

Urticaria and Angioedema

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Urticaria and angioedema are commonly encountered complaints in the primary care physician's office. Although the diagnosis is clear, discovering an etiology can be challenging, prompting referral most frequently to an allergist or dermatologist. Acute urticaria is more common in young children and can frequently be attributed to viral infections, medications, or foods. Attempting to discover the etiology of chronic urticaria can be perplexing, with as many as 80% of chronic urticarial cases historically considered idiopathic. Studies have since confirmed that a large percentage of these cases have an autoimmune etiology [1]. A recent pediatric study of chronic urticaria demonstrated a 30% prevalence of childhood autoimmune urticaria [2]. Either anti-IgE or antibody to the high-affinity IgE receptor (FcεRI) may trigger mast cell and basophil degranulation [3–11].

The evaluation of urticaria and angioedema should be systematic, and the history is the most important component. Diagnostic laboratory tests are selected based on significant findings in the history and physical examination. Morbidity from urticaria can be significant as studies have shown impairment in quality of life at home and work [12,13]. The most notable complaints were swelling, itching, and pain. Patients reported that urticaria had a significant impact on mobility, self-image, and social interactions [12]. Patients and parents should be educated regarding the medications available to make the symptoms tolerable, and reassured that most cases resolve.

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Epidemiology

Urticaria is defined as recurrent, generalized, erythematous, pruritic lesions that have circumscribed borders and blanch with pressure. Angioedema manifests typically as asymmetric swelling that occurs in nondependent areas caused by leakage of plasma into subcutaneous or mucosal tissue.

The estimated incidence of urticaria in the general population is 15% to 25% [14–16]. Urticaria affects 6% to 7% of preschool children and 17% of children with atopic dermatitis [17]. Among all age groups, most patients (approximately 50%) have both urticaria and angioedema, 40% have isolated urticaria, and 10% have angioedema alone [14].

Acute urticaria is arbitrarily defined as less than 6 weeks' duration. The time distinction is important because the evaluation of acute and chronic urticaria is different. A specific cause is more likely to be identified in acute urticaria. Because of its transient nature, however, an extensive assessment may be unnecessary. The cause of chronic urticaria is determined in less than 20% of cases. Because chronic urticaria can be a manifestation of systemic disease or infection, a more extensive evaluation might be necessary. When no specific trigger is identified, urticaria is considered idiopathic.

Pathogenesis

Mechanisms

Potential mechanisms for urticaria (Box 1) and angioedema can be classified as immune-mediated, complement-mediated, non-immune-mediated, and autoimmune-mediated [18]. Immune-mediated urticaria is characterized by IgE-mediated hypersensitivity. The cross-linking of protein to IgE located on the mast cell or basophil surface results in the release of inflammatory mediators including histamine, leukotrienes, prostaglandin D₂, platelet-activating factor, eosinophil chemotactic factor of anaphylaxis, and histamine-releasing factor [19]. Histamine is the primary mediator and elicits edema (wheal) and erythema (flare). Common triggers of the IgE-mediated response are medications, such as penicillin; Hymenoptera; fire ant venom; and foods, such as milk or egg.

A significant proportion of urticaria and angioedema is unrelated to IgE-mediated hypersensitivity. Complement proteins, such as C4a, C3a, and C5a (anaphylatoxins), can directly activate mast cells. Circulating immune complexes, such as in systemic lupus erythematosus, serum sickness, and acquired angioedema, can activate the complement cascade increasing these proteins.

Non-immune-mediated mechanisms of urticaria are characterized by the degranulation of mast cells by non-IgE mediators like physical stimuli (to be discussed later); chemicals, such as alcohol and radiocontrast dye; medications, such as morphine, codeine, and vancomycin; and foods, such as strawberries and shellfish. Some patients experience flares of urticaria with aspirin or other non-

Box 1. Mechanisms of urticaria in children

- Immune Mediated (IgE mediated hypersensitivity)
 - Foods
 - Hymenoptera venom
 - Medications
 - Transfusion reactions
- Complement Mediated (circulating Ab-Ag complexes activate complement cascade)
 - Acquired angioedema
 - Collagen vascular disorders
 - Serum sickness
 - Transfusion reactions
- Non-immune Mediated (degranulation of mast cells by non-IgE mediators)
 - Chemicals such as alcohol, radiocontrast dye
 - Medications such as codeine, morphine, thiamine, vancomycin
 - Cholinergic urticaria
 - Cold urticaria syndromes
 - Delayed pressure urticaria
 - Dermatographism
 - Vibratory urticaria
 - Solar urticaria
 - Aquagenic urticaria
- Autoimmune Mediated (degranulation of mast cells by auto-antibody)
 - Anti-FcεRI antibody
 - Anti-IgE antibody
- Unknown Mechanism
 - Idiopathic
 - Infection (especially viral)
 - Medications such as nonsteroidal anti-inflammatory drugs
 - Thyroid disorders

steroidal anti-inflammatory medications. The underlying mechanism of this reaction is unknown [20].

Autoimmune urticaria is thought to occur by IgG activation of mast cells and basophils either by cross-linking IgE (anti-IgE) or binding FcεRI. The autoantibodies are of the IgG1 and IgG3 subtype and are also complement fixing [10].

Histologic findings

Regardless of the mechanism of urticaria, the histologic pattern remains the same. Acute lesions show dilation of small vessels, a minimal perivascular

lymphocytic infiltrate, superficial dermal lymphatic vasodilation, flattening of the rete pegs, and swollen collagen fibers [21]. Chronic urticaria is characterized by a dense nonnecrotizing perivascular infiltrate consisting of T lymphocytes, mast cells, eosinophils, basophils, and neutrophils [22–25]. Identical changes are found in the deep dermis and subcutaneous tissues in angioedema. Urticarial vasculitis can be differentiated from chronic urticaria by a skin biopsy. Urticarial vasculitis is characterized by vascular damage with findings of fragmentation of neutrophils, red cell extravasation, and swelling of endothelial cells [26].

Etiology-based classification

Most cases of acute urticaria can be attributed to viral infections, medications, or foods. In younger children egg, milk, soy, peanut, and wheat are the most common allergens. In older children fish, seafood, nuts, and peanuts are more common offenders [27]. Food-induced contact urticaria is more common in children with atopic dermatitis. In some cases, acute urticaria and angioedema may represent an early manifestation of developing anaphylaxis. Chronic urticaria occurs less frequently in children compared with adults. In those in which a cause was found, 8% had physical urticaria, 3% had immunologic or collagen vascular disease, 2% had infections, and 2% had food allergy [18].

Physical urticarias

Physical urticarias comprise 20% to 30% of chronic urticarial cases [28]. The physical triggers that induce urticaria include mechanical, thermal, exercise, solar, and aquatic exposure. One percent to 10% of children with chronic urticaria may have a physical stimulus, such as dermatographism, cholinergic urticaria, and cold-induced urticaria [29]. Dermatographism is the most common mechanical type of physical urticaria, affecting 2% to 5% of the population [30,31]. Stroking of the skin with a tongue blade elicits linear wheals within a few minutes. Individual hives may last 30 minutes to 2 hours [32]. Although the mechanism seems to be IgE-mediated, no allergen has been identified [28]. There are no systemic symptoms, and common triggers include scratching and tight clothing. The resolution of symptoms is usually spontaneous, and only a subgroup of patients requires treatment with antihistamines.

Cholinergic urticaria is also common in children and is precipitated by heat, exertion, and emotional factors. The wheals are small and transient and can be reproduced by exercising, occlusive clothing, or emotional behavior. Because symptoms may include angioedema, wheezing, or syncope, it can be confused with exercise-induced anaphylaxis [33]. Mast cell activation secondary to agents released by the cholinergic nervous system is the proposed pathogenic mechanism. Specific tests induce urticaria and include an intradermal injection of

methacholine (positive in one third of cases) or submersion in a hot bath (raising the core body temperature 0.7°C).

Delayed-pressure urticaria can occur after application of pressure to the skin. It most commonly affects the palms, soles, and buttocks and can be disabling. It can be diagnosed by hanging a 15-lb weight across the shoulder while walking for 20 minutes [34]. The mechanism of the reaction is unknown. Treatment is based on avoidance of inciting factors. It has a poor response to antihistamines and typically requires treatment with corticosteroids and nonsteroidal anti-inflammatory drugs.

Cold urticaria or angioedema syndromes are induced by cold exposure, such as air, water, handling cold objects, or, more rarely, ingestion of cold foods or beverages. Although the mechanism is unclear, passive transfer studies suggest serum factors, such as autoantibodies, are involved. The diagnosis can be made by a cold test, such as placing an ice cube to the forearm for 4 minutes followed by the development of urticaria during rewarming. Not all cold-induced urticarias respond to this testing method, however, requiring a thorough history to make a correct diagnosis [1].

Cold urticarias are classified as acquired or familial disorders. Familial types have an autosomal-dominant mode of inheritance and include delayed cold urticaria and familial cold auto-inflammatory syndrome. The acquired disorders are further subdivided into those with a positive cold test (includes primary cold urticaria and cold urticaria secondary to cryoglobulins, infection, or leukocytoclastic vasculitis) and those with an atypical response to the cold test (includes systemic cold urticaria, cold-dependent dermatographism, cold-induced cholinergic urticaria, delayed cold urticaria, and localized cold reflex) [35]. Primary cold urticaria is the most common acquired type and affects patients from 3 months to 74 years of age [36,37]. The natural history is spontaneous resolution after 5 to 9 years [37,38]. The main management objective is the limitation of cold exposure to prevent shock during cold weather or aquatic activities. Cyproheptadine and doxepin have been shown to be effective in the treatment of cold urticaria [38,39]. Side effects include appetite stimulation, weight gain, and somnolence.

Rare physical urticarias include solar and aquagenic urticaria. Because case reports and series of patients with these forms of urticaria are sparse in number, little differentiation can be made between adults and children. In solar urticaria, hives develop within a few minutes of sunlight exposure. Solar urticaria is classified according to the wavelengths of light, 2800 to 5000 nm, inducing the urticaria. The proposed mechanism is secondary to a precursor molecule that is activated by exposure to a particular wavelength of light to become a photoallergen [28]. Treatment consists of avoidance of the inciting wavelength of light by use of protective clothing and a sunscreen. In aquagenic urticaria, contact with water precipitates small urticarial lesions. It can be demonstrated by applying a wet towel to the skin on the upper body for 30 minutes. The mechanism causing this reaction is unclear. Treatment includes protective barriers and pretreatment with antihistamines [40,41].

Autoimmune urticaria

As in many autoimmune diseases, the trigger for autoantibody production is unknown. Autoimmune urticaria is often diagnosed based on clinical suspicion after exclusion of triggers including drugs, foods, infection, and physical urticarias. Patients may have symptoms of malaise, indigestion, and feeling hot or cold [10]. Family or past medical history for autoimmune disease can also increase suspicion. There is evidence that a genetic predisposition for autoimmune disease in chronic idiopathic urticaria exists because there is an increased frequency of HLA-DRB1*04 (DR4) and DQB1*0302 (DQ8) in comparison with healthy controls [42].

As many as 12% to 14% of patients with chronic urticaria have circulating thyroid autoantibodies (antithyroglobulin or antithyroid peroxidase), which is significantly higher than the incidence of 3% to 6% in the normal population [43–45]. In children the prevalence of thyroid autoimmunity is lower than in adult studies, ranging from 0.35% to 4.3% [46–49]. The mechanism by which autoimmune thyroid disease may cause urticaria is unclear. One proposed hypothesis is that inflammation of the thyroid gland develops because of spontaneously occurring autoantibodies. Normally sequestered thyroid antigens are then released into the local and systemic circulation stimulating an immune response to thyroid-specific molecules [50]. Successful treatment may be related to suppression of inflammation in the thyroid gland [50]. Although a few studies showed that euthyroid patients with antithyroid antibodies and chronic urticaria had resolution of their urticaria with thyroid hormone replacement therapy, others have shown no benefit [45,46,51,52]. The effects of thyroid suppressive therapy on the course of urticaria need to be defined further using double-blind randomized controlled trials. Consultation with a pediatric endocrinologist may be helpful in management including dosing and monitoring of suppressive therapy.

Angioedema

Whereas edema occurs symmetrically in dependent areas, angioedema is characterized by its rapid onset and asymmetric distribution that is not in dependent areas. Angioedema alone can be secondary to medication; acquired C1 inhibitor deficiency; or hereditary C1 inhibitor deficiency, also called hereditary angioedema (HAE).

HAE represents 1% of all angioedema cases with an estimated prevalence of 1 in 10,000 to 1 in 150,000 [53]. Over 100 mutations of the C1 inhibitor gene have been reported [54]. HAE presents in childhood with 40% of patients having their first symptom by 5 years of age but is typically diagnosed in adulthood [54,55]. It is inherited as an autosomal-dominant trait with a spontaneous mutation rate of 25%. Symptoms are characterized by recurrent attacks of peripheral angioedema and abdominal pain (secondary to mesenteric edema). Fever and leukocytosis are unusual with an acute attack [53]. The areas of angioedema are

well circumscribed, nonpruritic, and nonpitting involving the face, larynx, gastrointestinal tract, or extremities. They develop over 12 to 36 hours and last between 1 and 3 days. Flares may be weekly, monthly, or yearly. Precipitating factors include minor trauma (including dental work); estrogen; emotional stress; and infection [56].

The mechanisms of angioedema involve coagulation factors XIIa and XII_f, the complement system, and activation of the kallikrein-kinin system, which ultimately results in the release of factors that cause vasodilation, increased capillary permeability, and edema.

There are three types of HAE. Type I is the most common (85%) and is caused by deficiency of functional C1 inhibitor protein. Type II (10%–15%) is caused by nonfunctional C1 inhibitor protein. A third type of HAE has been described in women in whom the C1 inhibitor protein has a structural abnormality that forms an inactive complex [57].

Acquired angioedema is very rarely seen in children. It is associated with B-cell proliferation disorders in which autoantibody is directed against C1 inhibitor protein. Medication-induced angioedema is associated with angiotensin-converting enzyme inhibitors and less commonly with angiotensin II receptor blockers [58].

Differential diagnosis

Erythema multiforme minor, urticarial vasculitis, mastocytomas, and urticaria pigmentosa (mastocytosis) have a similar presentation to urticaria. Erythema multiforme minor and urticarial vasculitis may be suspected when the duration of the urticarial lesion is greater than 24 hours. Erythema multiforme minor is an acute disorder characterized by persistent targetoid lesions that are typically less pruritic than urticaria. The etiology is usually a reaction to a medication or infection and is commonly associated with herpes simplex infection. In urticarial vasculitis, there may be palpable purpura and bruising that persists after the hive disappears. Causes range from a hypersensitivity vasculitis, such as Henoch-Schönlein purpura, to underlying connective tissue disease.

Solitary mastocytomas are more common in children [59]. The classic lesion is a hyperpigmented macule or papule that when mechanically irritated develops a wheal and flare (Darier's sign). More than half of childhood mastocytomas resolve during puberty [60]. Children with mastocytomas have not been reported to develop urticaria pigmentosa [61].

Urticaria pigmentosa is defined by an excessive number of mast cells in the skin, bone marrow, gastrointestinal tract, liver, spleen, or lymph nodes [62]. It is generally sporadic, although rare familial cases have been reported [63]. Flares are characterized by pruritus, flushing, palpitations, tachycardia, and syncope. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal pain [64]. Spontaneous recovery is usual, although in patients with extensive mast cell mediator release, vasodilatory shock may occur. Treatment involves

avoiding triggers, the use of medications for mast cell stabilization, and treatment of skin lesions.

Evaluation

History is the most important tool in the diagnosis and evaluation of urticaria. In a recent study of patients with chronic urticaria, careful history taking was shown to be the most important component in obtaining an etiology. The use of a detailed questionnaire further improved the identification of a cause [65]. The first step is to determine the duration of lesions; presence of pruritus; blanching; when the hives or angioedema occur; where lesions occur (pressure points); and what the patient or parent suspect as the cause [27]. Specific questions should address a history of viral infection; recent insect bites or stings; blood transfusion; suspected foods; skin contact to foreign material, heat, cold, or water; and drugs, specifically, alcohol, nonsteroidal anti-inflammatory drugs, opioids, and angiotensin-converting enzyme inhibitors. Fever, joint pain, and symptoms of hypothyroidism or hyperthyroidism should be noted on review of systems.

A thorough physical examination should be performed to rule out other disease processes that may be associated with urticaria, such as infection, vasculitis, connective tissue disease, lymphoproliferative disorders, and endocrine disease. Visualization of lesions during episodes is necessary to ensure that they are in fact urticaria. It is recommended that the family bring a picture of the patient's lesions if they are not symptomatic on evaluation. Dermographism, which can easily be tested, has linear wheals. Small wheals surrounded by erythema suggests cholinergic urticaria. Wheals limited to exposed areas suggests solar or cold urticaria, and wheals on the lower extremities suggests pressure urticaria or urticarial vasculitis [27]. A pen mark around the lesion may demonstrate the fading and appearance of new lesions.

Acute urticaria does not require extensive laboratory evaluation except to confirm a causative agent (eg, skin testing for a suspected food allergen). In chronic urticaria, findings from the history and physical examination should direct laboratory investigation. For example, antinuclear antibody testing may be indicated if a connective tissue disorder is suspected. In the absence of significant findings, a limited evaluation including complete blood cell count with differential, urinalysis, erythrocyte sedimentation rate, and liver function tests may be considered [66]. Measurement of thyroid function and antithyroid antibody may be helpful, given the association of chronic urticaria with thyroid disease [32]. A recent meta-analysis reviewing the value of laboratory testing in chronic urticaria, however, found no relationship between the number of identified diagnoses and the number of performed laboratory tests [67].

Laboratory testing for autoimmune urticaria includes autologous serum skin test, *in vitro* studies of basophil histamine release, and immunoassays. In the autologous serum skin test, the blood of a patient with active chronic urticaria can cause a localized wheal and flare response on intradermal injection [68]. In

histamine release, donor basophils that respond to anti-IgE are combined with the patient's serum and histamine release is the marker of activation. Immunoassay is dependent on the binding of antibody to the α subunit of Fc ϵ RI or IgE. In comparison, however, autologous serum skin test has a better specificity and sensitivity for basophil histamine release than immunoassay [68].

Laboratory evaluation for hereditary angioedema demonstrates a low serum complement factor 4 during attacks. The type of HAE is confirmed by obtaining levels of C1 inhibitor protein quantity and function [69].

The Dermatology Life Quality Index (DLQI) has been reported to be a valid, reliable, and clinically useful outcome measure for assessing quality of life in patients with chronic idiopathic urticaria. The high reliability demonstrates the lack of excessive random measurement error. Most DLQI items seemed to distinguish patients with varying degrees of quality of life impairment, and the moderate construct validity indicated that the DLQI was responsive to changes in patients' clinical status [70].

Treatment

A description of the disease triggers may be helpful for patients with physical urticarias, such as dermographism, cholinergic, and delayed pressure urticaria. Avoidance of triggers may be the only treatment necessary.

Antihistamines are the mainstay of treatment for acute and chronic urticaria. The goals are to alleviate pruritus, suppress hive formation, and maximize performance of daily activities. Most H₁-blocking antihistamines, such as diphenhydramine (Benadryl), hydroxyzine (Atarax, Mistril), chlorpheniramine (Chlor-Trimeton), and cyproheptadine (Periactin), have some effectiveness, whereas doxepin (Sinequan), a tricyclic antidepressant with both H₁ and H₂ receptor antagonist activity, reportedly has the greatest potency. Side effects, such as drowsiness, are a serious problem, and although there is apparent tolerance to the sedating effects after about 1 week, impaired performance on various tests, such as driving, have been reported [71].

Second-generation H₁ antagonists are generally considered the first choice in treatment [32]. They penetrate the central nervous system poorly and produce less or no drowsiness. The most commonly used are loratadine (Claritin); cetirizine (Zyrtec); desloratadine (Clarinex); and fexofenadine (Allegra). Although loratadine, desloratadine, and cetirizine come in syrup formulation and can be used down to 6 months of age, fexofenadine cannot be taken by children unable to swallow a pill. By comparison, 10 mg of cetirizine is approximately equivalent to a 30-mg dose of hydroxyzine with considerably less sedation [72]. Although a few studies suggest that cetirizine and its metabolite levocetirizine seem to have a greater and more significant suppressive effect on the cutaneous wheal and flare response, clinical studies have shown all the currently available H₁ antagonists to be superior to placebo [73]. In a double-blind, crossover, randomized study, levocetirizine 5 mg, ebastine 10 mg, fexofenadine 180 mg, loratadine 10 mg,

mizolastine 10 mg, or placebo in single doses were given to 18 healthy male volunteers. Wheal-and-flare responses to epicutaneous histamine dihydrochloride (100 mg/mL) challenge were measured at 0, 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hours after each dose. Levocetirizine was the most potent and consistently effective drug for inhibiting the histamine-induced wheal-and-flare surface areas. Ebastine, fexofenadine, and mizolastine ranked next and had almost identical effects for inhibiting the wheal. Loratadine was the least potent drug [73]. In a study comparing cetirizine with desloratadine, both were highly effective in suppressing skin reactivity, although cetirizine seemed to have a greater and more prolonged effect on wheal and flare suppression [74].

Two identical, 4-week, placebo-controlled, multicenter clinical trials determined that fexofenadine, 60 mg twice daily, improved health-related quality of life as measured by the DLQI (score, 0–30); increased work productivity as assessed by the Work Productivity and Activity Impairment instrument (0%–100%); and improved performance of daily activities in patients with moderate to severe chronic idiopathic urticaria [75]. There was a trend toward improved classroom productivity (N=26) with fexofenadine.

Unfortunately, in severe cases, the recommended doses are often inadequate to control symptoms. A double-blind placebo-controlled study looking at fexofenadine in urticaria showed that doubling the dose from 120 to 240 mg resulted in only a slight change in efficacy, and larger doses were not more effective [76]. Older antihistamines may be a consideration in the treatment of patients with severe and uncontrolled urticaria because they may have effects in addition to H₁ receptor blockade [77]. A combination of H₁ receptor antagonists, hydroxyzine, 25 mg, and cyproheptadine, 4 mg (Periactin), taken four times a day have provided symptomatic improvement [78].

If a second-generation H₁ antihistamine does not provide relief, one can try combining medications, such as a second-generation H₁ antihistamine in the morning and a sedating H₁ antihistamine at bedtime. The addition of an H₂ antihistamine, such as ranitidine (Zantac) or cimetidine (Tagamet), may be helpful because of the expression of H₂ receptors in the cutaneous vasculature.

A variety of medications have been used to treat chronic urticaria. Leukotriene receptor antagonists have been shown to improve hives and swelling compared with placebo [79]. Their role in the treatment of chronic urticaria, however, is yet to be defined. In a randomized placebo-controlled trial comparing desloratadine with montelukast (Singulair) in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria, desloratadine was found to be highly effective. The combination therapy did not seem to offer any substantial relief over monotherapy [80]. There was no difference between the groups treated with montelukast and placebo; however, the dropout rate was 68% (27 of 40) in the montelukast group and 88% (35 of 40) in the placebo group.

In Europe, mizolastine has been effective in the treatment of chronic idiopathic urticaria and primary acquired cold urticaria [44,81]. Ketotifen, a mast-cell stabilizer, has similarly been found efficacious in the treatment of physical urticarias, such as cold and cholinergic urticaria [82–85]. Corticosteroids are effective at

reducing urticaria severity, although the lowest therapeutic dose is recommended because of the potential for side effects from chronic therapy. Acute episodes refractory to antihistamines may, on occasion, be treated with standard doses (0.5–1 mg/kg/d), with or without a taper [86]. Corticosteroids may be particularly effective in urticarial vasculitis or delayed pressure urticaria. Doses as low as 5 mg of prednisone (or equivalent) daily or alternate day may suffice. The risk-benefit ratio of this treatment, keeping in mind the steroid-side effects, need to be carefully considered. Cyclosporine may be used as a steroid-sparing agent in resistant chronic urticaria [87–89]. The management of autoimmune urticaria may be the same as chronic urticaria. Patients with strongly positive basophil histamine release are more likely to respond to cyclosporine [89]. Other treatments include plasmapheresis and intravenous IgG [10,90].

Acute angioedema (non-HAE) may require treatment with corticosteroids. In patients with urticaria and severe angioedema involving pharyngeal swelling, diphenhydramine seems to be effective [32]. If laryngeal edema is suspected and the airway is compromised, however, epinephrine should be administered.

The treatment for HAE requires weighing the risks and benefits of treatment. In the United States, current treatment includes androgens, such as stanazolol (Winstrol) and danazol (Danocrine); antifibrinolytics; or fresh frozen plasma. Case reports of the successful use of oxandrolone (Oxandrin), an anabolic steroid with fewer side effects, in children have been reported [91]. The use of antifibrinolytics in children has also been recommended, although side effects may include rhabdomyolysis and myalgia. Replacement therapy with purified C1 inhibitor protein is available in Europe. Conditions for prophylaxis include dental procedures, elective surgery, and increased frequency of symptoms, which may require starting medication or doubling the dose. It is important to note that most cases of HAE do not respond to epinephrine, antihistamines, or glucocorticoids. In the event of laryngoedema, asphyxiation may necessitate endotracheal intubation or emergency tracheotomy for airway management.

Summary

In a large percentage of chronic idiopathic urticaria and angioedema, an underlying cause is not identified despite costly assessment. When the evaluation is negative, the patient should be reassured that the condition is not contagious, serious, or a sign of major disease, and although the cause is unclear, they have a definite diagnosis [67]. The outlook is good because 50% of chronic idiopathic urticaria cases experience resolution within 3 to 5 years [14].

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