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Special Article

Practical guide to acute urticaria

Guia prático de urticária aguda

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ABSTRACT

Acute urticaria is a frequent cause of consultations with allergists, being characterized by wheals and/or angioedema. Although self-limited and benign, it may cause significant discomfort and uncommonly represent a serious systemic disease or life-threatening allergic reaction. In this review prepared by the Urticaria Scientific Department of the Brazilian Association of Allergy and Immunology, the main questions about this topic are addressed to help specialists and general practitioners.

Keywords: Urticaria, angioedema, diagnosis, therapeutics.

RESUMO

A urticária aguda é uma causa frequente de consulta com alergistas, caracterizada por urticas e/ou angioedema. Embora autolimitada e benigna, pode causar desconforto significativo e raramente representar uma doença sistêmica grave ou reação alérgica com risco de vida. Nesta revisão, elaborada pelo Departamento Científico de Urticária da Associação Brasileira de Alergia e Imunologia, foram abordadas as principais questões referentes ao tema para auxiliar o médico especialista e generalista.

Descritores: Urticária, angioedema, diagnóstico, terapêutica.

Introduction

Urticaria is defined as a condition characterized by the appearance of wheals, angioedema, or both. Urticaria is classified according to the time elapsed since the onset of clinical manifestations, being considered acute when signs and symptoms persist for less than six weeks.[1,2] Due to its high prevalence – one in five people have at least one episode at some point in their lives – it is essential that aspects related to the mechanisms, diagnosis and treatment of acute urticaria are well known by all professionals

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who are faced with these patients.[2] This article aims to review important issues related to acute urticaria, frequently present in the clinical practice of specialists and general practitioners.

What are the main triggers of acute urticaria?

Table 1 highlights the common causes or triggers of acute urticaria, which should be identified by a detailed history and eliminated, if possible.[3] In 30% to 50% of cases, it is not possible to identify a specific cause for acute urticaria, which is classified as idiopathic.[4] However, this is perhaps not the most appropriate term, since part of the cases progresses to the chronic form, whose autoimmune mechanism is currently well described.[5,6]

The prevalence of different etiologies varies between different age groups. In childhood, the association of acute urticaria with food and/or medication is common, often leading to dietary restrictions and medication suspension. However, in more than 40% of cases, mild viral infections of the upper respiratory tract are the most frequent causes of acute urticaria in children.[3] In some patients, it is the combination of viral infections and medication that triggers urticaria.[5]

Overall, in 9% to 27% of cases, medications such as antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors are largely related to cases of acute urticaria, being the main cause in adults. In the pediatric age group, antibiotics and NSAIDs that are usually prescribed during infections are frequently reported, while in the elderly, specifically NSAIDs, are the drugs most implicated in urticaria.[7]

The role of drugs as a cause of acute urticaria in children may be overestimated, as there are data in the literature showing that, after adequate investigation, more than 90% of children with a plausible history of drug allergy were able to tolerate the suspected drug.[6]

Food-induced acute urticaria is primarily mediated by immunoglobulin E (IgE) and therefore symptoms occur from a few minutes to 2 hours after ingestion, and less than 7% of all urticaria cases in various studies have been associated withfood allergens.[6] In one variant, acute urticaria may develop only when physical exercise is performed, usually 2 to 3 hours after contact with the causative food.[7]

In young children, the food most often responsible is cow's milk, followed by eggs, peanuts, soy and wheat (depending on the geographic area studied); while in older children and adults, the most common food allergens are fish, seafood, nuts and fruits.[5]

Because it is self-limiting, an extensive diagnostic investigation is not necessary in general acute urticaria. Specific tests (specific IgE dosage, skin test with suspected allergens and/or provocation test) should only be performed if there is a triggering potential strongly suggested by the patient's clinical history.[2]

Table 1
Main causes of acute urticaria

• Infections: viral, bacterial and parasitic
• Foods: cow's milk, eggs, peanuts, soy, wheat, fish, seafood, nuts and fruits
• Medications: NSAIDs, antibiotics and ACE inhibitors
• Physical stimuli
• Hymenopteran insect venoms
• Idiopathic

NSAIDs = non-steroidal anti-inflammatory drugs; ACE inhibitor = angiotensin-converting enzyme inhibitor.

What are the possible etiopathogenic mechanisms involved in acute urticaria?

In all patients with urticaria, the formation of itchy, asymmetrical and transient wheals, associated or not with angioedema, occurs due to the degranulation of skin mast cells and the effects of histamine and other pro-inflammatory mediators released in this process.[2,8,9] Cutaneous mast cells are mainly located around the blood vessels and sensory nerves of the upper papillary dermis, deep dermis and subcutaneous tissue.[10]

Several triggers of acute urticaria such as drugs, insect venoms, latex and food can activate mast cells by a type I hypersensitivity mechanism (mediated by IgE). However, there are a variety of mechanisms that do not involve IgE, but that can activate mast cells causing urticaria. These include: Mas-related G protein-coupled X2 receptors (MRGPRX2), N-formyl peptide receptors (RPF), and C3a and C5a receptors.[11] The main molecules that bind to the MRGPRX2 receptor and induce mast cell activation are substance P, vasoactive intestinal peptide and a series of drugs (quinolones such as ciprofloxacin and levofloxacin; neuromuscular blockers such as atracurium and rocuronium; icatibant, among others)[11-15]. While the ligands for RPF are N-formyloligopeptides generated by bacteria, with N-formyl-methionyl-leucyl-phenylalanine being the most potent and best known[11,16].

In response to a series of etiological factors, immune complexes can be formed, activating the complement with the generation of C3a and C5a (anaphylatoxins), which bind to their respective receptors (C3a and C5a receptors) present in the membrane of mast cells, activating them.[11,17] Other receptors, such as Toll-like receptors (TLRs), which are capable of recognizing products from a range of microorganisms, are also expressed on mast cells and can lead to the activation of these cells, without the involvement of hypersensitivity mechanisms. type I[11,18]. In addition, skin-derived antimicrobial peptides, such as beta-defensins and cathelicidins, can activate mast cells releasing their mediators and induce the synthesis of the pruritogenic cytokine IL-31.[11,19]

Thus, once activated, mast cells degranulate and release cytoplasmic granules, which contain histamine, proteases and other mediators of inflammation that activate sensory nerves in the skin leading to itching, or even a burning sensation in the skin. In addition, histamine acts on blood vessels, promoting vasodilation, which clinically translates into erythema and local heat, and induces plasma extravasation, leading to tissue edema that gives rise to wheals and the influx of immune system cells such as basophils, neutrophils, eosinophils, T lymphocytes and other cells. After degranulation, cutaneous mast cells produce and secrete neoformed mediators such as prostaglandins, leukotrienes, platelet activating factor and various cytokines (IL3, IL4, IL5, IL13, TNF, MIP-1α, GM-CSF, among others). Mediators, together with immune cells, will contribute to the inflammatory response induced by degranulation, with consequent formation of new wheals and/or angioedema.[20]

When to restrict the use of NSAIDs in patients with acute urticaria?

Urticaria and angioedema are the main clinical manifestations associated with drug hypersensitivity reactions in Latin America, and NSAIDs are the most frequently involved class.[21] Thus, whenever we are faced with a case of acute urticaria, it is very important to assess whether the patient used this type of medication in the 24 hours prior to the onset of symptoms.[2]

Hypersensitivity reactions to NSAIDs can occur by IgE-mediated mechanisms, although they are less frequent. In these cases, symptoms appear quickly (within 2 hours) after exposure to a specific NSAID, and should not be reproduced when using a drug from another chemical group. Dipyrone, a pyrazole derivative, is the drug most related to reactions involving an IgE-specific mechanism. Thus, individuals with selective hypersensitivity to dipyrone should not present symptoms when using drugs from other chemical groups, such as ibuprofen (derived from arylpropionic acid) or diclofenac (derived from heteroarylacetic acid).[22,23]

Most of the time, however, the reactions occur by non-immunological and, therefore, non-specific mechanisms, related to the inhibition of the cyclooxygenase enzyme (COX). Thus, the more potent the COX inhibition, the greater the risk of reaction, regardless of the chemical group. Reactions by this mechanism may be a little later, occurring up to 24 hours after using the medication. Weak COX inhibitors (paracetamol) or selective/preferred COX-2 inhibitors (etoricoxib and nimesulide, respectively) are generally tolerated by most of these patients.[22,23] The identification of the mechanism involved in the reaction is of fundamental importance for the prevention of

future episodes, but the investigation should only be done after the complete resolution of the hives, since the antihistamines and eventually the corticosteroids used in the treatment directly interfere in the test results.

In addition to causing episodes of urticaria, NSAIDs can exacerbate ongoing urticaria, probably by this same COX inhibition mechanism. Up to 30% of patients with CSU may experience worsening of symptoms with the use of some strong COX inhibitor, but data related to worsening in acute urticaria are limited.[2]

In general, due to the difficulty in defining the mechanism of a hypersensitivity reaction to NSAIDs in the presence of symptoms, and due to the possibility that they act as a worsening factor, it is recommended that this class (especially strong COX inhibitors), are avoided during the course of acute urticaria. In general, paracetamol at a dose of 500 mg or an equivalent dose for children can be used safely.[23,24]

When to indicate a diet without food additive for the patient with acute urticaria?

Adverse reactions to food additives as a cause of acute urticaria, despite being frequently reported by patients or family members, are infrequent. Studies show that the estimated prevalence in adults is less than 1%, while in children it varies between 1% and 2%. The clinical manifestations of these reactions vary among patients, ranging from mild conditions such as flushing, rhinorrhea, urticaria/angioedema, to more severe and potentially fatal conditions, such as anaphylaxis.[25]

The diagnosis is always challenging for the specialist and should be suspected in the presence of a strongly suggestive clinical history. Some clinical data are considered important for the suspicion of reaction to additives, among them: adverse reactions to several unrelated foods; adverse reactions to a commercially prepared food, but not to homemade preparations; worsening of a pre-existing disease (eg, atopic dermatitis), with no apparent explanation.[25]

Food additives can be synthetic or natural. Synthetics have a low molecular weight, and therefore, in most cases, do not cause IgE-mediated reactions. However, some natural additives may contain molecules with sufficient molecular weight to induce an IgE-mediated response, such as carmine red.[25]

As most reactions to food additives do not involve a type I hypersensitivity mechanism, in a few cases the specific IgE dosage may help in the diagnostic elucidation. Thus, it is indicated to exclude the food containing the suspected additive, to later perform the double-blind placebo-controlled oral provocation test, considered the gold standard in the diagnosis.[25]

If it is not possible to perform the double-blind provocation test, it may be considered an open provocation test. If the indicated oral provocation test is positive, the exclusion diet of the food containing the additive responsible for the reaction must be indicated.[25]

When to indicate food diets for the patient with acute urticaria?

Urticaria is considered one of the most common manifestations of food allergy and, in general, it is estimated that about 1.3% of acute urticaria are caused by food.[26]

The therapeutic approach to acute urticaria involves the correct identification and elimination of the underlying causes, that is, avoiding the triggering factor is essential to ensure total control of symptoms, safety and quality of life for the patient. For a food to be removed from the diet, it is essential to establish a correct diagnosis of the relationship between food intake and the onset of symptoms.[2]

When theurticaria/angioedema appears within minutes or up to 2 hours after ingestion of the triggering food, there is a strong suspicion of a clinical correlation. Studies have shown that 100% of cow's milk allergic patients develop symptoms within 60 minutes of exposure, while 79% of egg allergic patients experience symptoms within 90 minutes, and in 95% of peanut/nut allergic patients symptoms appear within 20 minutes after ingestion.[26]

Food reactions can involve both immunological and non-immunological mechanisms, with the IgE-mediated mechanism being the most common. Although specific IgE dosage (in vivo or in vitro) establishes sensitivity to some foods and aids in diagnosis, the only definitive proof of the causal nature of a suspected agent, both in immunological and non-immunological reactions, is the complete remission of the symptoms after elimination of the suspect food and recurrence of symptoms after re-exposure, preferably performed by a double-blind placebo-controlled trial. Thus, once this relationship is proven, the exclusion of the food should be indicated.[2,26]

What are the main infectious agents related to acute urticaria?

Usually, the infectious agents of the upper respiratory tract are the most described triggers of acute urticaria, but gastrointestinal and urinary infections have also been suggested.[27,28]

In children, infections caused by herpes viruses (especially cytomegalovirus, Epstein-Barr virus, herpes virus type 6, and herpes simplex viruses 1 and 2) can alternate latent and reactivation forms, and are most often associated with acute urticaria or recurrent acute urticaria. Other viruses also associated with acute urticaria include adenovirus, rotavirus, parvovirus B19, and respiratory syncytial virus. In adults, hepatitis viruses (A, B and C) are the most frequently found.[27]

The seasonality of several viral acute respiratory infections and acute urticaria coincide, with the recent example of COVID-19 infection, where acute urticaria and pyrexia may be the first manifestations of the disease, reinforcing the importance of these infections as a potential cause of acute urticaria.[3,27,28]

Bacterial infections with *Streptococcus spp*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* should also be remembered for inducing acute urticaria. Parasites have also been described. Fungi have not been observed as a cause of acute urticaria.[6,29]

However, the role of clinically silent infections in childhood urticaria is debatable. This question requires case-control studies and follow-up of urticaria remission in response to infection-targeted therapy. And the possibility that a specific combination of several triggers is needed to trigger acute urticaria may be an explanation for why symptoms may never reappear.[27,28]

How to differentiate AU from other conditions that occur with urticarial lesions and/or angioedema?

An important issue in relation to patients with urticaria is to be sure that the clinical manifestation is indeed urticaria. A variety of systemic conditions can manifest with urticaria-like skin lesions, which may be transient or persistent and may be just a part of a more complex inflammatory process involving other organs and systems, as listed in Table 2.[28]

Elements of the clinical history that must be elucidated include the onset and duration of the condition, location and severity of symptoms, presence of associated symptoms, use of medications, allergies and recent infections. Physical examination should include vital signs, identification and characterization of current lesions and their full extent, dermographism test, and cardiopulmonary examination to help rule out anaphylaxis and infectious causes.[7]

It is critical to rule out anaphylaxis as the patient needs prompt treatment and careful monitoring. Urticaria/angioedema associated with signs and symptoms in systems other than the skin, such as pulmonary (wheezing, stridor), cardiovascular (hypotension, tachycardia), gastrointestinal (abdominal pain, vomiting, diarrhea) and nervous system (dizziness, loss of consciousness), may occur in patients with anaphylaxis.[2]

Urticarial syndromes are extremely heterogeneous and include arthropod sting reactions, contact dermatitis, erythema multiforme, erythema multiforme, serum sickness-like reaction, Sweet's syndrome, pityriasis rosea, cutaneous mastocytosis, bradykinin-mediated angioedema, including hereditary angioedema (HAE), urticarial dermatitis and pruritic urticarial papules of pregnancy or polymorphic eruption of pregnancy.[5,30]

The presence of symptoms such as fever, asthenia, arthralgia, neurological, respiratory or cardiovascular signs should alert specialists to the possibility of a systemic condition, such as autoinflammatory syndromes (periodic syndromes associated with cryopyrin or Schnitzler syndrome), hypereosinophilic syndrome (syndrome of Gleich) and urticarial vasculitis. The latter is probably the most important differential diagnosis of urticaria.[2,5]

Differentiating urticaria and urticarial syndromes represents a diagnostic challenge. For this reason, a comprehensive clinical evaluation often associated with a complete clinicopathological correlation is essential for the diagnosis, as the presence of typical urticarial lesions associated with non-response to antihistamines or systemic symptoms and skin biopsy can be useful to confirm the diagnosis or suggest a therapeutic alternative.[7]

Are there predictors of severity for AU?

Studies on the existence of factors indicative of the severity of acute urticaria are limited, since it is already well established that current guidelines do not recommend performing diagnostic tests or extensive

Table 2
Main conditions that can manifest with urticarial lesions and/or angioedema

Illnesses	Clinical features
Anaphylaxis	Wheezing, stridor, hypotension, tachycardia, abdominal pain, vomiting, dizziness, loss of consciousness
Reaction to arthropod stings	Long-lasting urticarial lesions, presence of central point; insect exposure history
Contact dermatitis (irritative or allergic)	Margins indistinct, papular, persistent lesions, epidermal component present
Pityriasis rosea	Lesions lasting for weeks, herald spot, Christmas tree pattern, often no itching
Erythema multiforme	Lesions lasting several days, iris-shaped papules, target appearance, may have fever
Morbilliform drug reactions	Maculopapular lesion associated with medication use
Serum sickness-like reaction	Urticarial lesions > 24 hours, systemic symptoms (fever, arthralgia, myalgia, arthritis, lymphadenopathy, glomerulonephritis, myocarditis and neuritis); after 1-2 weeks of antigen exposure (heterologous serum or certain infections or drugs)
Sweet's Syndrome	Urticarial plaques > 24 hours, systemic symptoms (fever, arthralgia, malaise, headache and myalgia); leukocytosis
Cutaneous mastocytosis	Brownish maculopapular lesions, diffuse thickening, blisters. Residual hyperpigmentation. Positive Darier's sign (most cases)
Hereditary angioedema	Sudden edema, longer duration (36-72h), frequent involvement of the gastrointestinal tract. Absence of association with urticaria and poor response to anti-H1
Urticarial dermatitis	Long-lasting, pruritic lesions, eczematous appearance, bilateral and symmetrical distribution on the trunk or proximal extremities. Greater involvement in the elderly
Urticarial papules of pregnancy	Fixed urticarial papular lesion, with progressive coalescence in plaques, in the abdomen and proximal extremities. Third trimester of pregnancy or after delivery
Autoinflammatory syndromes	
– Periodic syndromes associated with cryopyrin	Urticarial eruption from birth, persistent and migratory; systemic symptoms (fever, arthralgia, arthritis, malaise and conjunctivitis). FCAS: short term, after exposure to cold; MWS: prolonged episodes and unknown triggers; NOMID/CINCA: early onset. Association with bone overgrowth, mental retardation, optic nerve malformation, and chronic aseptic meningitis
– Schnitzler syndrome	Recurrent, asymptomatic, mildly pruritic papules, systemic symptoms (recurrent fever, arthralgia, and myalgia); increased erythrocyte sedimentation rate and monoclonal IgM gammopathy
Hypereosinophilic syndrome (Gleich Syndrome)	Recurrent episodes of angioedema and eosinophilia, associated with increased serum IgM
Urticaria vasculitis	Urticarial lesions > 24 hours, residual purpura, painful, pruritic in 40%, systemic symptoms (fever, arthralgia, arthritis and malaise); lymphadenopathy and renal and hepatic involvement

Anti-H1 = antihistamines, FACS = familial cold autoinflammatory syndrome, IgM = immunoglobulin M, MWS = Mucklee-Wells syndrome, NOMID/CINCA = neonatal-onset multisystem inflammatory disease.

etiological investigation in patients with acute urticaria, a consensus regarding predictive factors of severity for acute urticaria.[2] According to a publication by the World Allergy Organization (WAO), in adults, the longer duration of urticaria is an important risk for a worse prognosis.[31]

On the other hand, in a retrospective study involving children (< 18 years) with acute urticaria in an emergency department, it was evidenced that age (preschoolers and adolescents), etiology of urticaria (drugs and various infections), coexisting clinic (symptoms and gastrointestinal symptoms, pyrexia, and angioedema) and absence of a personal allergic history were significantly associated with disease severity but not longer duration.[32] In another publication, also involving children (< 18 years), the authors related the presence of angioedema (isolated or associated with urticaria) as an early sign of anaphylaxis, therefore a possible severe presentation.[28] However, such publications have numerous limitations such as severity classification, absence of a control group, incomplete data collection and small sample group, since the vast majority of cases do not seek emergency care (because it is self-limited, mild conditions), only when there are signs and symptoms of severity.[28]

Recently, the transcription factor *FoxP3* was proposed as a predictor of the severity of acute urticaria in children, in which low serum levels of *FoxP3* would be related to an increased probability of developing a more severe picture of acute urticaria. However, more robust studies are needed.[33]

What are the subsidiary tests indicated in the investigation of acute urticaria?

Acute urticaria is self-limiting and, in general, does not require any routine diagnostic measures in its investigation. Most of the time, it is associated with viral infections (especially in children), but it can occur spontaneously without any relation to any specific trigger.[1,20]

Exceptions occur when an association with an IgE-mediated allergy is suspected, such as to some types of foods and medications, insect venoms and latex. In these cases, performing allergic skin tests or serum specific IgE should be considered, in order to elucidate the diagnosis, and thus allow patients to avoid re-exposure to the urticaria-triggering allergen. Provocation tests may be necessary when tests for the detection of specific IgE are negative, or when the hypersensitivity mechanism is not mediated by IgE, as in non-selective hypersensitivity to NSAIDs.[1,2,20]

What should be the initial therapeutic approach for acute urticaria?

Treating urticaria is challenging as it requires identifying the underlying causes, which is not always possible, but represents the only chance to treat the problem rather than suppress the symptoms. It includes a set of general care that consists of removing or avoiding the factors that induce urticaria and/or angioedema, exemplified below:[2]

– control of etiological agents, for example physical, mechanical, psychogenic agents and insects;
– fight infectious agents using specific medications for the control and treatment of infections;
– specific treatment, with due follow-up by a specialist doctor, in cases of urticaria and angioedema associated with systemic diseases such as neoplasms, collagen diseases, endocrine disorders and others;
– drug treatment with second-generation antihistamines (anti-H1) (drugs of choice for the treatment of acute urticaria).

Second-generation H1 antihistamines (Table 3) are the drugs of choice to treat urticaria, as they are poorly lipid-soluble, and therefore do not cross the blood-brain barrier, causing drowsiness, impact on learning/performance, and the anticholinergic effects that lead to dry mouth and eyes, constipation, inhibition of urination, and possible cause of narrow-angle glaucoma. In addition, they have a longer half-life, allowing their administration at 12 or 24-hour intervals.[2,8]

First-generation antihistamines are the oldest and include: diphenhydramine, dexchlorpheniramine, hydroxyzine, and others. These agents are lipophilic and easily cross the blood-brain barrier, thus they bind to H1 receptors in the central nervous system, causing sedative side effects that occur in more than 20% of patients.[2,8] There are few data examining the use of H2 antihistamines for acute cases of urticaria, and most with controversial results, being reserved for more severe cases with persistent symptoms, even with the use of anti-H1.[2,8]

The main objective of the pharmacological treatment of acute urticaria with or without angioedema is to keep the patient completely free from wheals or angioedema and relieve pruritus with minimal side effects, aiming at the complete control of urticaria, considering the quality of life and safety of the patient. A large percentage of patients benefit and remain symptom-free with the use of second-generation H1 antihistamines at usual doses. However, in some cases, it is necessary to quadruple the dose of second-generation H1 anti-H1 to achieve the desired effect, and it should be maintained for 4 to 6 weeks in order to avoid disease relapses.[2,8]

The choice of a particular antihistamine should always be individualized, based on the needs of each patient and the physician's clinical experience. It is not recommended to use different anti-H1 drugs at the same time.

Pregnant and lactating women: In general, the use of any systemic treatment should be avoided in pregnant women, especially in the first trimester. However, they can be treated initially with loratadine 10 mg/day or cetirizine 10 mg/day, in addition to desloratadine, levocetirizine, and bilastine. First-generation H1 antihistamines, such as dexchlorpheniramine, can also be used safely in pregnancy. Breastfeeding women can be treated with cetirizine or loratadine 10 mg/day, since they are poorly excreted in breast milk, not causing sedation in children.[2]

Should acute urticaria be treated with oral or injected medication?

First-line drugs for the treatment of acute urticaria are second-generation H1 antihistamines, which are only available for oral administration. Antihistamines for injection are first generation, such as diphenhydramine and promethazine, which should be avoided due to undesirable side effects. Therefore, acute urticaria should preferably be treated with oral medication.[34]

When to use corticosteroids in the treatment of acute urticaria?

Short-term treatment with corticosteroids (7 days or less) may be considered when symptoms of acute urticaria are severe, with prominent angioedema, or if the condition persists longer and does not resolve despite use of second-class H1 antihistamines generation.[2] In adults, the usual dose of prednisone is 30 to 60 mg per day; in children, prednisolone is preferably used at a dose of 0.5 to 1 mg/kg/day.[2]

Antihistamine therapy should be continued during and after the course of corticosteroids, as some patients experience an exacerbation of urticaria as the corticosteroid is tapered or discontinued. If symptoms do not recur over the days after the corticosteroid is stopped, H1 antihistamines can also be discontinued. Repeated courses of corticosteroids should be avoided, as the risks of adverse effects outweigh the benefit for most patients.[2] Side effects associated with the use of corticosteroids, such as adrenal suppression, effects on growth and bone mineralization, are unlikely with their use for a period of less than two weeks, however, patients should be aware of possible changes in mood, gastric disturbances and transitory weight gaina.[8]

It is concluded that the addition of a corticosteroid to antihistamine therapy for the treatment of acute urticaria should not be performed routinely. However, a short oral course can be useful to reduce the duration and activity of the disease in severe forms and with prominent angioedema.[8]

When to use adrenaline in the treatment of acute urticaria?

The use of adrenaline is indicated only in cases where urticaria is a manifestation of an anaphylactic condition. According to the WAO, anaphylaxis is defined as a severe, systemic, generalized, and potentially fatal hypersensitivity reaction associated with signs and symptoms in organs other than the skin, such as the pulmonary tract (dyspnea, wheezing, and cough), gastrointestinal system (vomiting and or diarrhea), central nervous system (dizziness and loss of consciousness) or cardiac (changes in blood pressure, heart rate or shock).[8,30]

Epinephrine is the drug of choice when anaphylaxis is diagnosed and should be administered intramuscularly, preferably in the vastus lateralis muscle at a dose of 0.01 mg/kg (maximum dose of 0.3 mg in children and 0. 5 mg in adults) at a concentration of 1:1000 (1 mg/mL). It can be repeated every 5-15 minutes.[8,26]

In short, when faced with urticaria and/or angioedema in a patient who has involvement of other organs besides the skin, epinephrine is the drug of first choice.[8]

Are there predictive factors for progression to a chronic form of urticaria?

The natural history of progression from acute to chronic urticaria is still poorly understood. Comert et al. observed that in 281 adults with acute urticaria, the duration of episodes was shorter when the suspected trigger was food or infection. Likewise, patients with a history of rhinitis, food allergy and positive skin tests for pollen or dogs also had shorter episodes of acute urticaria. On the other hand, asthmatic patients had more prolonged episodes. However, the duration of the episodes was not directly related to the evolution to chronic conditions. Also in this study, 953 patients with chronic urticaria were also evaluated, and it was observed that hypersensitivity to NSAIDs and food allergy were independent factors associated with chronic urticaria. Thus, the authors suggest that history of hypersensitivity to NSAIDs and food allergy should be carefully observed in patients with acute urticaria, since their presence may predict an evolution to the chronic form.[35]

In the search for laboratory biomarkers predictive of progression to chronic urticaria, 114 patients with acute urticaria (of which 36% progressed to the chronic form) were evaluated both laboratory and with the autologous serum test (AST) at the first visit, and then at 7, 12, 24 and 48 weeks, and compared with healthy controls. It was observed that positive AST at the first visit was significantly determinant for the diagnosis of CSU at week 7. In addition, AST positivity was associated with basopenia and the presence of antithyroperoxidase antibodies. Thus, the authors

Table 3
Second-generation antihistamines

Name	Dosage	Via
Cetirizine	Adults and children > 12 years = 10 mg/day Children > 6 years = 5 mg to 10 mg/day Children aged 2 to 5 years = 5 mg/day Children aged 6 months to 2 years = 2.5 mg/day	Oral
Levocetirizine	Adults and children > 12 years = 5 mg/day Children 6 to 11 years old = 2.5 mg/day	Oral
Loratadine	Adults and children > 6 years = 10 mg/day Children aged 2 to 5 years = 5 mg/day	Oral
Desloratadine	Adults and children > 12 years = 5 mg/day Children aged 6 to 11 years = 2.5 mg/day Children aged 1 to 5 years = 1.25 mg/day Children 6 months to 1 year = 1 mg/day	Oral
Fexofenadine	Adults and children > 12 years = 180 mg/day Children 2 to 11 years old = 30 mg 2x/day Children aged 6 months to 2 years = 15 mg 2x/day	Oral
Ebastine	Adults and children > 12 years = 10 mg/day	Oral
Bilastine	Adults and children > 12 years = 20 mg/day Children 6 to 11 years (body weight > 20 kg) = 10 mg/day	Oral
Rupatadine	Adults and children > 12 years = 10 mg/day	Oral

conclude that these three factors were associated with the progression of acute to chronic urticaria.[36]

In a study of preschool patients, it was observed that only 7% of those with acute urticaria develop symptoms for more than 6 weeks. The predictive factors of chronicity were: urticaria of unknown etiology, negative serology for herpes virus and absence of atopic dermatitis.[37]

In general, there are still no well-defined predictive factors for progression to chronic urticaria. New multicenter studies involving larger samples are needed to define more precisely what these factors are, in each specific population.

Conclusion

Acute urticaria is a very common condition in medical practice, especially for allergists, dermatologists and general practitioners. Diagnosis is always challenging, especially in cases where there is no direct relationship to a specific trigger, such as food, medication, or viral infections. Extensive investigations are not recommended and examinations should be directed only at suspected agents.

On the other hand, treatment is simple and, in most cases, effective, based on the use of second-generation antihistamines. More severe cases, especially those presenting with angioedema, can be treated with corticosteroids in combination with antihistamines. Epinephrine should be restricted to cases of acute urticaria associated with involvement of other organs or systems (anaphylaxis).

Knowledge of current guidelines, as well as the main practical issues relevant to the topic, is essential for a medical practice of excellence, always aiming at the best solutions for the patient.

Conflict of interests

Regis Albuquerque Campos: clinical research, advisory board and speaker for Novartis®. Eli Mansour: speaker, event support and scientific advice for Novartis®, CSL Behring®, Takeda® and Sanofi®. Solange Oliveira Rodrigues Valle: clinical research, advisory board and speaker for Novartis®. Luis Felipe Chiaverini: clinical research, advisory board and speaker for Novartis® and Sanofi®; advisory board and speaker for Abbvie®; speaker for Mantercorp®. Carolina Tavares de Alcântara, Daniela Farah Teixeira Raeder, Fernanda Lugao Campinhos, Larissa Silva Brandão, Alfeu Tavares França, Rozana de Fátima Gonçalves, Janaina Michelle Lima Melo, Gabriela Andrade Coelho Dias, Leila Vieira Borges Trancoso Neves and Rosana Câmara Agondi report no conflicts of interest in this article.

References

1. Ensina LF, Valle SOR, Campos RA, Agondi R, Criado P, Bedrikow RB, et al. Guia prático da Associação Brasileira de Alergia e Imunologia para o diagnóstico e tratamento das urticárias baseado em diretrizes internacionais. Arq Asma Alerg Imunol. 2019;3(4):382-92.
2. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734-66. doi: 10.1111/all.15090.
3. Minasi D, Manti S, Chiera F, Licari A, Marseglia GL. Acute urticaria in the infant. Pediatr Allergy Immunol. 2020;31(Suppl. 26):49-51.
4. Losappio L, Heffler E, Bussolino C, Cannito CD, Carpentiere R, Raie A, et al. Acute urticaria presenting in the emergency room of a general hospital. Eur J Intern Med. 2014;25(2):147-50.
5. Peroni A, Colato C, Zanoni G, Girolomoni G. Urticarial lesions: if not urticaria, what else? The differential diagnosis of urticaria: part II. Systemic diseases. J Am Acad Dermatol. 2010; 62 (4): 557-70.
6. Pite H, Wedi B, Borrego LM, Kapp A, Raap U. Management of childhood urticaria: current knowledge and practical recommendations. Acta Derm Venereol. 2013;93(5):500-8.
7. Nettis E, Foti C, Ambrifi M, Baiardini I, Bianchi L, Borghi A, et al. Urticaria: recommendations from the Italian Society of Allergology, Asthma and Clinical Immunology and the Italian Society of Allergological, Occupational and Environmental Dermatology. Clin Mol Allergy. 2020;6;18:8.
8. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133(5):1270-7.
9. Church MK, Kolkhir P, Metz M, Maurer M. The role and relevance of mast cells in urticaria. Immunol Rev. 2018;282(1):232-47.
10. Siebenhaar F, Redegeld FA, Bischoff SC, Gibbs BF, Maurer M. Mast cells as drivers of disease and therapeutic targets. Trends Immunol. 2018;39(2):151-62.
11. Huston DP, Sabato V. Decoding the Enigma of Urticaria and Angioedema. J Allergy Clin Immunol Pract. 2018;6(5):181-2.
12. McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, et al. Identification of a mast cell specific receptor crucial for pseudo-allergic drug reactions. Nature. 2015;519:237-41.
13. Ali H. Mas-related G protein coupled receptor-X2: a potential new target for modulating mast cell-mediated allergic and inflammatory diseases. J Immunobiol. 2016;1:115.
14. Azimi E, Reddy VB, Seadi Pereira PJ, Talbot S, Woolf CJ, Lerner EA. Substance P activates Mas-related G protein-coupled receptors to induce itch. J Allergy Clin Immunol. 2017;140:447-53.
15. Jimenez-Rodriguez TW, Garcia-Neuer M, Alenazy LA, Castells M. Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers. J Asthma Allergy. 2018;11:121-42.
16. Migeotte I, Communi D, Parmentier M. Formyl peptide receptors: a promiscuous subfamily of G protein-coupled receptors controlling immune responses. Cytokine Growth Factor Rev. 2006;17:501-19.
17. Davis MDP, Van Der Hilst JCH. Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases. J Allergy Clin Immunol Pract. 2018;6(4):1162-70.

18. Sandig H, Bulfone-Paus S. TRL signaling in mast cells: common and unique features. Front Immunol. 2012;3:1-29.
19. Niyonsaba F, Ushio H, Hara M, Yokoi H, Tominaga M, Takamori K, et al. Antimicrobial peptides human beta-defensins and cathelicidin LL37 induce the secretion of a pruritogenic cytokine IL-31 by human mast cells. J Immunol. 2010;184:3526-34.
20. Maurer M, Zuberbier T, Metz M. The Classification, Pathogenesis, Diagnostic Workup, and Management of Urticaria: An Update. Handb Exp Pharmacol. 2022;268:117-33. doi: 10.1007/164_2021_506.
21. Jares EJ, Sanchez-Borges M, Cardona-Villa R, Ensina LF, Arias-Cruz A, Gómes M, et al. Multinational experience with hypersensitivity drug reactions in Latin America. Ann Allergy Asthma Immunol. 2014;113(3):282-9.
22. Sanchez-Borges M. NSAID hypersensitivity (respiratory, cutaneous, and generalized anaphylactic symptoms). The Medical clinics of North America. 2010;94(4):853-64.
23. Kowalski ML, Woessner K, Sanak M. Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug – related urticaria and angioedema. J Allergy Clin Immun. 2015;136(2):245-51.
24. Cunha FS, Mambriz APM, Araujo CA, Lacerda AE, Ensina LF, et al. Tolerância ao paracetamol em crianças com hipersensibilidade não seletiva aos anti-inflamatórios não esteroidais. Arq Asma Alerg Imunol. 2019;3(2):163-7.
25. Andreozzi L, Giannetti A, Cipriani F, Caffarelli C, Mastrorilli C, Ricci G. Hypersensitivity reactions to food and drug additives: problem or myth? Acta Biomed. 2019;90(3-S):80-90.
26. Pier J, Bingemann TA. Urticaria, Angioedema, and Anaphylaxis. Pediatr Rev. 2020;41(6):283-92.
27. Imbalzano E, Casciaro M, Quartuccio S, Minciullo PL, Cascio A, Calapai G, et al. Association between urticaria and virus infections: A systematic review. Allergy Asthma Proc. 2016;37(1):18-22.
28. Techasatian L, Phungoen P, Chaiyarit J, Uppala R. Etiological and predictive factors of pediatric urticaria in an emergency context. BMC Pediatr. 2021;21(1):92.
29. Minciullo PL, Cascio A, Barberi G, Gangemi S. Urticaria and bacterial infections. Allergy Asthma Proc. 2014;35(4):295-302.
30. Schaefer P. Acute and Chronic Urticaria: Evaluation and Treatment. Am Fam Physician. 2017;95(11):717-24.
31. Sánchez-Borges M, Asero R, Ansotegui IJ, Baiardini I, Bernstein JA, Canonica GW, et al.; WAO Scientific and Clinical Issues Council. Diagnosis and treatment of urticaria and angioedema: a worldwide perspective. World Allergy Organ J. 2012;5(11):125-47.
32. Liu TH, Lin YR, Yang KC, Tsai YG, Fu YC, Wu TK, et al. Significant factors associated with severity and outcome of an initial episode of acute urticaria in children. Pediatr Allergy Immunol. 2010;21(7):1043-51.
33. Maltsev SV, Sizyakina LP, Lebedenko AA. The role of transcription factor FoxP3 as a predictor of acute and chronic urticaria in children. Medical Herald of the South of Russia. 2021;12(3):50-4.
34. Abella BS, Berger WE, Blaiss MS, Stiell IG, Herres JP, Moellman JJ, et al. Intravenous Cetirizine Versus Intravenous Diphenhydramine for the Treatment of Acute Urticaria: A Phase III Randomized Controlled Noninferiority Trial. Ann Emerg Med. 2020;76(4):489-500.
35. Comert S, Celebioglu E, Karakaya G, Kalyoncu AF. The general characteristics of acute urticaria attacks and the factors predictive of progression to chronic urticaria. Allergol Immunopath. 2013;41(4):239-45.
36. Magen E, Zueva E, Mishal J, Schlesinger M. The clinical and laboratory characteristics of acute spontaneous urticaria and its progression to chronic spontaneous urticaria. Allergy Asthma Proc. 2016;37(5):394-9.
37. Cetinkaya PG, Soyer O, Esenboga S, Sahiner UM, Teksam O, Sekerel BE. Predictive factors for progression to chronicity or recurrence after the first attack of acute urticaria in preschool-age children. Allergol Immunopath. 2019;47(5):484-90.

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