

URTICARIA AND URTICARIA RELATED SKIN CONDITION/DISEASE IN CHILDREN

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DEFINITION

Urticaria is a rash, that typically involves skin and mucosa, and is characterized by lesions known as hives or wheals. A hive is a pruritic plaque usually erythematous and edematous; the edematous, central area (wheal) can be pale in comparison to the erythematous surrounding area (flare). These lesions blanch with pressure, and are the result of dilation of small venules and capillaries located in the superficial dermis. Similar pathologic alterations that occur in the deep dermis and subcutaneous tissue cause a skin/mucosa manifestation called angioedema. Urticaria and angioedema are very often associated: urticaria-angioedema syndrome (UA). UA is a skin condition with a very high prevalence among the general population, 10-20% of the general population experiences UA at least once in life. In children the prevalence is 2-6% (1)

PATHOPHYSIOLOGY

The cells responsible for causing urticaria include mast cells and basophils. These cells are able to release histamine, the most important mediator in the urticaria pathogenesis.

Mast cell and basophiles produce many other factors that may also play a role in the UA pathogenesis.

Mast cells mainly reside in tissues, and in addition to histamine, produce other preformed mediators, such as tryptase, proteoglycans, heparin and chondroitin sulphate A and B. Basophiles are usually found both in the circulation and in tissues during an active allergic inflammation process, and express chondroitin sulphate. A as well as histamine and preformed mediators. Upon stimulation mast cells and basophiles are able to synthesize leukotriens (LTB₄ and LTC₄), whereas only mast cells are able to secrete prostaglandin D₂ (PGD₂). Both mast cell and basophils can express IL-4, IL-13, but, in addition, mast cells express IL-5, IL-6, GM-CSF and TNF-alfa (2).

CLASSIFICATION

A classification of urticaria for clinical use has been recently published in a EAACI guideline (3). Spontaneous urticaria is defined as acute if wheals last less than 6 weeks, and chronic if wheals last 6 weeks or more. Physical urticaria includes cold contact, delayed pressure, heat contact, solar, dermographic, and vibratory urticaria. Other urticaria disorders include acquagenic, cholinergic, contact and exercise induced urticaria (Tab.1).

Spontaneous urticaria	- acute urticaria - chronic urticaria
Physical urticaria	- cold contact urticaria - delayed pressure urticaria - heat contact urticaria - solar urticaria - urticaria factitia - vibratory urticaria
Other urticaria disorders	- acquagenic urticaria - cholinergic urticaria - contact urticariai
Exercise induced urticaria	

Table 1: Classification of urticaria.

The acute episodic form is the most prevalent in the pediatric population, and it is often a recurrent phenomenon (recurrent urticaria).

Acute episodic urticaria is usually triggered by viruses, allergic reactions to foods and drugs, contact with chemicals and irritants, or physical stimuli. In many instances it is not possible to identify a specific cause (idiopathic urticaria) (4).

Chronic urticaria in children is caused by physical factors in at least 6% of cases (5,6). Less often, infections (4%), foods (4%), additives (2.6%), aeroallergens (2.2%) and drugs (1.6%), are found to be the trigger factors.

In some patients with chronic urticaria, auto-reactivity functional auto-antibodies directed against the immunoglobulin E (IgE) receptors have been described in both adults and children (chronic urticaria with auto-antibodies or autoimmune urticaria) (7, 8).

Nevertheless, the causative factor for chronic urticaria is identified in only 22% of cases (5).

Urticaria and angioedema can be a symptom of systemic diseases (collagenopathies, endocrinopathies, neoplasias, hemolytic diseases, celiac disease). (4). Syndromes that include urticaria/angioedema are: Muckle-Well syndrome, Schnitzler's syndrome, Gleich syndrome, Wells syndrome (3). In other cases, urticaria is related to other diseases as a result of the patient's history (urticaria pigmentosa, urticarial vasculitis, cold induced familial urticaria, hereditary angioedema) (3)

URTICARIA "MANAGEMENT"

Urticaria management should start with a check list to adequately characterize the clinical and anamnestic features of the episode (9) (Tab. 2).

Once episodic or chronic urticaria has been established, a specific diagnostic algorithm can be followed (Tab. 3-4). Different urticaria clinical features must guide the specific diagnostic test, especially if a physical factor is suspected (Tab. 5). There is no need to use the same blood tests for all cases of urticaria! (Tab. 5). Blood examinations (blood cell count with differential, ESR, CRP, hepatic and thyroid function, BUN and glycemia, anti-strept titer, complement, total and specific IgE), skin tests for common inhalants, food or drug allergens, food or additive challenges, elimination diets, auto-antibodies, infectious disease work-up (hepatitis B e C, TORCH, Epstein-Barr, urea-breath test for the diagnosis of *Helicobacter Pylori* infection, urine culture, stool culture, nasal or pharyngeal or vaginal culture, beta hemolytic streptococcus and staphylococcus) should be considered part of an extended diagnostic programme only in the case of chronic spontaneous urticaria and according to the patient's history (3, 4) (Tab. 6).

1) Lesion first appeared:		
2) Duration of urticaria:	☐ < weeks	☐ ≥ 6 weeks
3) Duration of individual wheals:	☐ < 24 hours	☐ ≤ 24 hours
4) Size of wheals:		
5) Colour:		
6) Skin's appearance after wheals have faded:		
7) Frequency of whealing:		
8) Diurnal variations?:		
9) Particular parts of body affected?:	☐ YES	☐ NO
If yes, which?		
10) Swelling of:	☐ eyelids	☐ lips ☐ throat
	☐ tongue	☐ face
11) Are lesions brought on by:	☐ rubbing	☐ pressure
	☐ exercise	☐ heat
	☐ cold	☐ exposure to UV light
	☐ immersion in cold and warm water	
12) Are there associated symptoms?:	☐ fever	☐ joint pain
	☐ weight loss	☐ abdominal pain
13) Are initiating or provoking factors (food or emotions) present?:		
14) History of injections, insect bites or recent illness:		
15) History of drug use:		

Table 2: Anamnestic and clinical features of the urticaria episodes.

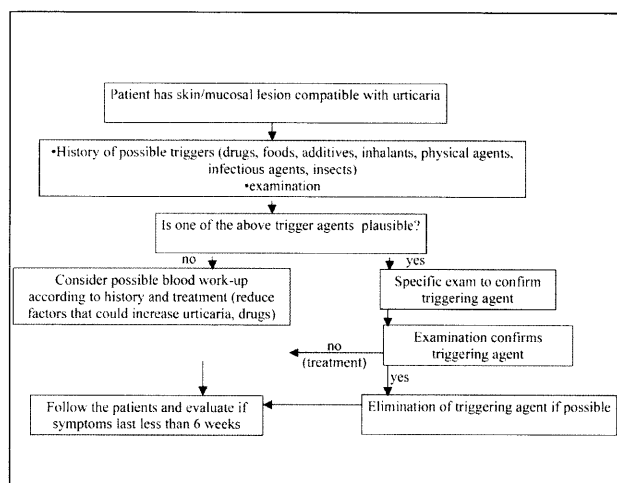


Table 3: Acute urticaria: diagnostic algorithm.

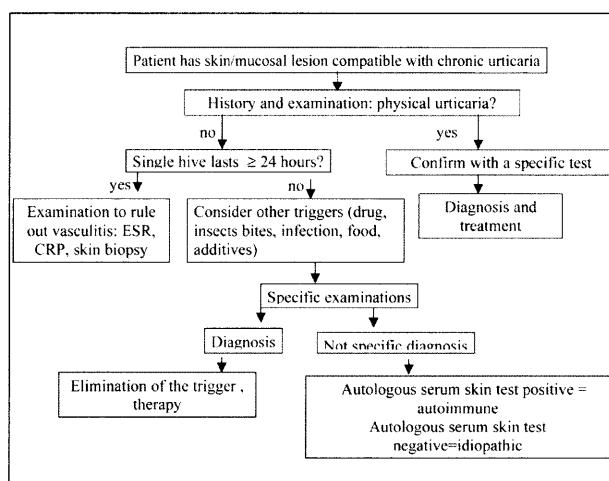


Table 4: Chronic urticaria: diagnostic algorithm.

Urticaria type	Clinical features	Test
Pressure	Erythematous, edematous, in size, at the site of pressure (soles of feet, palms of hands, waist) that last ≥ 24 hours, not associated with angioedema.	Apply pressure for 10 minutes increasing pressure (500 g/cm ² , 1000 g/cm ² , 1500g/cm ²) at 90 degrees on the skin or a weight (6 kg) for 20 minutes on the extensor aspect of the thigh ("reading" at 30 minutes, 3 hours, 6 hours, 24 hours): positive test = lesion erythematous and persistent.
Cold	Erythematous, edematous, itch lesion in the area in contact with cold liquid or cold object. Can be generalized. Can be associated with angioedema.	Apply an ice cube for 10 minutes on the forearm, within 5 - 10 minutes after removing the ice a wheal should appear. Stay in a cold room (4 C°) for 10 - 30 minutes.
Colinergic	Small, monomorphic, pruritic, pallid or pink wheal, mostly on trunk, neck and limbs associated with angioedema.	Excercise Intradermal test with methacolin
Autoimmune	Without specific clinical feature can be chronic	Autoinjection: intradermal with 50 of patient serum (positive if wheal volume is ≥ 9 mm ³ compared to the control after 60 minutes, positive if the wheal diameter is ≥ 1,5 mm compared to the control after 30 minutes). Reduction in peripheral basophils. Histamine release from basophils.
Dermografism	Immediate (starts 2-5 minutes after the stimulus, and lasts 30 minutes), intermediate (starts after 30 minutes-2 hours and lasts 3-9 hours), delayed (starts after 4-6 hours and lasts 24-48 hours).	Scratch (back or forearm) with dulled point or nail with moderate pressure (from 3200 to 4900 g/cm ²) for a length of 10 cm.

Table 5: Clinical features and specific tests in some types of urticaria.

Suspected etiology	Procedures
General screening:	Complete blood count, sedimentation rate urinalysis
Vasculitis:	Ig, antinuclear factor, immune complexes skin biopsy
Infections:	Cultures, serological studies, liver function tests, stool for ova and parasites, x-ray
Allergic:	IgE, skin tests, eosinophil count, challenge, elimination diet, tryptase
Physical: Cholinergic Dermatographism Cold Solar Heat	Metacholin test, running Spring-loaded dermatographometer Ice cube test Light exposure Warm water immersion
Hereditary angioedema	C3-C4, C1 esterase inhibitor
Other	T3-T4-TSH, skin biopsy, urea breath-test

Table 6: Laboratory evaluation of urticaria and angioedema.

Remove identifiable causes	
Non-drug therapy	Drug therapy
- Explanation and information - Avoid FANS - Minimize stress, over-heating alcohol - Exclusion diet when indicated	First line- all patients: -anti-H1 Second line- special indications: - anti-LT, anti-H2, Corticosteroids - Adrenaline Third line- specialist use only: - Cyclosporin and tacrolimus - Ig - Cyclophosphamide

Table 7: Therapeutic management of urticaria.

INFECTION INDUCED URTICARIA

Infections can trigger acute urticaria and exacerbations of chronic urticaria. Infections do not seem to be the cause, per se, of chronic urticaria.

Viruses, such as HBV, HCV, HAV, EBV, and in particular adenovirus and rhinovirus have been reported to be causes of acute urticaria and exacerbations of the chronic form. Little is known of the pathogenetic mechanism responsible for virus induced urticaria. The most likely explanation is that the virus induced release of pro-inflammatory lymphokines and cytokines may increase mast cell and basophile "releasability", facilitating their degranulation (6, 2).

Chronic persistent bacterial infections such as H.Pylori, streptococci, staphylococci, or Yersinia can also trigger urticarial symptoms (10). Bacterial infection (streptococcus and staphylococcus) may induce acute urticaria that often evolves into the chronic type. As antibiotics and NSAIDs are often prescribed during viral or bacterial infections, the infection-induced urticaria is often mistakenly attributed to the drug instead of the infective agent.

The most common skin manifestation associated with infection or reactions to drugs are maculopapular or ery-

thematous exanthemas, which typically start at the trunk or areas of pressure, and subsequently spread to the limbs. Itch and fever may or may not be present. Occasionally drug-induced erythematous exanthemas may progress into far more severe skin manifestations (erythrodermia, Stevens-Johnson Syndrome). For an accurate diagnosis of adverse reaction to drugs, the patient's history is the most useful tool available, such as cause-effect relationship between drug administration and beginning of symptoms, morphology and distribution of lesions. For example, an episode of hives shortly after administration of an antibiotic or angioedema shortly after NSAIDs intake is highly indicative of an allergic reaction. The presence of a sign not involving the skin is suggestive of an adverse drug reaction (fever, malaise, lymphadenopathy, diarrhea, arthralgia, tachycardia, hypotension, dyspnea); the correct use of lab tests (i.e. eosinophil count, hepatic function, viral tests) may offer some assistance in the differential diagnosis between viral exanthema and adverse reactions to drugs (11). However, very often the viral exanthema and the drug reaction cannot be differentiated, and a prudent change of antibiotic or suspension of treatment may be warranted.

The role of H. pylori (Hp) in chronic urticaria is debated (7). Even if the rate of Hp infection in patients with chronic urticaria is similar to that found in the general population, the immune response to Hp in patients with chronic urticaria seems to be different and characterized by a higher IgE secretion. Moreover, in some papers eradication of Hp was associated with a resolution of urticaria (10). However, no convincing demonstration of a causative role of Hp in chronic urticaria is presently available.

The role of parasitic infections in the pathogenesis of chronic urticaria is very uncertain (10).

In conclusion, even if the relationship between urticaria and infection is often suspected clinically, the lack of double blind studies makes it difficult to prove such an association, especially in a setting of different stimuli that can induce urticaria.

ALLERGIC URTICARIA

Allergic urticaria is the best known urticaria type. The pathogenetic mechanism is well known. Affected individuals are sensitized to specific allergens (most

often foods, penicillins, cephalosporins or inhalant allergens), towards which they produce specific antibody of IgE class (6). Such antibodies bind to the IgE high affinity receptor present on mast cells and basophiles. The allergen binds to the IgE attached to the receptor, induces the cross linking of receptors, and subsequent degranulation of mast cells and basophiles. Examples of this urticaria type are: food induced urticaria/angioedema in subjects with food allergy, penicillins or cephalosporin induced urticaria in subjects that produce IgE against such drugs.

The patient's history establishes a temporal relationship between food or drug intake and the onset of urticaria. All types of food can induce urticaria in sensitized individuals, however the foods most often involved are eggs, milk, seafood and fruit. The drugs that most often cause urticaria are the beta lactams. Non-steroidal-ant inflammatory drugs (NSAIDs) can cause urticaria by inducing degranulation of mast cells and basophiles, but not in an IgE mediated fashion. NSAID induced urticaria is typically associated with angioedema. These episodes are most often acute, recurrent and only seldomly chronic.

The most useful tools for diagnosis are skin tests (prick test), measurement of serum specific IgE, challenge and occasionally elimination diets (12).

PSEUDO FOOD ALLERGY AND URTICARIA

Pseudo food allergies are quite prevalent and seem to be responsible for chronic urticaria more often than food allergy (13). Pseudo food allergies are due to histamine release from skin mast cells and seem to be triggered by several agents (NSAIDs, additives such as salicylates and benzoates, and food colours such as tartrazine) (14). In rare cases urticaria can be the consequence of inhalation of volatile aromatic compounds found in white wine and tomatoes (15).

Diagnosis in these cases is based only on challenges and elimination diets, as in these instances skin tests are often not reliable.

INSECT BITE INDUCED URTICARIA

This is probably the most common type of urticaria in children. It is characterized by groups of pruritic hives or papules on the exposed parts of the body (arms, legs). Several insects, including mosquitoes and fleas, can cause hives or papules. The pathogenetic mechanism can be either immuno-mediated (an IgE mediated response is followed by a delayed response) or, most often, irritative. After several insect bites, children may develop tolerance.

Hymenoptera sting-related allergic reactions can be more severe. In sensitized subjects hymenoptera stings can induce urticaria and angioedema either at the site of injection or systemically, and they can also cause anaphylaxis. Venom immunotherapy is recommended not only for life-threatening reactions, but also for urticaria if risk factors or quality of life impairment are present (16).

CONTACT URTICARIA

Contact urticaria can be immune mediated or not immune mediated.

The non immune-mediated form does not require prior exposure to the trigger agent, appears usually within 45 minutes after exposure, and is caused mainly by artificial or natural chemicals. The diagnosis is carried out with application tests.

The immunologic form needs a prior exposure to the offending agent, appears within 10-20 minutes after the exposure, and is caused by protein (animal, vegetal, plant etc). The diagnosis is carried out with the use of skin tests (prick test) or measurement of specific serum IgE (CAP)(1). Occasionally the same substance (as for example in the case of the *Thaumatococcus pinnatifidus* tree parasite-) can cause urticaria in a toxic/irritative manner and/or with an immunomediated mechanism (17).

PHYSICAL URTICARIA

Physical urticaria can be triggered by mechanical, thermal or light stimuli (Tab. 5).

Dermatographism is the most common type of physical urticaria, and it can be elicited by applying pressure to the skin by scratching it with a dull point at a pressure point of 3200-4900 g/cm² (18).

Cholinergic urticaria is usually triggered by warmth, exercise, or emotions. It can be localized or generalized. It is rare in children; in fact, it only represented 2.7% in a pediatric series (5). Usually it is localized on the neck, flexor aspect of elbow and knee, and arm pits. Typically the eruption lasts 30-60 minutes.

Cold induced urticaria can be typical or atypical. This form is very rare in children.

AUTOIMMUNE URTICARIA

The presence of histamine releasing factors was first reported in patients with chronic idiopathic urticaria, in whom the intradermic injection of autologous serum determined a wheal and flare response (19). These histamine releasing factors were recently identified as auto-antibodies against IgE or IgE receptors (1).

Auto-antibodies are found in up to 30-40% of children with chronic urticaria (8), but in none of those with other allergic diseases such as atopic dermatitis. Such auto-antibodies are found in other autoimmune diseases such as bullous pemphigous, vulgar pemphigous and dermatomyositis. Such auto-antibodies are often present in allergic or drug induced urticaria, and in children and adults (mostly women) with similar-allergic respiratory symptoms (20).

Although the effect of urticaria therapy does not change according to the presence of a positive or negative autologous- skin test (4), it has been reported that adult patients with positive AST tend to have a more severe disease (21). Therefore in these cases a more aggressive treatment could be justified.

Indeed it could be even hypothesized that auto-antibodies are not actually pathogenetic, but are secondary to the presence of urticaria in individuals with a predisposition to develop autoimmunity. Moreover, their presence does not change the therapeutic approach or the prognosis of the disease, therefore their presence does not have a high clinical significance.

Autoimmune urticaria is characterized by hives that last at least 8-12 hours (but always < 24 hours), with daily recurrence, to which angioedema can be associated.

From a diagnostic point of view, other causes of chronic urticaria (particularly the physical urticaria), must be excluded.

The diagnosis is based on the autologous serum - skin test that must be performed during the acute phase of the urticaria. Another useful test is the histamine release from basophiles induced by the serum from the affected patient. The concordance between those 2 tests is about 80% (8). There are no clinical features that can help in distinguishing between chronic urticaria with auto-antibodies as opposed to the one without auto-antibodies. Moreover children, as opposed to adults with chronic autoimmune urticaria, do not have other autoimmune diseases associated or sign of autoimmune thyroid disease, celiac syndrome or HP infection (21).

On the other hand, chronic urticaria in children can be associated with other autoimmune diseases, mostly of the thyroid (22).

VASCULITIC URTICARIA (VU)

Vasculitic urticaria is rare in children; it can be associated with an immunocomplex disease, such as serum sickness or autoimmune disease such as systemic lupus erythematosus or Henoch-Schoenlein pur-

pura, or can be idiopathic. The skin biopsy, which is necessary for the diagnosis, typically shows a necrotizing vasculitis of small vessels, and immunocomplexes and complement deposits.

Hives last more than 24 hours, and leave purpuric signs. VU is often associated with arthralgias, abdominal symptoms, and elevated inflammatory markers. It does not respond to antihistamine treatment (1).

URTICARIA PIGMENTOSA (CUTANEOUS MASTOCITOSIS)

Cutaneous mastocytosis, is a rare disease in children. It usually appears in the first 2 years of life, and the most common manifestation is an isolated mastocytoma, a brownish lesion, sometimes mistakenly considered a mole, that can become red or can be itchy. Cutaneous mastocytosis can occur also as pigmentosa urticaria, i.e as an itchy generalized maculopapular rash. Scratching the lesion may cause a wheal and flare reaction (Darier sign).

The diagnosis of systemic mastocytosis needs the help of highly specialized laboratories, and is based on the presence of a major sign (multifocal dense infiltrates of > 15 mast cells in the bone marrow or in other extracutaneous organs) + one minor sign (serum alpha- tryptase levels > di 20 microgram/mL , CD2 o CD25 expression in bone marrow or other c-kit positive tissues mast cells, c-kit mutations in mast cells, presence of > 25% spindle-shaped bone marrow or other c-kit positive tissues mast cells) o three minor signs (23). Urticaria pigmentosa has a benign prognosis in most patients. Rarely, more severe symptoms can be present (rash, diarrhea, gastrointestinal bleeding and bronchospasm).

HEREDITARY ANGIOEDEMA (HAE)

HAE is not a real form of urticaria. It can be congenital or acquired. The hereditary form (Quincke edema) is due to a reduced level or reduced function of C1 esterase inhibitor. This is a very rare type of angioedema, with a prevalence of 1/1500000 in the general population, and is transmitted in an autosomal dominant way. Only 10% of cases are new mutations. The clinical picture of this rare disease is characterized by recurrent angioedema attacks that can be potentially lethal if they involve the sub-mucosal tissue of the glottis. Those patients need an adequate clinical and diagnostic follow up. The treatment of the severe attacks is based on the administration of the concentrated purified inhibitor. Intubation and mechanical ventilation of patients may be needed (24).