ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Practical guide to urticaria for special patient groups

Guia prático de urticária para grupos especiais de pacientes

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ABSTRACT

Chronic urticaria is a condition that affects more than a million Brazilians with a significant impact on quality of life. Although there are well-established guidelines for diagnosis and treatment, the management of chronic urticaria may be challenging in pediatric, older, and pregnant patients. With the purpose of helping specialists manage these cases, the Urticaria Scientific Department of the Brazilian Association of Allergy and Immunology prepared this review with the most common doubts and difficulties about this topic in those patient groups.

Keywords: Chronic urticaria, child, aged, pregnant women, breast feeding.

RESUMO

A urticária crônica é uma condição que afeta mais de um milhão de brasileiros, com grande impacto na qualidade de vida. Mesmo com diretrizes bem difundidas para o seu diagnóstico e tratamento, seu manejo pode ser desafiador em pacientes pediátricos, idosos e gestantes. Para auxiliar o médico especialista nestes casos, o Departamento Científico de Urticária da Associação Brasileira de Alergia e Imunologia elaborou esta revisão com as principais dúvidas e dificuldades referentes ao tema nestes grupos de pacientes.

Descritores: Urticária crônica, criança, idoso, gravidez, lactação.

Introduction

Urticaria is a condition characterized by the presence of wheals, angioedema, or both, which can be classified according to duration as acute, when it persists for less than 6 weeks, or chronic, when it lasts for more than 6 weeks.[1] Although there is consensus for the diagnosis and treatment,[1,2] its management

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can be challenging even for the specialist, when it comes to patients belonging to groups less studied in the literature, such as children, the elderly and pregnant women.

Thinking about the difficulties and main doubts related to urticaria in these "special" groups, the scientific department of Urticaria of the Brazilian Association of Allergy and Immunology (ASBAI) prepared this question and answer guide to help the specialist in his clinical practice.

Children

1. What are the main causes of acute and chronic urticaria in childhood?

Acute urticaria in childhood is mainly caused by viral infections, but also by hypersensitivity reactions (mainly related to food and medication). It is often not possible to identify whether or not there is a specific trigger for the symptoms, and some of these cases progress to the spontaneous chronic form. Chronic spontaneous urticaria (CSU) does not have a specific trigger, and occurs most often by mechanisms of autoreactivity and/or autoimmunity. Induced urticaria are those triggered by specific stimuli such as cold, heat, pressure, among others, and whose mechanisms are not fully understood.

The main cause of acute urticaria in children is viral infections, mainly of the upper respiratory tract.[2,3] The isolated microorganisms most commonly involved in acute urticaria are: herpes simplex virus type 1 (HSV1), Epstein-Bar virus (EBV), adenovirus, rhinovirus, cytomegalovirus, parvovirus B19, respiratory syncytial virus, rotavirus, beta-hemolytic *Streptococcus* of the group A and *Mycoplasma pneumoniae*.[4-6]

Less frequently, acute urticaria can be caused by hypersensitivity reactions to food, drugs, insect venom, latex, and contrast media.[5-7] However, the etiologic diagnosis must be supported by a clinical history consistent with a hypersensitivity reaction, and confirmed by skin tests, specific serum IgE measurement and/or provocation test to prevent the patient from being mislabeled as allergic. Acute urticaria can often occur spontaneously, when there is no cause-effect relationship with specific agents.[2-3]

About 20% of chronic urticaria (UC) in children are related to specific triggers – induced urticaria – with the most frequent being cold, cholinergic and symptomatic dermographism.[8-10]

Viral, bacterial and parasitic infections have been reported as aggravating or causing UC in children with a frequency ranging from 0 to 37.8%.[8] However, confirmation of the causal relationship of these infections in patients with UC requires caution, as many cases remit due to the natural course of UC and are not related to the treatment of the infection.[3,8]

2. Is there a difference in the prevalence of chronic urticaria in children compared to adults and between genders?

The prevalence of UC may be slightly higher in children than in adults, but with no gender preference.

Currently, few data are available on the epidemiology of chronic urticaria in children. In a recent meta-analysis, when assessing the point prevalence of UC in children aged 0 to 19 years, this rate was slightly higher (0.73% to 1.97%) than in adults (0.8%). However, there was no significant difference in prevalence between boys and girls.[9] In Europe, childhood prevalence ranged from 1.1% to 1.5%, being numerically higher in older age groups (7-17 years) compared to younger ones (0-6 years).[11] There are still no data on the prevalence of chronic urticaria in children in the Brazilian population.

3. What is the age of onset of CSU in children? Can it happen in the infant?

CSU can occur at any age, but the median age at onset of symptoms in studies of children ranged between 6 and 8 years.

Based on international prevalence data, CSU is the most common type of UC in children (78%).[3] However, information on the age of onset of CSU in this age group is still scarce. Most studies of prevalence in children included infants, but demonstrated that the prevalence of UC in children up to 6 years of age is lower when compared to older children.[11] In Canada, the median age at disease onset in children was 6 years, but in age-specific subgroup analysis, the median was 1.5 years among children under 4 years of age.[10] In Brazil, in a retrospective analysis of children with UC in follow-up, the median age at onset of symptoms was 8 years.[12]

4. Is there a difference in the clinical presentation of CSU compared to adults?

The clinical presentation of CSU in children is similar to that in adults, but the frequency of angioedema is variable in different populations.

In general, the clinical presentation of CSU is similar to that of adults, but the frequency of angioedema in children appears to be lower in international studies, ranging from 5% to 30%.[10,11,13] On the other hand, in Brazilian children followed up at two reference centers for urticaria, the presence of angioedema was reported as 59.2%.[12]

5. What is the pathogenesis of CSU in childhood? Is it different from adults?

The most accepted theory today is that the pathogenesis of CSU involves mechanisms of self-reactivity, both in adults and children.

The main event in the pathogenesis of any urticaria is mast cell degranulation after stimulation by multiple triggers, which results in the release of histamine and other inflammatory mediators. However, in CSU there is no external trigger that promotes mast cell degranulation.[11]

There are few data in the literature regarding the mechanisms of chronic spontaneous urticaria in childhood. However, it is very likely that mast cell degranulation occurs by autoimmune mechanisms, as in adults.[11]

The most accepted theory today is that serological factors trigger mast cell activation, such as the presence of IgG autoantibodies against IgE or its receptor, and autoreactive IgE against different antigens, such as IL-24 and thyroid peroxidase.[14,15]

The initial stimulus for the production of these autoantibodies capable of chronically activating mast cells is still the subject of studies, but infectious conditions and other autoimmune diseases could justify the evolution of CSU. Acute viral infections have been proposed as a potential pathogenic factor, as they produce autoantibodies that eventually can be high, disease-specific, pathogenic, and trigger a chronic autoimmune disease.[10,16]

Studies in children with CSU reported an autoimmune mechanism in at least half of the cases.[17-19] A study that compared data from Brazilian adults and children with CSU did not document a significant difference in the prevalence of autoimmunity between the groups, which supports the hypothesis that the pathogenesis is similar in different age groups.[20] In addition, autoimmunity may be related to an earlier and more spontaneous resolution of chronic urticaria in children.[10]

6. How should the diagnostic approach of UC in childhood be carried out? Is additional investigation with specific serum IgE or prick-test necessary?

The diagnostic approach for chronic urticaria in childhood is similar to that of adults. Complementary investigation with specific serum IgE or prick-test is not necessary and must be individualized according to the clinical history.

A detailed anamnesis is the first step in the diagnostic approach to cases of chronic urticaria, regardless of age. The history should question the frequency and duration of the lesions (hives are fleeting, last less than 24 hours in the same site and do not leave scars), the presence of associated or isolated angioedema, history of atopy, other comorbidities, and association with systemic symptoms such as fever, arthralgia, asthenia, myalgia, diarrhea, pain complaints, among others. A history of fixed lesions lasting more than 24 hours, involuting with residual lesions, or associated with systemic symptoms should suggest another diagnosis, such as urticaria, vasculitis and autoinflammatory syndromes.[2,21]

Although less frequent, the association with possible triggers should also be questioned, particularly eating habits and medications in use. However, when history does not suggest a temporal relationship between exposure to a specific allergen and the onset of hives, allergy testing for foods, inhalants, additives, or medications is not recommended. Likewise, if the history suggests a cause-effect relationship, the appropriate investigation for the suspected allergen should be performed, either with specific serum IgE, skin prick testing, or allergen restriction with subsequent provocation testing.[8] It is worth remembering that restriction of any suspected allergen should result in the resolution of chronic urticaria. If not, CSU should be considered.

In suspected cases of induced UC, ask under what circumstances urticaria appears, or what specific stimulus induces the appearance of lesions. The suspicion of an induced urticaria should always be confirmed with the specific test. If it is not possible to identify a specific stimulus for the appearance of lesions, the diagnosis of CSU is considered.[1,21]

Regardless of age group, the recommended tests in the investigation of chronic urticaria are blood count, C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), to rule out other diseases, especially infectious ones. The current consensus also suggests asking for anti-TPO antibody and total IgE in the investigation, since their results can help in the management of CSU conditions. Autologous serum testing can be performed to screen for autoantibodies in selected cases, depending on the clinical history.[1]

The investigation of infections, such as *H. pylori*, parasitosis, viruses and other bacteria should be individualized according to the history or suggestive laboratory tests. Screening for parasites and protozoa is suggested only in children living in endemic areas, such as Brazil, but with associated gastrointestinal symptoms and high eosinophil counts in the blood count.[3,8]

7. Which type of induced urticaria (UCInd) is most common in children? Is there a difference in the technique of performing provocation tests for UCInd in this age group?

Symptomatic dermographism is the most common type of UCInd in children, followed by cold urticaria and cholinergic urticaria. Provocation tests are performed similarly to adults.[19,22,23]

In a recent study in Turkey with 117 children with UCInd, symptomatic dermographism was the most common (65%) and had a better prognosis when compared to other subtypes of UCInd (40% remission in 5 years). Cholinergic urticaria was the type with the worst prognosis, with male dominance and higher baseline serum tryptase levels.[23] In the study by Miles et al., cold and cholinergic urticaria were the most frequent subtypes.[22] Other subtypes of UCInd, such as solar, late-pressure, and aquagenic, were less common in pediatric population studies.[19,22,23] The provocation tests are performed in the same way as for adults and are listed in Table 1.

8. How to approach the child with recurrent angioedema without urticaria?

The diagnosis of angioedema is clinical and a detailed history associated with physical examination will help in the etiologic diagnosis in most cases. Complementary tests should be individualized according to the clinical history.

For an adequate approach to recurrent angioedema, it is important to question in the anamnesis the age of onset, location, whether unilateral or bilateral, symmetry, whether there is an association with pruritus and/or urticaria, frequency, duration of episodes, triggering factors (food, medication, insect bite, exercise, trauma, etc.), recent infections, family history of angioedema, as well as the response to previous treatments with antihistamines and/or corticosteroids. Based on this information, it is possible to classify angioedema by endotype and establish the main pathway of pathogenic mechanism[24]:

– *histaminergic pathway:* by activating mast cells with the release of histamine, leukotrienes and prostaglandins, and other mediators. This is the most common route among children. This group includes allergic angioedema (from food, insect bites, medication, latex, among others); and angioedema induced by non-steroidal anti-inflammatory drugs (NSAIDs), whose main mechanism of hypersensitivity is cyclooxygenase inhibition;

– *bradykinin pathway:* in this pathway, both angioedema due to angiotensin converting enzyme (ACE) inhibitors and hereditary and acquired angioedema due to C1 inhibitor deficiency stand out. It is important to investigate whether there is a family history of angioedema, childhood/adolescent onset, recurrent abdominal pain, appearance of upper airway edema, lack of response to antihistamines, corticosteroids or adrenaline, presence of prodromes before the appearance of edema, and/or absence of wheals;

– *various causes:* more frequent in adults than in children. The most common causes include viral infections (Herpes Simplex, Coxsackie A and B, Hepatitis B, Epstein-Barr), bacterial (acute otitis media, acute sinusitis, acute tonsillitis and urinary tract infection), and other rarer childhood diseases such as vasculitis, autoimmune thyroiditis and idiopathic angioedema. Always consider differential diagnoses such as contact dermatitis, skin infections, lymphedema, autoimmune and thyroid diseases, parasitosis, Melkersson-Rosenthal syndrome, and, in the case of intestinal edema, other causes such as mesenteric infarction, vasculitis, and inflammatory bowel disease.[25]

9. What quality of life assessment tools, control and severity of urticaria can be used in children?

Few tools are validated for use in children, with the exception of the quality of life questionnaire, which has a specific model for this age group (CDLQI – Quality of Life Score in Children's Dermatology).

The UAS7 (Urticaria Activity Score, in seven days) is a prospective tool that assesses urticaria activity daily for seven days before the consultation, based on the number of lesions and the intensity of itching. Due to the need for daily filling by the patient, the UAS7 was only validated for people over 18 years of age. Eventually it can be used in older children, with

Table 1
Provocation tests for induced chronic urticaria (UCInd)*

Type of UCInd	Test location	Test	Reading time	Positive test
Symptomatic dermographism	Forearm or upper back	Apply moderate mechanical force to the skin with a blunt-tipped object, dermograph or FricTest®	10 minutes	Hives and itching
Cold urticaria	Forearm	Apply ice cube in plastic bag or TempTest® (4ºC) for 5 minutes	10 minutes after the test	Hives
Heat urticaria	Forearm	Heat source or TempTest® (44°C) for 5 minutes	10 minutes after the test	Hives
Delayed pressure urticaria	Forearm, upper back, thighs, or shoulder	Put a weight on the shoulder or forearm (7 kg with a 3 cm wide strap) for 15 minutes (Warin's Technique)	6 hours after the test	Angioedema and erythema
Solar urticaria	Buttocks	UVA 6 J/cm^2 and UVB 60 mJ/cm^2, or visible light (projector)	10 minutes after the test	Hives
Urticaria or vibratory angioedema	Forearm	Vortex mixer for 10 minutes at 1000 rpm	10 minutes after the test	Angioedema or hives
Cholinergic urticaria	Test 1: Exercise bike or treadmill	Exercise on a stationary bike or treadmill for 30 minutes, increasing by 3 beats every minute	Immediately and 10 minutes after the end of the test	Small hives on the body and itching
	Test 2: Hot shower	Or shower at 42 °C with a temperature monitor. Continue bathing after body temperature rises ≥ 1°C above basal temperature		

* Adapted from Magerl et al. [51]

the help of a guardian; but its interpretation must be done with discretion.[26]

The Urticaria Control Test (UCT) retrospectively assesses the control of urticaria in the last four weeks through four questions answered by the patient at the time of consultation. It has also not been validated in children, but the original study included patients under 20 years of age and can be used in well-educated adolescents.[27,28]

Similar to the UAS7, the Angioedema Activity Score (AAS) is a prospective assessment tool for angioedema only, consisting of five questions, which must be answered daily for four consecutive weeks prior to the appointment. However, it has only been validated in adults, and its applicability in children may be a little more complicated.[29]

The quality of life questionnaires in urticaria (CU-Q2oL) and angioedema (AE-QoL) assess everyday factors and can be applied during the consultation. Both have only been validated in adult patients.[30,31] However, the Children's Dermatology Quality of Life Score (CDLQI) and the Pruritus Severity Scale in Children and Adolescents (ISS-Ped) were created to assess the quality of life of children aged between 4 and 16 years, and the severity of pruritus in children aged 2 to 18 years, respectively. Although not specific, these scales can help in the follow-up of children with UC.[32,33]

10. What differential diagnoses should be considered in children with urticarial conditions?

In children, always remember urticaria, vasculitis and autoinflammatory diseases.

In urticaria vasculitis, fixed lesions are observed, lasting more than 24 hours in the same location, with a burning sensation, mild pruritus and residual hyperpigmentation. It can be classified as primary (idiopathic) or secondary to medications, infections and rheumatologic diseases. It is subclassified into normo and hypocomplementemic; the latter with systemic symptoms and association with rheumatological diseases. Skin biopsy is required for diagnosis.[34,35]

Autoinflammatory diseases should be suspected mainly when there are systemic inflammatory symptoms associated with persistent or recurrent fever.[3,34] Urticaria is a feature present in the three periodic syndromes associated with cryopyrins (Cryopyrinopathies). Cryopyrinopathies represent a spectrum of three diseases that share several features but differ in severity (in ascending order): Familial Cold Associated Inflammatory Syndrome (FCAS), Muckle-Wells Syndrome, and Neonatal Multisystem Inflammatory Disorder (NOMID) or CINCA Syndrome (chronic-infantile-neurological-cutaneous-articular). Cases are characterized by recurrent episodes of neutrophilic urticaria (often the first symptom), associated with arthralgia, myalgia, headache, fever, and sensorineural hearing loss. Ocular involvement, such as conjunctivitis, keratitis, and uveitis, can be seen in all three subtypes. Exacerbations of the condition can be triggered by cold, minor trauma or stress, and the duration of attacks varies from approximately 12 hours (in FCAS) to 1 to 3 days (in Muckle-Wells and CINCA/NOMID). In the most severe spectrum (CINCA/NOMID), the condition begins in the neonatal period, with urticarial rash, fever, arthropathy with dysmorphia, neurological system involvement (such as developmental delay, seizures, hydrocephalus, aseptic meningitis, and increased intracranial pressure), progressing to chronicity in adolescence and adulthood.[34,36]

Despite not having urticaria as a striking feature, the next syndromes should be remembered during childhood. In familial Mediterranean fever, patients typically present with a well-demarcated, unilateral or bilateral, erythematous-edematous, erysipeloid-like plaque on the anterior surface of the lower limbs. In addition, they have episodes of recurrent high fever for 1 to 3 days, asthenia, monoarthritis of large joints, abdominal pain, and serositis. In mevalonate kinase deficiency (Hyper-IgD Syndrome), IgD levels are typically, but not necessarily, elevated, and several types of skin lesions can occur, including urticaria. Fever episodes usually start before the age of four, in addition to abdominal pain, diarrhea, vomiting, serositis, headache, polyarthralgia, hepatosplenomegaly and headache. In TNF Receptor Associated Periodic Syndrome (TRAPS), the most typical skin lesion is defined as a “painful erythema” (centrifugal and migratory erythematous plaque associated with myalgia). However, on some occasions, the lesions present as urticarial plaques that often leave an ecchymosis at the site, in addition to recurrent fever, abdominal pain, musculoskeletal and ocular involvement.[36]

11. What is the treatment strategy for UC in children? Are there differences in treatment response compared to adults?

According to the international consensus, the same therapeutic regimen as adults is indicated for children.

Treatment of UC in children should always be performed with non-sedating 2nd generation (2G) antihistamines (anti-H1) with proven efficacy and safety in the pediatric population (cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, rupatadine and bilastine).[21] As in adults, it is recommended to start treatment with 2G anti-H1 at a standard dose, reassess the condition in 2 to 4 weeks and, if symptoms are not controlled, double or even quadruple the dose (1st step). In cases that are refractory to 2G anti-H1 in quadruplicate doses, the association with Omalizumab (2nd step), authorized in Brazil from 12 years of age for CSU, or Ciclosporin (3rd step) is indicated.[1]

Children with CSU treated at a reference and excellence center (UCARE) in São Paulo, showed better disease control (64.5%) and a lower rate of non-response to 2G H1 anti-H1 (23%) when compared to adults.[20] In addition, data from children with CSU from different regions of Brazil (Southeast and Northeast) showed that most of them (88.4%) had symptom control with 2G H1 anti-H1 (45% with standard dose, 25% with doubled, and 16% with quadrupled dose).[12]

In cases refractory to 2G anti-H1, a series of 10 cases of Brazilian children with CSU using omalizumab showed that the mean treatment time was 18.8 months. Regarding the response to omalizumab, 70% were controlled, 10% had a partial response and 20% did not respond to treatment. No child manifested an adverse event.[37]

12. What is the prognosis of chronic urticaria in childhood?

CSU in children is a self-limiting disease with a favorable prognosis in most cases, with an average spontaneous resolution of 83% up to 2 years of disease.

In a recent study, 250 children with CSU were analyzed, with a mean duration of symptoms of 12 to 15 months, a remission rate of 83% in 2 years, and no relationship of worse prognosis with the association of atopy.[13] In another study, the remission rate was 72% within 5 years. The higher risk of non-remission was related to the greater severity of CSU.[38] In contrast, in Canada, the CSU resolution rate per year in children was low (10%), similar to adults.[10]

Seniors

1. Are there differences in the clinical presentation of CSU compared to adults under 60 years old?

The elderly have a shorter duration of disease, less association with induced chronic urticaria (UCInd), angioedema, atopy and exacerbation by non-steroidal anti-inflammatory drugs, in addition to lower positivity in the autologous serum test (AST).

In the United States, the estimated prevalence of CSU in patients over 60 years of age is 0.23%.[39] However, a Korean study showed a second prevalence peak between 70 and 79 years old, possibly due to the presence of UC-related comorbidities more frequently in this age group.[40]

The predominance of CSU in females is controversial in the elderly.[2,4,5] In addition, disease duration, association with chronic induced urticaria (UCInd), presence of angioedema, and NSAID exacerbation appear to be shorter than in adults under 60 years of age.[41-43] Elderly people with CSU have allergic diseases less frequently. However, there is a higher prevalence of hypertension, diabetes, Hashimoto's thyroiditis, chronic renal failure and cancer in this age group.[42,44] In addition, in a Spanish study, a lower positivity of the autologous serum test was observed among the elderly, probably due to immunosenescence, in addition to eosinopenia in laboratory tests and low total IgE.[44]

2. What are the main differential diagnoses of CSU in the elderly?

The main differential diagnoses of CSU in the elderly are: drug-induced urticaria, UCInd, urticaria vasculitis, Schnitzler syndrome, urticarial dermatitis and bullous pemphigoid.

In the elderly, one of the important differential diagnoses is drug-induced urticaria, due to the frequent use of multiple drugs in this age group. The recurrent course, the temporal relationship with the use of the medication, and the control of urticaria with the withdrawal are information that help in the diagnosis. However, confirmation by skin

tests or provocation is necessary so that important medications are not replaced by more complex ones without real need.[21,45]

Urticarial dermatitis is characterized by the presence of erythematous, urticarial, often eczematous, pruritic papules with symmetrical distribution, usually on the trunk, of long duration, occurring more frequently in elderly patients.[46]

Bullous pemphigoid is a common disease in people over 60 years of age, which evolves with the appearance of tense blisters with serous or hematic content, located mainly in the inguinal region, axillae, abdomen and limbs.[47] Blisters typically develop within an erythematous, indurated plaque. However, some patients may present with multiple erythematous urticarial plaques, without the presence of blisters, and with some degree of pruritus. At this early stage, the lesions often have a serpiginous appearance, and about 10-35% of patients develop oral ulcers before the appearance of the skin lesions. The diagnosis of bullous pemphigoid requires a skin biopsy, which demonstrates a superficial infiltrate of lymphocytes and histiocytes with eosinophil enrichment classically associated with subepidermal bullae. In the direct immunofluorescence study, C3 and IgG deposits are observed in a linear pattern on the epidermal basement membrane.[48]

Schnitzler syndrome is a rare acquired autoinflammatory disease. Essential diagnostic criteria include urticarial rash and IgM or IgG monoclonal gammopathy associated with recurrent fever above 38 °C without any other cause, abnormal bone remodeling with or without bone pain, dermal neutrophil infiltrate on skin biopsy, leukocytosis and/or or elevated C-reactive protein.[35] The peak age of Schnitzler syndrome is in the sixth decade of life, but it should be suspected from the age of 40 in patients with the aforementioned diagnostic criteria.[49,50]

Urticaria vasculitis and UCInd are other differential diagnoses previously discussed.[35,51]

Chronic urticaria may be related to malignancy but disappears after the cancer heals, and this association is extremely rare (estimated at 1/1500 or less). Two possible mechanisms may link cancer to mast cell and UCE activation. The first consists of the production and release of signals derived from the tumor or stroma (such as prostaglandins, leukotrienes, vascular endothelial growth factor, etc.) that promote the accumulation and activation of mast cells; and the second, the production and release of tumor-derived antigens detected by IgE in the blood. In practice, routine screening for malignancies is not recommended. However, there are four features of CSU that may suggest an association with cancer: (1) resistance to antihistamines, (2) onset before cancer diagnosis (generally 2-8 months); (3) resolution after cancer treatment; and (4) recurrence if the cancer recurs.[52] In addition, it is mandatory to assess, through the clinical history, if there are signs and symptoms that indicate the investigation, such as fever and sudden weight loss.[21]

3. How to perform the diagnostic approach of the patient with recurrent angioedema without urticaria starting after the age of 60?

The diagnostic approach to angioedema is the same for all ages, with emphasis on continuous and recurrent medications; duration, location of angioedema and response to treatment; associated signs and symptoms; family history of angioedema; laboratory tests and provocation tests according to clinical suspicion (Table 2).

Angioedema triggered by drugs is a relevant cause in the elderly, either through the bradykinin pathway or through the release of histamine. In the histaminergic form, NSAIDs can trigger angioedema caused by one or more drugs with a different chemical structure, in addition to exacerbating CSU. This type of angioedema has a faster evolution and presents a good response to antihistamines and corticosteroids.[45]

In the bradykinin-mediated form, angioedema is caused by ACE inhibitors and other drugs involved in bradykinin metabolism, such as angiotensin II receptor blockers (ARB), statins, sacubitril, estrogens, anti-androgens, and gliptins. In these cases, angioedema has a slower duration, about 3 to 5 days, and an inadequate response to antihistamines, corticosteroids, and adrenaline. ACE inhibitors should be discontinued in all patients with recurrent angioedema, even if the angioedema started several years after starting treatment. The most frequent locations of ACE-induced angioedema are the face, tongue, oropharynx, and larynx.[45,53]

Acquired angioedema with C1 inhibitor deficiency also occurs predominantly in adults and the elderly, and may be secondary to lymphoproliferative diseases, neoplasms and collagen diseases, or due to autoantibodies against the C1 inhibitor. It is not common for hereditary angioedema (HAE) to start

Table 2
Complementary diagnostic evaluation of recurrent angioedema without urticaria

Type of angioedema	Diagnostic tests and procedures
Histaminergic angioedema	
– IgE mediated	– Immediate reading prick test and specific IgE serum dosage for food, medication and insect venom
– Spontaneous chronic angioedema	– Blood count, Hemosedimentation rate/C-reactive protein levels
– NSAID angioedema	– Provocation test
Bradykinin angioedema	– C4, quantitative and functional C1 inhibitor, C1q – Genetic test

after the age of 60, but the disease may have an earlier onset and the diagnosis may be delayed.[54]

4. What are the expected adverse effects of treating CSU in the elderly? Is there any special care in this age group?

2G anti-H1 drugs have a good safety profile, being little or not sedating, but they can cause drowsiness and anticholinergic effects in some patients, especially those with hepatic and renal failure. The adverse effects most related to omalizumab are pain at the application site and headache. As for cyclosporine, they are hypertension and nephrotoxicity. The use of corticosteroids should be restricted to short periods, due to potentially serious adverse effects in the elderly, such as hypertension, obesity, osteoporosis, cataracts and glaucoma.

In the elderly, the use of multiple drugs, both for CSU and other comorbidities, combined with the physiological changes associated with aging, can interfere with the pharmacokinetics and pharmacodynamics of drugs, altering the response, increasing the interaction between drugs and their adverse effects.[55]

2G H1 antihistamines are the first-line treatment for CSU due to their efficacy and safety profile. The use of first-generation H1 antihistamines is not recommended due to anticholinergic and sedative effects secondary to penetration into the central nervous system. In addition, undesirable adverse effects may occur for the elderly, such as urinary retention, arrhythmias, peripheral vasodilation, postural hypotension, mydriasis, changes in mental status and risk of falling.[11]

In cases of inadequate control of urticaria with a standard dose of 2G anti-H1 for 2 to 4 weeks, the dose should be increased up to four times that recommended in the package insert.[21] Despite this, there are few clinical trials of efficacy and safety in the elderly that support this recommendation. 2G H1 antihistamines are usually non-sedating, but in increased doses they can cause sedation, especially cetirizine, loratadine and rupatadine. Generally, its effects on the central nervous system are not exacerbated after the ingestion of alcohol or other

psychotropic drugs, but caution is recommended in their use.[11]

No evidence of increased risk of cardiotoxicity was observed, even with increased doses of 2G anti-H1. However, in the elderly, attention should be paid to conditions at greater risk, such as increased QT interval, cardiovascular diseases, hypokalemia, hypomagnesemia, use of drugs that cause QT interval prolongation or inhibition of 2G H1 anti-H1 metabolism.[56]

Generally, no dose adjustment of 2G H1 antihistamines is necessary in the elderly, except when the drug undergoes extensive hepatic metabolism in a patient with hepatic impairment, or the drug is excreted in the urine in patients with renal impairment (Table 3). Bilastine is the only 2G H1 anti-H1 that does not undergo hepatic metabolism. However, cetirizine, levocetirizine, and fexofenadine are also safe due to poor metabolism by the liver. The enzymatic pathway of desloratadine is not well established, but no dose adjustment is necessary in patients with hepatic impairment. Loratadine, in turn, has relevant passage through the liver and potential interaction with all inhibitors of CYP3A4 and CYP2D6 enzymes. Therefore, caution should be exercised when using it in patients with liver disease or who use drugs that inhibit the aforementioned enzymes. Furthermore, loratadine is safe in the elderly and does not require dose adjustment in this age group.[55]

In CSU refractory to a quadruplicate dose of 2G anti-H1, it is indicated to add omalizumab at a dose of 300 mg subcutaneously every four weeks. The most common adverse effects are pain at the application site, headache and arthralgia. No difference was observed in the occurrence of side effects and response to anti-IgE treatment between adults younger than 60 years and the elderly in efficacy and safety studies.[57,58]

In patients who do not respond within six months of treatment with omalizumab, consideration should be given to adding cyclosporine to 2G H1 antihistamine at a quadrupled dose.[1,21]

The efficacy of cyclosporine in CSU has been demonstrated in placebo-controlled studies, but there is a significant risk of adverse effects. Its use should be cautious in the elderly, as they may have reduced renal function and multiple comorbidities. However, it is generally a safe drug when used in doses of 3 mg/kg per day. Absolute contraindications to its use in the elderly are difficult-to-control arterial hypertension, renal dysfunction and T-cell lymphoma. Relative contraindications are: controlled arterial hypertension, active infection, concomitant use of other immunosuppressants, migraine and gout.[46]

Before starting treatment, it is recommended to carry out a complete blood count, liver and kidney function, uric acid, electrolytes, lipidogram, parasitology of feces, urine I, serology for hepatitis B and C, anti-HIV, PPD and chest X-ray. During the use of cyclosporine, the levels of systemic blood pressure, renal and hepatic function and electrolytes should be monitored monthly, as the main adverse events are arterial hypertension and nephrotoxicity. Drug interactions may occur, with drugs that may increase (diltiazem, verapamil, macrolides, amiodarone, antifungals, fluoxetine, corticosteroids, furosemide and diuretics), or reduce (phenobarbital, carbamazepine) plasma levels of cyclosporine. Live virus vaccines should be avoided.[46]

In exacerbations unresponsive to 2G anti-H1, a short course of corticosteroids (5-10 days) may be indicated. However, prolonged use of systemic corticosteroids is not recommended due to the risk of potentially serious adverse effects in the elderly, such as hypertension, obesity, osteoporosis, cataracts, and glaucoma.[59]

Pregnant and lactating women

1. Does hives tend to improve or worsen during pregnancy?

It is believed that hives may improve during pregnancy, but more studies are needed.

Urticaria is not a disease of pregnancy and, therefore, has a similar behavior to that of non-pregnant people affected. It is known that urticaria is not teratogenic, does not affect fetal development and does not alter labor.[60] The main trigger of crises is stress, and they are more frequent in the 1st and 3rd trimester of pregnancy. An international multicenter study (PREG-CU) suggests an improvement in urticaria during pregnancy. In this study, 288 pregnant women answered a questionnaire about the evolution of urticaria during pregnancy. About half of the pregnant women said that their symptoms improved, 28.9% indicated that there was no change and 20% said that there was a worsening. After delivery, 43.8% of patients remained with the same symptoms, there was a worsening in about 37%, and improvement in less than 20%.[61]

Table 3
Recommendations for the use of second-generation H1 antihistamines in the elderly with hepatic and renal impairment*

Medicines	Kidney failure (RI)	Liver failure (HI)	Additional comments
Bilastine	No dose adjustment required	No dose adjustment required	Concomitant use of inhibitor P-glycoprotein drugs should be avoided in patients with moderate and severe IR. Cardiotoxicity was not observed even with increased dose.
Cetirizine	Dosage adjustment required according to renal function. Contraindicated in severe IR	No dose adjustment required	Caution in patients with epilepsy, with a predisposition to urinary retention and concomitant use of alcohol and central nervous system (CNS) depressant drugs. Cardiotoxicity was not observed even with increased dose.
Desloratadine	Caution in severe IR	No dose adjustment required	No adverse effects were observed with the concomitant use of alcohol and CNS depressant medications. Cardiotoxicity was not observed even with increased dose.
Ebastine	No dose adjustment required	Caution in patients with mild to moderate HI. Do not exceed 10 mg/day. Contraindicated in severe IH	Caution in patients with cardiac risk such as hypokalemia, QT interval prolongation, in treatment with drugs that cause QT prolongation or inhibit the liver enzyme P450 3A4, such as antifungals and macrolides.
Fexofenadine	No dose adjustment required	Please note that data is limited	Cardiotoxicity was not observed even with increased dose.
Levocetirizine	Dosage adjustment required according to renal function. Contraindicated in severe IR	No dose adjustment required	Cardiotoxicity was not observed even with increased dose.
Loratadine	No dose adjustment required	Caution in severe IH (reduce starting dose)	Cardiotoxicity was not observed even with increased dose.
Rupatadine	Contraindicated in IR	Contraindicated in HI	Interaction with concomitant use of ketoconazole and erythromycin. Cardiotoxicity was not observed even with increased dose.

*Adapted from Ventura et al.[55]

2. Are the anti-H1 2nd G drugs indicated for treatment in this group? Is it safe to increase the dose?

Yes, some 2nd generation H1 antihistamines are category B and may be indicated during pregnancy, however, increasing the dose should be done with caution.

Any systemic medication should be prescribed with care in pregnant women, especially during the first trimester. There are no reports of birth defects in women who used anti-H1 2G during pregnancy. Although the safety of the medication has not yet been fully established in pregnant women, category B 2G H1 anti-H1 drugs are the most indicated (cetirizine, levocetirizine, loratadine, desloratadine, bilastine). Regarding the increase in the dosage of these anti-H1, there are no safety studies and they should be used with caution during pregnancy. In addition, in the case of loratadine, it should be remembered that the drug is metabolized in the liver and increased doses are not indicated (which does not apply to desloratadine).[1]

3. Are there any adverse effects of anti-H1 2G on breast milk production?

No, but antihistamines can be excreted in milk. Therefore, only second-generation ones are indicated in lactating women.

Drugs cross the mammary alveolar epithelium and are excreted in breast milk. 2G anti-H1 drugs are the most suitable for women who are breastfeeding, due to their non-sedating properties. Most of them are classified as "compatible" in the Hale Lactation Category, that is, they are drugs with no reported adverse effects on the infant in controlled studies with breastfeeding women. These are: cetirizine, desloratadine, fexofenadine, levocetirizine and loratadine.[62-64]

4. Is it safe to use omalizumab during pregnancy?

Yes. Omalizumab is non-embryotoxic, teratogenic, does not cause fetal anomalies, and appears to be a safe and efficient alternative for pregnant women.

Omalizumab is a humanized monoclonal antibody, widely used as a complementary medication in severe asthma and chronic urticaria that do not respond to usual medication. Several studies show that its use is safe during pregnancy. It is neither embryotoxic nor teratogenic and does not cause congenital anomalies.[21,65] Case reports of women who used omalizumab before and during pregnancy showed that the babies were born at term and had normal development.[66,67] In addition, it has already been used in pregnant monkeys, in doses up to 10 times that recommended in humans, without showing harm or harm to the fetus.[68] Although not approved for the treatment of urticaria in pregnancy, it appears to be a safe and efficient alternative in patients who are refractory to conventional treatment.[67]

5. Is there a difference in response to treatment compared to non-pregnant patients?

Not. Pregnancy does not interfere with the response to urticaria treatment. The urticaria treatment flowchart is the same as recommended in other patient groups.

Most national and international guidelines recommend the same treatment flowchart of urticaria in pregnant and non-pregnant women. However, there is a scarcity of scientific publications that address the management of urticaria in this group, and the safety of medications has not been fully established. In any case, the use of the lowest dose necessary for complete control of urticaria is recommended and, similar to other groups, the objective of treatment during pregnancy is to achieve total control of the disease.[11,21] Data regarding the behavior of urticaria during pregnancy are also scarce, but UC appears to be more likely to improve than to worsen during pregnancy.[61] In addition, no study has so far shown that UC during pregnancy is more refractory to treatment.[21]

6. Is it safe to use corticosteroids in pregnant/lactating women who are unresponsive to antihistamine treatment?

If used for short periods of time, corticosteroids are considered safe in pregnant and lactating women. However, these medications are not recommended for routine use in urticaria in all patients, regardless of pregnancy or breastfeeding.

The use of systemic corticosteroids, due to their safety profile, is restricted to the control of exacerbations, not only in pregnant women, but in all patients with urticaria, and should not be prescribed for prolonged use. In these situations, a short course of corticosteroids at the usual anti-inflammatory dose may be used sporadically to reduce disease duration and activity. A phasing out is unnecessary. Therefore, corticosteroids are not a therapeutic alternative to antihistamines in chronic urticaria.[69,70]

Corticosteroids are used to control various diseases during pregnancy, and their use appears to be safe, especially for short periods. Although unlikely in these situations, there is a potential risk of association with gestational diabetes, preeclampsia, neonatal adrenal insufficiency, and low birth weight. Thus, the benefit of its use must outweigh the potential risks.

Small amounts of corticosteroids, such as prednisone and prednisolone, are excreted in milk. Despite this, the use of systemic corticosteroids during lactation is considered safe; however, it is recommended to delay breastfeeding for a few hours after the daily dose of corticosteroid to minimize possible risks.[11,60]

7. What are the main differential diagnoses of CSU during pregnancy?

Urticarial pruritic papules and plaques of pregnancy (PPUG), atopic rash of pregnancy, pemphigoid gestationis, intrahepatic cholestasis of pregnancy, and pustular psoriasis of pregnancy are the dermatoses that should be considered in the differential diagnosis of urticaria in pregnancy.

Differential diagnoses of urticaria should be considered in all patients, including pregnancy.[21,34]

Pregnancy is a period characterized by dermatological changes, with some specific dermatoses of this condition, as well as pruritus without injury. Hives can occur during, but are not pregnancy-specific. The dermatoses of pregnancy are rare and there are no adequate tests for the diagnosis, making their management difficult. The main cutaneous manifestations and the maternal-fetal risk of pregnancy dermatoses are described in Tables 4 and 5, respectively.[11,60,71,72]

Autoimmune progesterone dermatitis is a rare, recurrent disease that affects women of childbearing age. Cutaneous manifestations are polymorphic, ranging from eczematous, vesicular-papular or erythema multiforme-like lesions, and there may be a transient urticarial phase. Therefore, it should be considered in the differential diagnosis of urticaria in pregnancy.[60,72]

Whenever there is diagnostic doubt, it is interesting to advise patients to photograph the lesions to help elucidate the condition.[60] Additionally, in every patient diagnosed with urticaria and an inadequate response to high doses of antihistamines, a possible differential diagnosis should be considered.[11,21]

Conclusion

Clinically, chronic urticaria presents with a well-defined clinical picture, which allows its identification regardless of age group. However, some differential diagnoses must be kept in mind in specific groups of patients, especially if there are other associated symptoms or if the lesions do not have the typical features. Despite the lack of robust studies in certain groups of patients, the recommended treatment does not differ from the rest of the population with urticaria and follows the same flowchart proposed in the international consensus.

Conflict of interests

Eli Mansour: speaker, event support and scientific advice from Novartis®, CSL Behring®, Takeda® and Sanofi®. Regis Albuquerque Campos: speaker, advisory board and clinical research participant for Novartis®. Solange Oliveira Rodrigues Valle: speaker, consultancy and research for Novartis®. Luis Felipe Chiaverini Ensina: clinical research, advisory board and speaker for Novartis® and Sanofi®; advisory board and speaker for Abbvie®; speaker for Mantercorp®.

Table 4
Cutaneous manifestations of pregnancy-specific dermatoses*

Gestational dermatosis	Cutaneous manifestations
Urticarial Pruritic Papules and Plaques of Pregnancy (PPUG)	Initially small, urticarial, papular and fixed lesions, with progressive coalescence they become plaques. Additionally, they may show changes nd eczema, vesicles, or target lesions.
Atopic eruption of pregnancy	May present with eczematous or papular lesions. The eczematous type affects the typical areas of atopic dermatitis such as the face, neck and flexor areas. In the second type, papular lesions, with small erythematous papules, occur on the extremities and trunk.
Pemphigoid gestational	In the acute phase, the eruptions are urticarial and intensely pruritic papules, plaques, vesicles and bullae, initially in the abdomen and later affecting the extremities. In later stages, vesicles and bullae predominate, sparing the face, mucous membranes, palms and soles.
Intrahepatic cholestasis of pregnancy	Skin itching of sudden onset, in the second and third trimester, including the palms and soles. Absence of primary lesions, and with progression may have secondary alterations, ranging from mild excoriations to severe nodular prurigo.
Pustular psoriasis of pregnancy	Symmetric erythematous plaques with sterile pustules at the edges of the plaques. Associated constitutional symptoms often present and include malaise, fever, delirium, diarrhea, vomiting, and tetany.

*Adapted from Peroni et al.[72] and Lehrhoff et al.[71]

Table 5
Pregnancy-specific dermatoses and the associated maternal and fetal risk*

Gestational dermatosis	Maternal risk	Fetal risk
Urticarial Pruritic Papules and Plaques of Pregnancy (PPUG)	There is not	There is not
Atopic eruption of pregnancy	There is not	There is not
Pemphigoid gestational	Greater long-term risk of Graves' disease	Preterm birth, low birth weight
Intrahepatic cholestasis of pregnancy	Induction of labor, cholesterol and cholestatic stones, steatorrhea, and intrapartum hemorrhage	Meconium in amniotic fluid, preterm delivery, intrauterine fetal death
Pustular psoriasis of pregnancy	Constitutional symptoms, hypocalcemia with tetany, seizures	Intrauterine fetal death, stillbirth, neonatal death

* Adapted from Lehrhoff et al.[71]

References

1. 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.
2. 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.
3. Ben-Shoshan M, Grattan CE. Management of Pediatric Urticaria with Review of the Literature on Chronic Spontaneous Urticaria in Children. J Allergy Clin Immunol Pract. 2018;6(4):1152-61.
4. 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 Immunopathol (Madr). 2019;47(5):484-90.
5. Guo C, Saltoun C. Urticaria and angioedema. Allergy Asthma Proc. 2019;40(6):437-40.
6. Minasi D, Manti S, Chiera F, Licari A, Marseglia GL. Acute urticaria in the infant. Pediatr Allergy Immunol. 2020;31(S26):49-51.
7. Sabroe RA. Acute Urticaria. Immunol Allergy Clin North Am. 2014;34(1):11-21.
8. Caffarelli C, Paravati F, El Hachem M, Duse M, Bergamini M, Simeone G, et al. Management of chronic urticaria in children: A clinical guideline. Ital J Pediatr. 2019;45(1):1-25.
9. Fricke J, Ávila G, Keller T, Weller K, Lau S, Maurer M, et al. Prevalence of chronic urticaria in children and adults across the globe: Systematic review with meta-analysis. Allergy Eur J Allergy Clin Immunol. 2020;75(2):423-32.
10. Netchiporouk E, Sasseville D, Moreau L, Habel Y, Rahme E, Ben-Shoshan M. Evaluating comorbidities, natural history, and predictors of early resolution in a cohort of children with Chronic Urticaria. JAMA Dermatology. 2017;153(12):1236-42.
11. Saini S, Shams M, Bernstein JA, Maurer M. Urticaria and Angioedema Across the Ages. J Allergy Clin Immunol Pract. 2020;8(6):1866-74.
12. Brandão L, Araujo C, Moura AC, Bruscky D, Dela Bianca AC, Camelo-Nunes I, et al. Chronic urticaria in children: a real-life study. J Allergy Clin Immunol. 2021;147(2):AB25.
13. Lachover-Roth I, Rabie A, Cohen-Engler A, Rosman Y, Meir-Shafrir K, Confino-Cohen R. Chronic urticaria in children – New insights from a large cohort. Pediatr Allergy Immunol. 2021;32(5):999-1005.
14. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: What we know and what we do not know. J Allergy Clin Immunol. 2017;139(6):1772-81.
15. Schmetzer O, Lakin E, Topal FA, Preusse P, Freier D, Church MK, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. J Allergy Clin Immunol. 2018;142(3):876-82.
16. Barzilai O, Ram M, Shoenfeld Y. Viral infection can induce the production of autoantibodies. Curr Opin Rheumatol. 2007;19(6):636-43.
17. Sahiner UM, Civelek E, Tuncer A, Yavuz ST, Karabulut E, Sackesen C, et al. Chronic urticaria: Etiology and natural course in children. Int Arch Allergy Immunol. 2011;156(2):224-30.
18. Caffarelli C, Cuomo B, Cardinale F, Barberi S, Dascola C, Agostinis F, et al. Aetiological Factors Associated with Chronic Urticaria in Children: A Systematic Review. Acta Derm Venereol. 2013;93(3):268-72.

19. Azkur D, Civelek E, Toyran M, Mısırlıoglu ED, Erkoçoglu M, Kaya A, et al. Clinical and etiologic evaluation of the children with chronic urticaria. Allergy Asthma Proc. 2016;37(6):450-7.
20. Ensina LF, Bastos PGA, de Lacerda AE, de Araujo CA, Camelo-Nunes I, Solé D. Comments on Balp et al. Pediatr Allergy Immunol. 2018;29(6):669-70.
21. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy Eur J Allergy Clin Immunol. 2018;73(7):1393-414.
22. Miles LM, Gabrielli S, Le M, Netchiporouk E, Baum S, Greenberger S, et al. Clinical Characteristics, Management, and Natural History of Chronic Inducible Urticaria in a Pediatric Cohort. Int Arch Allergy Immunol. 2021;182(8):757-64.
23. Bal F, Kahveci M, Soyer O, Sekerel BE, Sahiner UM. Chronic inducible urticaria subtypes in children: Clinical features and prognosis. Genuneit J, editor. Pediatr Allergy Immunol. 2021;32(1):146-52.
24. Giavina-Bianchi P, Aun MV, Motta AA, Kalil J, Castells M. Classification of angioedema by endotypes. Clin Exp Allergy. 2015;45(6):1142-3.
25. Pattanaik D, Lieberman JA. Pediatric Angioedema. Curr Allergy Asthma Rep. 2017;17(9):60.
26. Hawro T, Ohanyan T, Schoepke N, Metz M, Peveling-Oberhag A, Staubach P, et al. The Urticaria Activity Score - Validity, Reliability, and Responsiveness. J Allergy Clin Immunol Pract. 2018;6(4):1185-90.
27. Weller K, Groffik A, Church MK, Hawro T, Krause K, Metz M, et al. Development and validation of the Urticaria Control Test: A patient-reported outcome instrument for assessing urticaria control. J Allergy Clin Immunol. 2014 May;133(5):1365-72, 1372.e1-6.
28. Valle SOR, Dortas-Junior SD, Dias GAC, Motta AA, do-Amaral CSF, Martins EAPR, et al. Ferramentas para avaliação e acompanhamento da urticária crônica. Arq Asma, Alerg e Imunol. 2018;2(2):209-24.
29. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development, validation, and initial results of the Angioedema Activity Score. Allergy. 2013;68(9):1185-92.
30. Baiardini I, Pasquali M, Braido F, Fumagalli F, Guerra L, Compalati E, et al. A new tool to evaluate the impact of chronic urticaria on quality of life: chronic urticaria quality of life questionnaire (CU-Q2oL). Allergy. 2005;60(8):1073-8.
31. Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and construct validation of the angioedema quality of life questionnaire. Allergy. 2012;67(10):1289-98.
32. Prati C, Comparin C, Catucci Boza J, Ferreira Cestari T. Validação para o português falado no Brasil do instrumento Escore da Qualidade de Vida na Dermatologia Infantil (CDLQI). Med Cutan Ibero Lat Am. 2010;38(6):229-33.
33. Bruscky DMV, Melo ACCDB, Sarinho ESC. Cross-cultural adaptation and validation of the itching severity scale in children and adolescents with atopic dermatitis. Rev Paul Pediatr. 2017;35(3):244-51.
34. Davis MDP, van der Hilst JCH. Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases. J Allergy Clin Immunol Pract. 2018;6(4):1162-70.
35. Zuberbier T, Maurer M. Urticarial Vasculitis and Schnitzler Syndrome. Immunol Allergy Clin North Am. 2014;34(1):141-7.
36. Hernández-Ostiz S, Prieto-Torres L, Xirotagaros G, Noguera-Morel L, Hernández-Martín, Torrelo A. Autoinflammatory Diseases in Pediatric Dermatology-Part 1: Urticaria-like Syndromes, Pustular Syndromes, and Mucocutaneous Ulceration Syndromes. Actas Dermosifiliogr. 2017;108(7):609-19.
37. Japiassu LG, Bastos PGA, Araújo CA, Camelo-Nunes I, Solé D, Ensina LF. Omalizumabe no tratamento da urticária crônica espontânea em pacientes pediátricos: série de casos. Arq Asma Alerg Imunol. 2018;2(1):78.
38. Cortellazzo Wiel L, Conversano E, Giangreco M, Fagotto L, Genovese MRL, Badina L, et al. Natural history and predictors of recovery in children with chronic spontaneous urticaria. Pediatr Allergy Immunol. 2021;32(1):201-4.
39. Wertenteil S, Strunk A, Garg A. Prevalence estimates for chronic urticaria in the United States: A sex- and age-adjusted population analysis. J Am Acad Dermatol. 2019;81(1):152-6.
40. Kim BR, Yang S, Choi JW, Choi CW, Youn SW. Epidemiology and comorbidities of patients with chronic urticaria in Korea: A nationwide population-based study. J Dermatol. 2018;45(1):10-6.
41. Chuamanochan M, Kulthanan K, Tuchinda P, Chularojanamontri L, Nuchkull P. Clinical features of chronic urticaria in aging population. Asian Pacific J Allergy Immunol. 2016;34(3):201-5.
42. Magen E, Mishal J, Schlesinger M. Clinical and laboratory features of chronic idiopathic urticaria in the elderly. Int J Dermatol. 2013;52(11):1387–91.
43. Ban G-Y, Kim M-Y, Yoo H-S, Nahm D-H, Ye Y-M, Shin Y-S, et al. Clinical features of elderly chronic urticaria. Korean J Intern Med. 2014;29(6):800.
44. Curto-Barredo L, Pujol RM, Roura-Vives G, Gimenez-Arnau AM. Chronic urticaria phenotypes: clinical differences regarding triggers, activity, prognosis and therapeutic response. Eur J Dermatology. 2019;29(6):627-35.
45. Longhurst HJ, Gonçalo M, Godse K, Ensina LF. Managing Chronic Urticaria and Recurrent Angioedema Differently with Advancing Age. J Allergy Clin Immunol Pract. 2021;9(6):2186-94.
46. Valle SOR, Motta AA, Amaral CS, Ensina LFC, Mallozi MC, Spengler MG, et al. What is new in chronic spontaneous urticaria? Brazilian J Allergy Immunol. 2016;4(1):9-25.
47. França AT, Valle SOR. Urticária e angioedema: diagnóstico e tratamento. 3rd ed. Rio de Janeiro: Revinter; 2014.
48. Brodell LA, Beck LA. Differential diagnosis of chronic urticaria. Ann Allergy, Asthma Immunol. 2008;100(3):181-8.
49. Gellrich FF, Günther C. Schnitzler syndrome. Hautarzt. 2019 Jun 5. English. doi: 10.1007/s00105-019-4434-4.
50. Zuberbier HCT, Maurer M. Urticarial Vasculitis and Schnitzler Syndrome. Immunol Allergy Clin North Am. 2014;34(1):141-7.
51. Magerl M, Altrichter S, Borzova E, Giménez-Arnau A, Grattan CEH, Lawlor F, et al. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA 2 LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy. 2016;71(6):780-802.
52. Larenas-Linnemann D, Saini SS, Azamar-Jácome AA, Jensen-Jarolim E, Maurer M. Very rarely chronic urticaria can be caused by cancer and if so, resolves with its cure. Allergy Eur J Allergy Clin Immunol. 2018;73(9):1925-6.
53. Faisant C, Armengol G, Bouillet L, Boccon-Gibod I, Villier C, Lévesque H, et al. Angioedema Triggered by Medication Blocking the Renin/Angiotensin System: Retrospective Study Using the French National Pharmacovigilance Database. J Clin Immunol. 2016;36(1):95-102.
54. Giavina-Bianchi P, Arruda LK, Aun MV, Campos RA, Chong-Neto HJ, Constantino-Silva RN, et al. Diretrizes brasileiras para o diagnóstico e tratamento do angioedema hereditário - 2017. Arq Asma, Alerg Imunol. 2017;1(1):23-48.
55. Ventura MT, Cassano N, Romita P, Vestita M, Foti C, Vena GA. Management of Chronic Spontaneous Urticaria in the Elderly. Drugs Aging. 2015;32(4):271-82.
56. Cataldi M, Maurer M, Taglialatela M, Church MK. Cardiac safety of second-generation H1-antihistamines when updosed in chronic spontaneous urticaria. Clin Exp Allergy. 2019;49(12):1615-23.
57. Nettis E, Cegolon L, Di Leo E, Canonica WG, Detoraki A, Baiardini I, et al. Omalizumab in elderly patients with chronic spontaneous urticaria: An Italian real-life experience. Ann Allergy, Asthma Immunol. 2018;120(3):318-23.

58. Martina E, Damiani G, Grieco T, Foti C, Pigatto PDM, Offidani A. It is never too late to treat chronic spontaneous urticaria with omalizumab: Real-life data from a multicenter observational study focusing on elderly patients. Dermatol Ther. 2021;34(2):e14841.
59. Antia C, Baquerizo K, Korman A, Bernstein JA, Alikhan A. Urticaria: A comprehensive review: Epidemiology, diagnosis, and work-up. J Am Acad Dermatol. 2018;79(4):599-614.
60. Lawlor F. Urticaria and Angioedema in Pregnancy and Lactation. Immunol Allergy Clin North Am. 2014;34(1):149-56.
61. Kocatürk E, Al-Ahmad M, Krause K, Gimenez-Arnau AM, Thomsen SF, Conlon N, et al. Effects of pregnancy on chronic urticaria: Results of the PREG-CU UCARE study. Allergy. 2021;76(10):3133-44.
62. Hale TW. Medications and mother's milk. 15th ed. Center IR, ed. Pharmasoft Publishing; 2012. p. 352-2519.
63. Murase JE, Heller MM, Butler DC. Safety of dermatologic medications in pregnancy and lactation. J Am Acad Dermatol. 2014;70(3):401.e1-401.e14.
64. Giugliani ERJ, Vieira GO, Elias CLLF, Closs CTK, Issler RM da S, Alves RMNR, et al. Uso de medicamentos e outras substâncias pela mulher durante a amamentação. Soc Bras Pediatr Dep Cient Aleitamento Matern. 2017;4:1-18.
65. Sánchez-Borges M, Ansotegui IJ, Baiardini I, Bernstein J, Canonica GW, Ebisawa M, et al. The challenges of chronic urticaria part 2: Pharmacological treatment, chronic inducible urticaria, urticaria in special situations. World Allergy Organ J. 2021;14(6):100546.
66. Losappio LM, Mirone C, Schroeder JW, Scibilia J, Balossi L, Pastorello EA. Omalizumab Use in Chronic Spontaneous Urticaria during Pregnancy and a Four Years' Follow-Up: A Case Report. Case Rep Dermatol. 2020;12(3):174-7.
67. Ensina L, Cusato-Ensina A, Camelo-Nunes I, Solé D. Omalizumab as Third-Line Therapy for Urticaria During Pregnancy. J Investig Allergol Clin Immunol. 2017;27(5):326-7.
68. Cuervo-Pardo L, Barcena-Blanch M, Radojicic C. Omalizumab use during pregnancy for CIU: a tertiary care experience. Eur Ann Allergy Clin Immunol. 2016;48(4):145-6.
69. Melo JML, Borges LV, França AT, Dias GA, Ensina LFC, Agondi RC, et al. Guia prático do tratamento com omalizumabe para urticária crônica espontânea. Arq Asma Alerg Imunol. 2020;4(3):289-99.
70. Bauer A, Dickel H, Jakob T, Kleinheinz A, Lippert U, Metz M, et al. Expert consensus on practical aspects in the treatment of chronic urticaria. Allergo J Int. 2021;30(2):64-75.
71. Lehrhoff S, Pomeranz MK. Specific dermatoses of pregnancy and their treatment. Dermatol Ther. 2013;26(4):274-84.
72. Peroni A, Colato C, Schena D, Girolomoni G. Urticarial lesions: If not urticaria, what else? The differential diagnosis of urticaria. J Am Acad Dermatol. 2010;62(4):541-55.

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