

# Therapeutic Perspectives on the Treatment of Urticaria Associated with Angioedema

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## Abstract

Urticaria is common in pathology. Urticaria and angioedema with persistent symptoms have a significant effect on quality of life and activity. Typical manifestations of urticaria are not difficult to diagnose. Association of urticaria with angioedema is relatively common, about 50% of cases. This association can be life-threatening requiring intensive care. Urticaria treatment is not easy and when angioedema associated therapeutic measures should be complex. Etiological treatment is the most desirable option for physician and patient, but in many cases the cause cannot be identified. Non-sedating H<sub>1</sub>-antihistamines are considered first-line treatment of urticaria.

**Keywords:** Urticaria; Angioedema; Allergy

## Introduction

Allergic manifestations have become more and more frequent lately. Urticaria with or without angioedema is a common skin disorder with different levels of severity. Recognizing of different forms of urticaria and angioedema is very important for making the correct diagnosis and best treatment.

Urticaria is characterized by the sudden appearance of acute or chronic pruritic wheals. The lesions consist of red, raised, itchy circumscribed areas of dermal edema that usually are multiple and vary in size and form. Each individual lesion lasts for a few hours, while new lesions appear in other areas.

Angioedema is defined as sudden severe edema of the deeps dermis and subcutaneous and submucosal tissue. Lesions of angioedema can persist for 72 hours. Angioedema causes severe swelling, usually in the face, lips, eyelids and genitalia. Occasionally the tongue and laryngopharynx are also involved, which is a dangerous situation because it can close off the passage of air into the lungs [1-4].

## Classification of Urticaria

Urticaria

- ✓ Spontaneous urticaria:
  - Acute
  - Chronic
- ✓ Physical urticaria:
  - Dermographism
  - Delayed pressure urticaria
  - Cold urticaria
  - Solar urticaria
  - Aquagenic urticaria
  - Vibratory urticaria
- ✓ Other types of urticaria
  - Cholinergic urticaria
  - Contact urticaria
  - Exercise induced urticaria

Urticaria and angioedema may be classified by duration and trigger factors. Urticaria is classified as acute and chronic. Lesions of acute urticaria last less than six weeks. If wheals last for more than six weeks, the urticaria can be termed chronic.

Appearance of linear wheal at site of brisk stroke with firm object characterized dermographism. Wheals in delayed pressure urticaria occur after 4-6 hours at places of sustained pressure applied to the skin. In physical urticaria the application of a physical stimulus (cold water/air, 2800-5000 Å wavelength of sunlight, vibratory forces) to the skin causes the formation of local wheals. Large hives induced by exercise alone suggest exercise-induced urticaria and punctuate wheals associated with exposure to heat; exercise and anxiety characterized cholinergic urticaria [1,5,6].

Of the types of angioedema associated with urticaria mention the following [1,5]:

- ✓ Allergic angioedema;
- ✓ NSAID-induced angioedema;
- ✓ Angioedema occurred within infections and infestations;
- ✓ Angioedema associated with some physical urticarias;
- ✓ Angioedema with allergic contact urticaria.

## Pathogenesis

Acute urticaria may involve both immune and non-immune pathways. Histamine is the main mediator of urticaria. In allergic rashes caused by foods, medications, and insect bites histamine is produced by immune-mediated mechanism mediated by IgE. IgE antibodies bind to specific receptors of mast cells causing histamine release. Urticaria caused by non-immune mechanism is found in physical urticaria such as dermographism, delayed pressure urticaria, cold urticaria, solar urticaria, aquagenic urticaria and vibratory urticaria. Mast cells and basophils are effector cells involved in causing urticaria. These cells release vasoactive substances represented by histamine, bradykinin, leukotriene C<sub>4</sub>, prostaglandin D<sub>2</sub>. These substances cause

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vasodilatation and increased vascular permeability. This produces erythema and edema leading to urticaria lesions. Itching, an important feature of urticaria is mediated by histamine receptors as erythema and flushing [7,8].

## Etiology

A specific etiology can be identified in only 50% of patients with acute urticaria.

**Drugs:** A list of drugs, such as antibiotics (penicillin, cephalosporin, macrolides, vancomycin), NSAIDs, opiates, narcotics can cause acute urticaria with or without angioedema. Most common mechanism of urticaria related to drug administration is non-allergic mechanism, but with IgE's participation.

**Food allergens:** The most common food products involved in the appearance of urticaria in young children are milk, eggs, wheat, soy and peanuts. Other food allergens involved in causing urticaria in older children are peanuts, tree nuts, seafood and shellfish.

**Environmental allergens:** Potential environmental allergens trigger hives include dust mites, molds and animal dander.

**Insects:** Urticarial lesions may result from insect bite or sting. The most common are bites of mosquitoes, bees and spiders.

**Systemic diseases:** Systemic diseases associated with urticaria and angioedema include infectious, autoimmune diseases and malignancies. In children, viral infections are considered to be the most common cause of acute urticaria.

**Physical urticaria:** Physical stimuli include the following: cold, heat, scratch, pressure, vibration. Dermatographism is the most common physical urticaria.

**Idiopathic causes:** In acute urticaria the trigger is often revealed. Most chronic urticarias are idiopathic [9-13].

## Epidemiology

Episodes of urticaria and angioedema in children are usually mild but can cause significant discomfort depending on the severity. Urticaria affects 15% to 25% of the population at some point in their lifetime. The prevalence in preschool children is 6% to 7%. Both urticaria and angioedema occur concomitantly in 50% of patients, 40% have only urticaria, and 10% have isolated angioedema [1-4].

The II Pediatric Clinic's cases, from January 2011 until January 2012, have noted 1180 patients who presented different allergic manifestations of teguments, representing 18% out of the total of 6400 patients that were interned over the course of that year. Urticaria caused by food was diagnosed in 35% of the 1180 allergic patients, meaning 436 patients. The rest of the urticarial manifestations appeared as results of infections, medicine use or specific disease. Of the patients with urticaria, 51%, meaning 601 patients, also presented angioedema manifestations. To identify the allergens, the specific IgE pediatric panel was made for 20 allergens.

## Clinical Presentation

Physical examination of the patient is an important step for diagnosis. Hives appear as papular erythematous blanching lesions. These lesions appear suddenly and may cover all or part of the body, but not mucosal surfaces. Each wheal may last from a few minutes to six hours. While some lesions disappear, new ones arise. They can be of any size and various forms. Most often they are round or

oblong. Linear lesions suggest dermatographism. Hives are patchy at first. Evolving, patches can be merged until the rash covers most of the body. The patches have a central blanched area surrounded by a red halo. An important feature of urticaria is itching, which can often be very intense. Rarely patients can experience pain. Skin rash remission should be no residual pigmentary changes.

Urticaria may be associated or not with angioedema. Angioedema is characterized by marked swelling especially around the eyes and mouth. Due to marked edema the eyes may appear swollen shut. It can involve the extremities, the genitalia, so swelling can occur anywhere. Mucosal tissue edema in severe cases may involve the tongue, throat, and larynx causing dyspnea and acute respiratory failure. Acute allergic angioedema may develop with anaphylaxis in which case signs and symptoms of shock become manifest. Angioedema usually is not accompanied by itching. If there angioedema patients experience pain, sensation of pressure and burning [14-18].

## Diagnostic Approach

Diagnosis of urticaria and angioedema is based on detailed medical history paying attention to potential trigger factors. The most common trigger factors are allergies, atopic disease, medication use, sign and symptoms of infection. Family history of atopy (allergic rhinitis, asthma, and aspirin allergy), angioedema, autoimmune, and thyroid disease should not be overlooked. It is important to know about the onset of symptoms, presence or absence of itching, pain and heat. Another important step for diagnosis is physical examination. Characteristic appearance and evolution of urticaria lesions turn to a correct diagnosis.

IgE measurement and skin tests may be useful in patients with suspected food allergies or inhalant allergies. In most cases of chronic urticaria with angioedema major objective of the evaluation is to exclude underlying diseases. In these cases laboratory tests include: complete blood count, chemistry panel, erythrocyte sedimentation rate, antinuclear antibody, and urinalysis. Other diagnostic testing discussed are thyroid function, skin biopsy, presence or absence of rheumatoid factor [1,15,19].

## Differential Diagnosis

**Atopic dermatitis:** Diagnostic criteria for atopic dermatitis include the following: pruritus, early age of onset, chronic and relapsing course and history of atopy.

**Contact dermatitis:** A detailed medical history that will pay attention to environmental exposures guide the clinician to the correct diagnosis. In acute urticaria lesions seem to be a vesicular eruption. It progress to chronic contact dermatitis with continued allergenic exposure. This skin disorder is characterized by minimal edema, scaling, fissuring and lichenification.

**Systemic mastocytosis:** Patients with systemic mastocytosis may present with episodic systemic flushing and pruritus if there are cutaneous abnormalities.

**Urticarial vasculitis:** Is characterized by an urticarial eruption. This may be associated with normo- or hypocomplementemia, angioedema, arthralgias, abdominal or chest pain, pulmonary disease, episcleritis, uveitis.

**Serum sickness:** Common symptoms of serum sickness include fever and urticarial rashes.

**Drug eruption:** Most drug reactions are exanthematous. There are severe reactions manifested by angioedema, mucous membrane erosion, blisters, Nikolsky sign, confluent erythema and skin necrosis [16,17,20].

## Treatment

The main goal of treatment for urticaria with or without angioedema is to achieve complete symptom relief. First step in management is to identify and eliminate triggers of urticaria, and the second directed medical treatment to relieve symptoms. Treating the cause is the most desirable option for both patient and clinician but it is not applicable in all cases. Avoidance of triggers and stimulus can be initiated in patients with IgE mediated urticaria and physical urticaria. The treatment of associated infectious and inflammatory disease, including gastritis, bacterial sinusitis and parasitic, should not be skipped.

The treatment of urticaria with or without angioedema depends on the severity of symptoms. Acute urticaria with angioedema may develop life-threatening airway obstruction. If angioedema affects the respiratory tract, the first step should be securing airway. There are cases where intubation or tracheostomy is required. To reduce edema subcutaneous or intramuscular adrenaline is indicated [1,15,21].

## Medications

### H<sub>1</sub> antagonists

First-line treatment for both acute and chronic urticaria is anti-H<sub>1</sub> antihistamines. Most symptoms of urticaria are mediated by H<sub>1</sub>-receptors located on nerves and endothelium. H<sub>1</sub>-receptor antagonists are most effective in treating urticaria although not all patients respond.

First generation antihistamines because of anticholinergic effects and sedative actions are not recommended for the management of various kinds of urticaria.

New generation of antihistamines include drugs that are minimally sedating and non cholinergic effects. Thus the new generation of antihistamines is considered first-line treatment of urticaria. The most common second-generation antihistamines are: levocetirizine, desloratadine, loratadine and fexofenadine. The effect of second generation antihistamines is dose-dependent and important aspect is that they do not produce side effects at high doses. Two other important features of second-generation antihistamines are rapid onset and long duration of action. Patients with chronic urticaria can use second generation antihistamines in a single daily dose preferably given at bedtime. In patients treated with second-generation antihistamines has been shown to reduce the intensity of itching and wheals [1,22-24].

### H<sub>2</sub> antagonists

H<sub>2</sub> antagonists are not effective as monotherapy in hives. H<sub>2</sub> antagonists including ranitidine and cimetidine in combination with and H<sub>1</sub> antagonist has been shown to be more effective than an H<sub>1</sub> antagonist alone. These agents are used to reduce gastric acid secretion [16,18].

## Corticosteroids

The EAACI/GA<sup>2</sup>LEN/EDF/WAO management guideline recommends the use of corticosteroids only in severe cases.

Short-term corticosteroid therapy may reduce urticaria. It can be given in acute urticaria unresponsive to antihistamines and exacerbations of chronic spontaneous urticaria. These agents help to relieve symptoms such as swelling and inflammation and also reduce the likelihood of relapse [1,15,18].

## Sympathomimetic agents

Intravenous epinephrine should be administered to patients with airway obstruction, acute respiratory failure or shock [25,26].

## Other agents

There are some data suggesting that the combination of leukotriene receptor antagonists to therapy with antihistamines be effective for some patients [27-29].

Cyclosporine therapy is initiated only in cases refractory to treatment with high dose antihistamines. It may be useful in patients with autoimmune chronic urticaria. Intravenous immunoglobulins (IVIG), plasmapheresis and antagonists of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) are recommended only to be initiated by specialists for patients with severe diseases [1].

Other therapies used but include sulfasalazine, hydroxychloroquine, methotrexate, tacrolimus, danazol, colchicine, dapsone, and cyclophosphamide [1,30].

Omalizumab is a therapeutic alternative for patients with chronic spontaneous urticaria, cholinergic urticaria, cold urticaria and solar urticaria [31].

Symptomatic treatment of acute urticaria is second generation antihistamine monotherapy lasting for 2-3 weeks. In severe cases it can be associated with a short course of corticosteroids.

In patients with chronic urticaria second generation antihistamines can be administered up to 4 doses daily. Therapeutic alternatives are represented by adding montelukast, hydroxychloroquine, dapsone, oral glucocorticosteroids, cyclosporine A [1,29].

Treatment of dermographism is that for spontaneous chronic urticaria and consists of second generation antihistamines.

Antihistamines are not effective in delayed-pressure urticaria. In severe cases, oral corticosteroids are associated.

For patients with physical urticaria forms H<sub>1</sub> antihistamines oh new generation are the first choice of treatment. To achieve remission of cold urticaria can be given oral doxycycline or penicillin intramuscularly. For patients with solar urticaria therapeutic possibilities include: plasmapheresis, cyclosporine A, hydroxychloroquine [7,9].

Special forms of urticaria refer to: cholinergic urticaria, exercise-induced urticaria and aquagenic urticaria. In these types of urticaria second generation of antihistamines are administered regularly or before a typical situation [1] (Table 1).

Group of urticaria	Subtypes	Treatment
Spontaneous urticaria	Acute urticaria	<ul style="list-style-type: none"> <li>➤ Non-sedating H1-antihistamines</li> <li>➤ Severe cases: urticaria associated with <u>angioedema</u> – Glucocorticosteroids (0.5-1 mg/Kg/day); <u>anaphylactic shock</u> – Epinephrine (0.01 mg/Kg/dose)</li> </ul>

	Chronic urticaria	<ul style="list-style-type: none"> <li>➤ Non-sedating H1-antihistamines (up to 4 doses daily)</li> <li>➤ Non-sedating H1-antihistamines may be associated with:                             <ul style="list-style-type: none"> <li>• Montelukast</li> <li>• H2-antihistamines</li> <li>• Hydroxychloroquine</li> <li>• Dapsone</li> <li>• Oral glucocorticosteroids</li> <li>• Cyclosporine A</li> </ul> </li> <li>➤ Other options:                             <ul style="list-style-type: none"> <li>• Plasmapheresis</li> <li>• Intravenous immunoglobulins</li> <li>• Omalizumab</li> </ul> </li> </ul>
<b>Physical urticaria</b>	Dermographism	<ul style="list-style-type: none"> <li>➤ Non-sedating H1-antihistamines</li> <li>➤ alternative therapeutic: options for treatment of chronic urticaria</li> </ul>
	Delayed pressure urticaria	<ul style="list-style-type: none"> <li>➤ Non-sedating H1-antihistamines –high dose</li> <li>➤ Other treatment options:                             <ul style="list-style-type: none"> <li>• Non sedating H1-antihistamines + Montelukast</li> <li>• Non sedating H1-antihistamines + glucocorticosteroids</li> </ul> </li> </ul>
	Cold urticaria	<ul style="list-style-type: none"> <li>➤ Non-sedating H1-antihistamines</li> <li>➤ Penicillin i.m./p.o.</li> <li>➤ Docyclyline p.o.</li> <li>➤ Omalizumab</li> </ul>
	Solar urticaria	<ul style="list-style-type: none"> <li>➤ Non-sedating H1-antihistamines</li> <li>➤ Other treatment options:                             <ul style="list-style-type: none"> <li>Plasmapheresis+PUVA</li> <li>Intravenous immunoglobulins</li> <li>Omalizumab</li> <li>Cyclosporine A, Hydroxychloroquine</li> </ul> </li> </ul>
	Aquagenic urticaria	➤ Non-sedating H1- antihistamines in increased dose ( regularly or as needed)
	Vibratory urticaria	Avoidance
<b>Other types of urticaria</b>	Cholinergic urticaria	<ul style="list-style-type: none"> <li>➤ Non-sedating H1- antihistamines in increased dose ( regularly or as needed)</li> <li>➤ Omalizumab</li> <li>➤ Danazol</li> </ul>
	Contact urticaria	➤ Non-sedating H1- antihistamines in increased dose ( regularly or as needed)
	Exercise induced urticaria	➤ Non-sedating H1- antihistamines in increased dose ( regularly or as needed)

**Table 1:** Treatments in urticaria [1,24].

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