addition to the history and physical examination. Physicians should obtain a complete blood count with differential, a basic metabolic panel, liver enzymes, and a urinalysis in all patients with chronic urticaria [5]. Some experts advocate measurements of erythrocyte sedimentation rate, thyrotropin, and antithyroid antibodies (antimicrosomal and antithyroglobulin thyroid antibodies). Most experts agree that further testing should be determined by specific positive findings from the history and physical examination [33]. For example, there is no need to obtain an antinuclear antibody titer in a patient with urticaria who has no significant rheumatologic complaints or findings. If patients have atypical lesions or systemic symptoms, a referral to a specialist is appropriate.

Additional tests, usually performed in specialty clinics, may be useful in patients with chronic urticaria. Some allergists order immediate hypersensitivity skin tests or IgE RAST tests for foods if the history is suggestive. Approximately 40% of patients with chronic urticaria have evidence of an autoimmune process that may contribute to their hives. An in vitro test for antibodies to the α subunit of the Fc ϵ RI (Fc ϵ RI α) can be ordered from specialized immunology laboratories. However, this test has not been approved by the Food and Drug Administration. Evidence of autoimmunity can also be demonstrated by the autologous serum skin test. In this test, a small amount (0.05 mL) of the patient's serum is injected intradermally into the patient's own skin (therefore, autologous). If a wheal and flare develops, this is thought to be due to an antibody to either Fc ϵ RI α or to IgE itself. A positive test may reassure the patient, prevent further anxiety, and avoid unnecessary testing to find an external cause [34]. In addition, systemic symptoms may necessitate checking antinuclear antibody titer and complement studies. Lastly, a skin biopsy examined by standard staining and immunofluorescence can be useful to rule out urticarial vasculitis [12].

Treatment

Acute

Acute urticaria is generally self-limited. Antihistamines work well in patients with acute urticaria, especially if taken prophylactically ([Table 1](#)). First-generation antihistamines, such as diphenhydramine and hydroxyzine, often cause sedation and must be taken three or four times daily to be effective. Second-generation antihistamines, such as cetirizine, fexofenadine, loratidine, and desloratidine, are taken once daily, are better tolerated, and are often effective. Some patients benefit from a second-generation antihistamine daily with a first-generation drug given at bedtime for breakthrough symptoms. A brief course of corticosteroids may be needed for severe episodes [\[35\]](#). Epinephrine (0.3 mL of 1:1000 intramuscularly) rapidly reverses the signs and symptoms of urticaria and angioedema. Patients with life-threatening angioedema or anaphylaxis should always have access to epinephrine and be instructed and prepared to use it if needed. Beta-blockers can interfere with the action of epinephrine and should be discontinued if it is safe to do so [\[36\]](#).

Table 1.

Medications for acute urticaria

Drug	Recommended dose for adults	Comments	
H1-antihistamines		Mainstay of therapy; grade A recommendation [48] , [49] , [50] , [51] , [52] , [53] , [54] and [55]	
Chlorpheniramine	4 mg every 4–6 h or sustained-release 8–12 mg every 8–12 h; max: 24 mg/d	Sedating in 50%	
Cyproheptadine	Initial: 4 mg three times daily; usual: 4–20 mg/d; max: 0.5 mg/kg/d	Appetite stimulant; best for cold urticaria	
Diphenhydramine	25–50 mg every 4–6 h; max: 300 mg/24h		
Hydroxyzine HCL	25 mg every 6 h	Often used at 50 mg three to four times daily; best for cholinergic urticaria	
Doxepin	10–150 mg/d	H1- and H2-blocking properties; sedating; appetite stimulant; higher doses have antidepressive and anxiolytic effects	
Loratidine	10 mg every day	Second generation; often used in higher doses for urticaria	
Fexofenadine	180 mg every day	Second generation; often used in higher doses for urticaria	
Cetirizine hydrochloride	10 mg every day	Second generation, often used in higher doses for urticaria	
H2-antihistamines		Not first-line therapy; may provide small benefit when used with H1-antihistamines; grade B recommendation [56] , [57] and [58]	
Ranitidine	150 mg twice daily		
Cimetidine	400 mg twice daily		
Famotidine	20 mg twice daily		
Antileukotrienes		Not first-line therapy, may provide benefit in combination with antihistamines; supporting evidence in: [59] and [60] . Opposing evidence in: [48] .	
Montelukast sodium	10 mg every day		
Zafirlukast	20 mg twice daily		
Steroids		Usually very effective; should be used for severe episodes and avoid chronic use if possible; grade A recommendation [61]	
Prednisone	1 mg/kg in divided doses initially and quickly taper	Flares may occur with cessation of steroids, especially with abrupt cessation	

Chronic

Management of chronic urticaria also includes H1-type antihistamines. In most cases of chronic urticaria, additional measures are needed to control symptoms. Some specialists empirically use antihistamines at doses twice those approved by the Food and Drug Administration. However, insurance companies often require prior authorization. Because 15% of the histamine receptors of the skin are of the H2-type, addition of H2-antihistamines (eg, ranitidine or famotidine) may be helpful in treatment of urticaria. Doxepin, a tricyclic antidepressant, has potent H1- and H2-antihistamine activity and can be used as well. The main drawback of this medication, sedation, can often be managed by starting at 10 mg every night and slowly increasing the dose to a maximal antihistamine dose of 75 to 125 mg every night. Additional issues with doxepin include dry mouth, urinary retention, and increased appetite. Mast cells release a variety of mediators in addition to histamine. Thus, antileukotriene medications may be added

with some success. Severe symptoms may also require oral steroids to achieve control. However, because of the long-term side effects, chronic use of steroids should be limited when possible [16].

Corticosteroids may be needed in delayed pressure urticaria. Sunscreen and avoidance are the most effective treatments for solar urticaria. A specialized clinic can determine the wavelengths of light affecting the skin and desensitization may be possible. In some instances, specific H1-type antihistamines may be more efficacious for certain types of urticaria. For example, hydroxyzine is often used for cholinergic urticaria [37] and cyproheptidine for cold-induced urticaria [38] and [39].

Specialists who see patients with refractory urticaria often use a variety of anti-inflammatory, immunomodulatory, and antimetabolic medications [6] and [40]. Case reports suggest that hydroxychloroquine, nifedipine, sulfasalazine, dapsone, colchicine, cyclosporine, azathioprine, methotrexate, and intravenous immunoglobulin may be useful in selected patients. Of these, only cyclosporine has been shown to be effective in double-blind, placebo-controlled studies [41] and [42]. Many of these medications are limited by their side effect profiles.

In addition to medications, prevention plays an important role in the management of urticaria. For instance, patients with physical urticaria can minimize or avoid triggering factors. If a systemic disease is present, the urticaria may improve by treating the underlying disease, as in the case of thyroid disease. Other exacerbating factors that may be modifiable for some patients are anxiety, medications (eg, NSAIDs), or cutaneous vasodilatation (eg, from alcohol, hot showers, exercise). Psychosocial stress plays a large part in many patients by exacerbating urticaria, although the mechanism for this is unclear [43]. Overall urticaria patients should be encouraged to accept their illness and focus on achieving symptomatic control with the most effective treatment while minimizing side effects.

Prognosis

The prognosis of most patients with chronic urticaria is excellent. Although the data are variable depending upon the population studied, spontaneous resolution occurs within 12 months in up to half of patients. Within 5 years, approximately 20% of patients have resolution [5] and [6]. Others can have symptoms lasting decades. Most patients are well managed with nonsedating antihistamines and few patients require additional systemic immunomodulatory medications. Patients who had chronic urticaria with resolution may experience a recurrence after several years. Patients with physical urticaria, those with autoimmune urticaria, and those with a significant component of pressure-induced urticaria have a more severe clinical course [44], [45] and [46].

Summary

Urticaria has been referred to as a “vexing” problem and remains so for both patients and physicians [47]. Acute urticaria is typically due to a hypersensitivity reaction while chronic urticaria has a more complex pathogenesis. Antihistamines remain the mainstay of symptomatic treatment for both. In severe cases, referral to a specialist is prudent for determining a specific cause when possible, maximizing control of the disease with fewer medications, and considering the use of more potent immunomodulatory medications. Further research is needed to elucidate the pathogenesis of “idiopathic” urticaria and to develop safe and effective agents for this disease.

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