

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

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de Alergia e Imunologia

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Evolution of the diagnosis and management of urticaria

Evolução do diagnóstico e tratamento da urticária

Rosana Câmara Agondi¹

Not long ago, the main urticaria subtype was called chronic idiopathic urticaria (CIU); some defined it as an allergic disease, while others defined it as a psychiatric disorder. Autoimmunity has always been involved in the pathophysiology of chronic urticaria. Our growing practical experience with the use of omalizumab, based initially on case reports and later on clinical trials and real-world studies, has set off a boom in research on the pathophysiology, pathogenesis, and treatment of urticaria. Currently, CIU is called chronic spontaneous urticaria (CSU), with autoimmunity as the main pathogenic mechanism involved.

Two autoimmune mechanisms are proposed for CSU: *autoimmune*, where IgG anti-IgE high affinity receptors or IgG anti-IgE autoantibodies are observed, involving a type IIb hypersensitivity reaction; and *autoallergic*, where IgE autoantibodies that recognize autoantigens are observed, such as thyroid peroxidase, involving a type I hypersensitivity reaction. Mast cells are the key cell type, and histamine is a major mediator involved in CSU.

All these advances in a short space of time have led to many changes in the CSU treatment algorithm. The latest international guideline recommends a treatment algorithm consisting of

only 3 levels, with an effective and safe response in more than 80% of patients.

However, we want more! Increased disease control and improved quality of life of patients with CSU make us more eager to better understand the prognosis of the disease.

In this issue, Pereira et al. analyzed a potential biomarker, already suggested in the literature, for disease activity and treatment response. The presence of basopenia implies greater disease activity, a type IIb autoimmune mechanism, and a delayed response to omalizumab. In a retrospective study, the authors evaluated peripheral blood basophil counts, disease control, and response to omalizumab.⁴

Conversely, there are still many challenges to be faced in the clinical investigation and treatment of chronic inducible urticaria (CIndU). CIndU includes 9 subtypes and, unlike CSU, most of these subtypes can develop episodes of anaphylaxis. Triggers are well known, but not by most patients. For example, in a patient who develops hives and/or angioedema when exposed to a hot sunny day, a detailed history-taking is required and probably 2 or more provocation tests will be necessary to confirm the diagnosis. Azizi et al. describe the characteristics of a CIndU subtype, cholinergic urticaria, its mechanisms, impact on

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quality of life, and differential diagnoses as well as its challenging investigation.⁵

While we have greatly improved our knowledge of CSU and, at a lower level, of CIndU, we still have much to learn. The diagnosis of CSU is basically clinical. Therefore, we must value history-taking and physical examination, in addition to recognizing and ruling out differential diagnoses, such as urticarial vasculitis and bradykinin-mediated angioedema.

In this respect, a guideline on the topic, acute or chronic urticaria, can be of major help. Dias et al. developed a practical guide based on the international guideline on urticaria including the main topics on the disease. This review describes in detail everything from definition to treatment of patients with urticaria, including special populations such as older adults and pregnant women.⁶

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;77:734-66.
2. Kolkhir P, Giménez-Arnau AM, Kulthanan K, Peter J, Metz M, Maurer M. Urticaria. *Nat Rev Dis Primers*. 2022;8:61.
3. 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;71:780-802.
4. Pereira H, Lopes JC, Carrapatoso I, Todo-Bom A. Chronic spontaneous urticaria: correlation of basophil counts with disease control and response to anti-IgE therapy. *Arq Asma Alerg Imunol*. 2024;8(2):146-50.
5. Azizi GC, Dortas-Junior SD, Bastos-Junior RM, Lupi O, Valle SOR. Testes de provocação na urticária colinérgica: necessidades não atendidas [Letter]. *Arq Asma Alerg Imunol*. 2024;8(2):178-9.
6. Dias GAC, Agondi RC, Brandão LS, Mansour E, Santos PFAM, Campinhos FL, et al. Atualização do Guia Prático da Associação Brasileira de Alergia e Imunologia para o Diagnóstico e Tratamento da Urticária baseado na diretriz internacional. *Arq Asma Alerg Imunol*. 2024;8(2):91-115.

An update on the Brazilian Association of Allergy and Immunology Practical Guide for the Diagnosis and Management of Urticaria based on the international guideline

Atualização do Guia Prático da Associação Brasileira de Alergia e Imunologia para o Diagnóstico e Tratamento da Urticária baseado na diretriz internacional

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ABSTRACT

Urticaria is a condition characterized by the presence of hives, angioedema, or both. It can be classified according to its duration as acute, when it persists for less than 6 weeks, or chronic, when it persists for more than 6 weeks and greatly affects quality of life. Updated recommendations on diagnosis and management are developed by experts from all over the world who meet every 4 years in Berlin and review all new evidence that supports changes to the international guideline. This paper discusses the main recommendations proposed in the current version of the international guideline.

Keywords: Urticaria, angioedema, diagnosis, evidence-based practice.

RESUMO

A urticária é uma condição caracterizada pela presença de urticas, angioedema, ou ambos, que pode ser classificada de acordo com o tempo de duração em aguda, quando persiste por menos de 6 semanas, ou crônica, quando por mais de 6 semanas e afeta significativamente a qualidade de vida. A atualização das recomendações quanto ao seu diagnóstico e tratamento é elaborada por especialistas de todo o mundo, que se reúnem a cada quatro anos em Berlim para revisar todas as novas evidências que justifiquem modificações na diretriz internacional. Este artigo discute as principais recomendações propostas na versão atual da diretriz internacional.

Descritores: Urticária, angioedema, diagnóstico, prática clínica baseada em evidências.

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Introduction

The purpose of this guide is to provide a practical discussion of the main recommendations from the current version of the International Guideline for the Definition, Classification, Diagnosis, and Management of Urticaria. The update and revision of the international guideline was conducted according to the methods recommended by Cochrane and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. The conference took place in a hybrid format, both in Berlin and online, on December 3, 2020. The updated version was acknowledged and accepted by the European Union of Medical Specialists (UEMS) and published in early 2022. It was a joint initiative of the Dermatology Section of the European Academy of Allergy and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA²LEN) and its Urticaria and Angioedema Centers of Reference and Excellence (UCAREs and ACAREs), the European Dermatology Forum (EDF), and the Asia-Pacific Association of Allergy, Asthma, and Clinical Immunology (APAAACI) with the participation of 64 delegates of 50 national and international societies and from 31 countries.^{1,2}

The updated guideline covers the definition and classification of urticaria and outlines expert-guided and evidence-based diagnostic and therapeutic approaches for the different subtypes of urticaria.

Definition

Urticaria is a common and heterogeneous inflammatory skin condition characterized by the appearance of wheals—edematous lesions of variable size, usually surrounded by erythema, itchy and fleeting in nature, and typically lasting ≤ 24 hours without leaving residual marks^{1,3} (Figure 1). Angioedema, in contrast, manifests as sudden and pronounced swelling in the lower dermis and subcutis or mucous membranes, often accompanied by pain, burning, or itching. Angioedema has a slower resolution than that of wheals, sometimes lasting up to 72 hours (Figure 2).¹

Classification

Urticaria is classified based on its duration as either acute or chronic and by the role of specific triggers as spontaneous or inducible. Acute urticaria



Figure 1

Wheals

Source: Personal archive of R. Agondi.



Figure 2

Angioedema

Source: Personal archive of G. Dias.

(AU) is defined as the appearance of wheals and/or angioedema for 6 weeks or less. Chronic urticaria (CU) is defined as the occurrence of wheals and/or angioedema for more than 6 weeks. Symptoms in CU may occur daily, almost daily, or with an intermittent or recurring course.¹

CU may occur spontaneously, referred to as chronic spontaneous urticaria (CSU), or as a result of specific triggers, known as inducible chronic urticaria (CIndU). CIndU is further subclassified into symptomatic dermographism, cold urticaria, heat urticaria, delayed pressure urticaria, solar urticaria, vibratory angioedema, cholinergic urticaria, aquagenic urticaria, and contact urticaria (Table 1).^{1,3} Patients can have more than one type of CU simultaneously.³

Epidemiology and natural course

Urticaria is a common condition resulting from mast cell activation, presenting with wheals, angioedema, or both. The lifetime prevalence of AU is approximately 20%. CU, whether spontaneous or inducible, is

debilitating, significantly impairs quality of life, and affects performance at work and school. The prevalence of CU ranges from 0.1% to 1.0%, with a recent study reporting a prevalence of diagnosed CU of 0.41% in the Brazilian population.⁴

The average duration of AU is 1 week, with the rate of progression from acute to chronic varying from 5% to 39% across most studies. CU typically lasts between 1 and 4 years, with spontaneous remission occurring in approximately 45% of cases after 5 years of disease. In patients followed at a urticaria referral and excellence center in Brazil, the median duration of CU was 24 months at the time of diagnosis, while those who entered remission had a median duration of 72 months at discharge.⁵ Another Brazilian center reported an average duration of 10.2 years in patients undergoing follow-up.⁶

Recurrence of urticaria symptoms occurs in about one-third of patients. CIndU generally has a longer duration than CSU, which varies according to each subtype.³

Table 1

Classification of chronic urticaria¹

Chronic spontaneous urticaria	Chronic inducible urticaria
Spontaneous appearance of wheals and/or angioedema for > 6 weeks	Symptomatic dermographism
Without a specific trigger	Cold urticaria
	Heat urticaria
	Solar urticaria
	Delayed pressure urticaria
	Vibratory angioedema
	Aquagenic urticaria
	Cholinergic urticaria
	Contact urticaria

Pathophysiological aspects

Mast cells play a central role in urticaria. Histamine and other mediators, such as cytokines released from activated skin mast cells, lead to sensory nerve activation, vasodilatation, and plasma extravasation, as well as cell recruitment (T lymphocytes, eosinophils, and neutrophils) to lesions. The mast cell-activating stimuli in urticaria are heterogeneous and include, for example, T cell-driven cytokines and autoantibodies. Histologically, wheals are characterized by edema of the upper and mid dermis, with dilatation and augmented permeability of the postcapillary venules of the upper dermis.^{1,3}

Type I hypersensitivity reactions are primarily associated with AU and occur due to specific interactions between IgE antibodies, which are bound to the surface of mast cells, and specific allergens, leading to mast-cell activation. Medications, foods, and insect venom are major causes of this type of reaction.³

Although the pathogenesis of CU is not fully understood, two pathogenic mechanisms have been proposed for mast-cell activation in CSU, both involving autoimmune processes. The first mechanism is known as autoimmune CSU or type IIb autoimmunity (CSU^{aiIIb}), associated with immunoglobulin (Ig) G autoantibodies to FcεRI (IgG anti-FcεRI) or IgG anti-IgE. The second proposed autoimmune mechanism is termed autoallergic CSU or type I autoimmunity (CSU^{aiTI}) and involves IgE antibodies to autoantigens. The most studied and recognized autoantigens in this context are thyroid peroxidase (IgE anti-TPO) and interleukin-24 (IgE anti-IL-24)^{1,3} (Figure 3).

Diagnosis of urticaria

Diagnosis of acute urticaria

AU does not typically require additional workup (Table 2). In most cases, it is associated with viral infections (especially in children), but may also

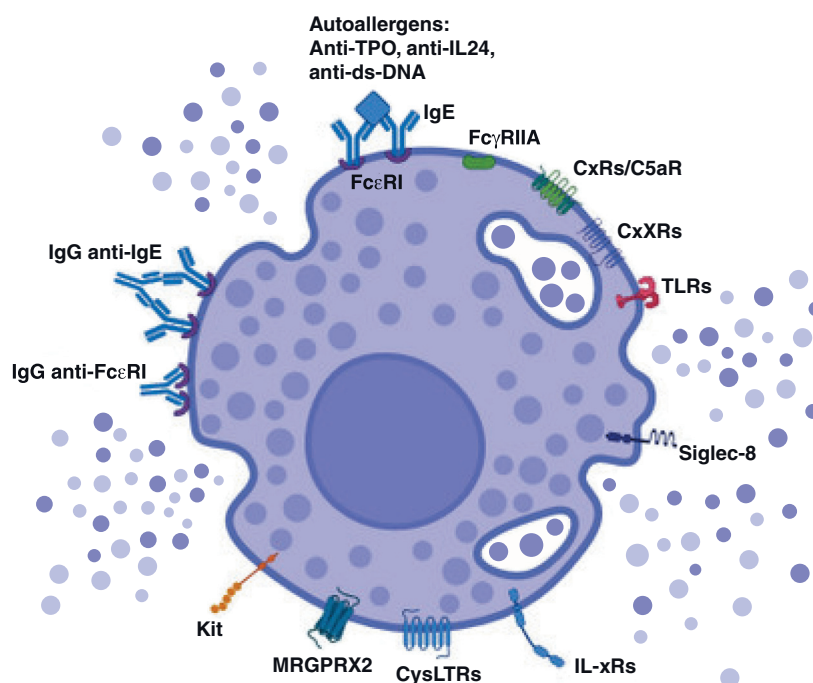


Figure 3

Mechanisms of type I and type IIb autoimmunity

Several receptors that induce mast cell degranulation are illustrated.^{7,8}

CxRs = complement receptors, CxXRs = chemokine receptors, CysLTRs = cysteinyl leukotriene receptors, FcεRI = IgE receptor-I, FcγRIIA = IgG receptor-IIA, IL-xRs = interleukin receptors, MRGPRX2 = MAS-related G protein-coupled X2 receptor, Siglec-8 = sialic acid-binding immunoglobulin-like lectin-8, TLRs = Toll-like receptors, TPO = thyroperoxidase.

Table 2

Recommended diagnostic tests in the investigation of urticaria

Type	Subtype	Recommended routine diagnostic tests	Extended diagnostic program ^a
Spontaneous urticaria	Acute spontaneous urticaria	None	None ^b
	Chronic spontaneous urticaria	Differential blood count, ESR and/or CRP, IgG anti-TPO, and total IgE ^c	Identify suspected triggers (eg, medications); diagnostic tests for 1) infectious diseases, 2) functional autoantibodies (eg, basophil test), 3) thyroid disorders (thyroid hormones and autoantibodies), 4) skin allergy tests and/or allergen avoidance test, 5) concomitant CIndU, 6) systemic disease.
Inducible urticaria	Cold urticaria	Ice cube provocation test and/or TempTest 4.0 ^{d,e}	Differential blood count, ESR or CRP, and rule out differential diagnoses, especially infections
	Delayed pressure urticaria	Dermographometer/Warin test ^{d,e}	None
	Heat urticaria	Heat provocation test and TempTest 4.0 ^{d,e}	None
	Solar urticaria	Provocation test with U-V and visible light of different wavelengths ^{d,e}	Rule out other light-induced dermatoses
	Symptomatic dermographism	Fric-test [®] 4.0/dermographometer ^{d,e}	Differential blood count, ESR or CRP
	Vibratory angioedema	Provocation test with a vortex-mixer ^{d,e}	None
	Aquagenic urticaria	Provocation test with a water compress ^{d,e}	None
	Cholinergic urticaria	Ergometry provocation test ^{d,e}	None
	Contact urticaria	Open provocation test with the suspected allergen ^{d,e}	None

CIndU = chronic inducible urticaria, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, Ig = immunoglobulin, TPO = thyroid peroxidase.

^a Depending on the suspected cause.^b Unless strongly suggested by patient history, for example, allergy.^c For patients in specialist care.^d All tests are performed with different levels of the potential trigger to determine the threshold.^e For details on the provocation test, refer to CIndU.

occur spontaneously without any identifiable trigger (idiopathic).⁹ Exceptions occur in the suspicion of AU in association with IgE-mediated allergies. In these cases, allergy skin tests or serum-specific IgE measurements should be considered. In our population, foods, medications, and Hymenoptera insect venom are major causes of IgE-mediated urticaria.¹⁰

Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are common causes of AU through non-IgE-mediated mechanisms. NSAID-induced urticaria often presents with angioedema alone, without wheals. Thorough investigation of these cases is crucial to ensure that the patient receives adequate guidance and to avoid further reactions.^{11,12}

Extra caution is needed in cases of medication-induced urticaria to avoid misdiagnosing a patient as allergic to a particular medication without adequate investigation.^{11,13}

Diagnosis of chronic spontaneous urticaria

The cornerstones of CSU diagnosis are a thorough clinical history and a physical examination showing evidence of wheals and/or angioedema. However, basic laboratory tests may also be performed, including differential blood count, C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), and total IgE and IgG anti-TPO for all patients with CSU. These tests are important to rule out other conditions associated with urticaria, such as chronic infections, lymphoproliferative diseases, autoimmune disorders, and autoinflammatory diseases.¹ In addition, CRP is a useful marker for assessing urticaria activity, as elevated CRP levels may be directly linked to more severe cases of urticaria.¹⁴ Total IgE and IgG anti-TPO levels are useful for evaluating the autoimmune endotype and treatment response. Although extensive laboratory investigation is not typically recommended, additional tests may be necessary depending on the patient's clinical history, physical examination, and routine diagnostic test results (Table 2).¹

In CSU, diagnostic evaluation should focus on seven key objectives (referred to as the “7 Cs”): confirm the diagnosis and exclude differential diagnoses; look for the underlying causes; identify cofactors, that is, relevant conditions that modify disease activity; check for comorbidities; identify the consequences of CSU; assess predictors of the course of disease and response to treatment; and monitor disease control, activity, and impact (Table 3).^{1,15}

Identification of underlying causes and factors

Determining the underlying cause of CSU remains uncertain and challenging. Based on recent evidence, the main hypotheses for CSU pathogenesis include autoimmunity (CSU^{aiTI} and CSU^{aiTIIb}) and, in some cases, unknown mechanisms that play a role in skin mast cell degranulation.^{15,16}

History and physical examination may provide clues about the underlying cause, and basic laboratory test results may be indicative of CSU^{aiTI} or CSU^{aiTIIb}. Elevated CRP levels and low eosinophil and basophil counts are indicative of probable CSU^{aiTIIb}. Measurement of total IgE and IgG anti-TPO levels should be included in the evaluation of patients with CSU, as those with CSU^{aiTIIb} are more likely to have low total IgE and elevated IgG anti-TPO.^{1,16}

A positive basophil activation test (BAT) may also be indicative of CSU^{aiTIIb}, with a positive predictive value for diagnosis of 69%.^{1,17,18} However, the BAT is not commonly used in medical practice, as it is not widely accessible in most Brazilian urticaria reference centers.

Knowing the relevant conditions that can modify disease activity and factors that exacerbate CSU helps both physicians and patients better manage the disease. Therefore, during each consultation, patients should be asked about factors that exacerbate their CSU.

Medications can worsen CSU in about one-third of patients. NSAIDs are the most common triggers, except for selective and preferential COX-2 inhibitors and/or acetaminophen, which are considered safer options for patients with CSU. When indicated, patients should be advised to avoid NSAIDs to prevent exacerbations.^{1,19,20}

Certain foods may also exacerbate CSU by acting as “pseudoallergens.” These low-molecular-weight compounds may bind to MRGPRX2 receptors on the surface of mast cells, triggering their activation and the release of mediators.²¹ Based on patient response, a diet low on these “pseudoallergens” or avoidance of histamine-rich foods, such as fish, seafood, fermented foods (bacon, cheese), and some vegetables (spinach, eggplant, tomatoes), may be considered as an individualized diagnostic and therapeutic measure. However, it should be noted that these diets remain controversial and should not be routinely recommended, as they may further reduce the already compromised quality of life of patients with CSU. If a food is suspected to worsen CSU, an

Table 3
Objectives of diagnostic workup in patients with CSU

Patients with CSU – What should we assess?		
	Clinical history	Physical examination ^a Basic tests ^b
Confirm	Rule out differential diagnoses.	
Cause	Check for indicators of type I (autoallergic) or type IIb (autoimmune) CSU.	
Cofactors	Identify potential triggers or aggravators.	
Comorbidities	Check for concomitant CIndU, autoimmunity, and mental health.	
Consequences	Identify problems with sleep, activities of daily living, sexual life, and social performance.	
Course	Monitor CSU activity (UAS), control (UCT), and impact (CU-Q2oL).	
Components	Evaluate potential biomarkers or predictors of treatment response.	

^a Including review of patient photo documentation.
^b Differential blood count, ESR/CRP rate, total IgE, and IgG anti-TPO.
CIndU = chronic inducible urticaria, CSU = chronic spontaneous urticaria, CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire, ESR/CRP = erythrocyte sedimentation/C-reactive protein, Ig = immunoglobulin, TPO = thyroid peroxidase, UAS = Urticaria Activity Score, UCT = Urticaria Control Test.

exclusion diet for 3-4 weeks is recommended for diagnostic purposes.^{1,15,22}

Stress may worsen skin symptoms in about one-third of patients with CSU. Stress-related neuropeptides can activate mast cells through the MRGPRX2 receptor.²¹ Patients should be assessed for the impact of stress on their condition and informed that stress reduction may be a useful strategy for controlling urticaria.^{1,19}

Acute viral and chronic bacterial infections may exacerbate CSU and modify disease activity. However, evidence suggests that chronic viral infections, such as hepatitis B or C, do not modulate CSU activity. Therefore, routine screening for chronic viral infections is not recommended. Regarding chronic bacterial infections, studies on *Helicobacter pylori* have shown mixed and contradictory results. The effect of *H. pylori* eradication on the course of CSU

remains controversial, and *H. pylori* infection should be investigated based on clinical history. The role of fungal infections in CSU is still poorly understood, and more studies are needed to better define their prevalence and relevance.¹⁹

Identification of comorbidities and consequences of CSU

In CSU, the most common comorbidities include CIndUs, autoimmune diseases (especially autoimmune thyroid disease), and atopy. Mental disorders such as depression, anxiety, sexual dysfunction, and sleep disturbances are also frequent. Findings from the patient's clinical history, physical examination, and basic laboratory tests that indicate a comorbidity should always be evaluated.¹⁹

Identification of predictors for disease course and

treatment response

Currently, there are no definitive predictors of disease duration, activity, and treatment response in CSU.¹⁹ However, these variables are often linked to clinical characteristics and laboratory markers, which can help physicians to guide patients about the severity and expected duration of their disease and treatment response. For example, concomitant CIndU, severe disease activity (elevated CRP and D-dimer levels), and/or angioedema indicate a longer duration of CSU and poorer response to antihistamines. Conversely, low IgE levels are associated with a reduced response to omalizumab, while a positive BAT and low IgE levels may suggest a better response to cyclosporine.¹⁴ However, it should be noted that low total IgE levels are not a contraindication to treatment with omalizumab.

Diagnosis of inducible urticarias

CIndUs include both physical and nonphysical urticarias. CIndUs may be diagnosed through clinical history, physical examination, and provocation tests²³ (Table 2).

Symptomatic dermographism (or dermographic urticaria)

Symptomatic dermographism is characterized by the appearance of linear and itchy wheals due to shearing forces on the skin, which may result from friction, scratching, or rubbing. It is rarely associated with angioedema.

It is the most common CIndU, affecting 2% to 5% of the general population and accounting for 30% to 50% of CIndU cases, in addition to being frequently associated with CSU. The diagnosis of symptomatic dermographism is confirmed by applying a stroking pressure to the skin with a blunt object, such as a spatula or the blunt end of a pen. Standardized tests such as the Fric Test[®] or dermographometers are preferred. The test is considered positive when an itchy wheal appears at the test site within 10 minutes of provocation.²³

Delayed pressure urticaria (DPU)

Patients with DPU develop wheals and/or angioedema 4 to 6 hours after the application of a sustained pressure to the skin. Lesions may appear within 4 to 12-24 hours and may last up to 72 hours. Provocation tests for DPU include:

- Suspension of weights (7 kg on a 3-cm shoulder strap) on the patient's shoulder for 10 to 15 minutes.
- The Warin test, which involves the use of a 15-cm diameter sphere to exert localized pressure on the outer aspect of the forearm beneath a cuff to which is attached a bag containing 4-kg worth of materials, for 5 minutes.
- Application of weighted rods lowered vertically onto the skin and supported in a frame on the back, high, or forearms.
- The use of a dermatographometer, applied perpendicularly at 100 g/mm² (981 kPa) for 70 seconds on the upper back (directly beneath the scapula).

The tests are considered positive when wheals and/or angioedema appear at the test site 4-6 hours after provocation.²³

Cold urticaria

Cold urticaria is characterized by the appearance of wheals after contact with cold objects, air, or liquids. Cold provocation tests include the traditional ice cube test and the TempTest[®].^{2,4}

- The ice cube test involves applying a melting ice cube contained within a plastic bag on the patient's forearm for 5 minutes. Test response should be assessed 10 minutes after the end of the test and is considered positive if the test site shows the appearance of a wheal.
- The TempTest[®] is a validated device for the diagnosis of cold and heat urticaria by measuring temperature thresholds and disease activity. The patient's forearm is placed on the TempTest[®] temperature element for 5 minutes. The test is considered positive if a 2-mm wide wheal (width of the TempTest[®] element) appears 10 minutes after the start of the provocation test.²³

Heat urticaria

Heat urticaria is a rare form of CIndU characterized by the appearance of wheals immediately after contact heating of the skin. Diagnosis is confirmed by applying a hot stimulus (eg, a metal/glass sphere filled with hot water or hot water baths of up to 44°C) to the skin of the volar forearm for 5 minutes. Test response should be assessed after 10 minutes. Alternatively, the TempTest[®] may be used.²³

Solar urticaria

Patients with solar urticaria develop wheals within minutes of skin exposure to sunlight (UV-A [320-400 nm wavelength] or visible light [400-600 nm wavelengths]). Less frequently, lesions may also be triggered by UV-B (280-320 nm) or infrared radiation (> 600 nm). Provocation tests include:

- A slide projector (for visible light).
- Black fluorescent light (UV-B and UV-A).
- Fluorescent sunlight lamp (UV-B and UV-A).
- Infrared lamp (infrared range).

The minimum erythema dose (MED) of urticaria is determined by exposing a 1 cm² area of skin to a light source from 10 cm away and reading the result after 10 minutes.²³

Vibratory angioedema/urticaria

Patients with vibratory angioedema/urticaria present with itching and wheals within minutes of skin exposure to vibration.

Provocation test for diagnosis may be performed using a laboratory vortex mixer. The patient's forearm is held on a plastic plate laid on the vortex mixer that is continuously run between 780 rpm and 1380 rpm for 5 minutes. Test response should be assessed after 10 minutes.²³

Aquagenic urticaria

Aquagenic urticaria is a rare form triggered by contact with water, regardless of its temperature. The diagnosis is confirmed by applying a compress or a towel soaked with 35-37 °C water or physiological saline to the patient's trunk. The compress or the towel should be removed after 40 minutes or earlier, if the patient reports itching or if wheals appear at the test site. The test is positive if the lesions develop within the contact area up to 10 minutes after the compress/towel is removed.²³

Cholinergic urticaria

Cholinergic urticaria is characterized by the appearance of punctiform wheals due to increased body temperature from exercise, local heat application, emotional stress, spicy foods, or hot drinks.

In addition to diagnostic purposes, provocation test in cholinergic urticaria also has the goal of ruling out exercise-induced anaphylaxis. The diagnosis is confirmed when the patient's core temperature

increases by more than 1 °C from baseline after passive warming in a hot water bath (≤ 15 min at 42°C).

A standardized protocol using ergometry with heart rate monitoring has been proposed to diagnose and measure the thresholds for cholinergic urticaria. The patient is seated on a bicycle ergometer and instructed to cycle until an increase in heart rate of 15 beats per minute (bpm) every 5 minutes is achieved until it reaches 90 bpm above baseline after 30 minutes. Time to whealing is correlated with disease severity—faster onset means more severe cholinergic urticaria.^{23,24}

Differential diagnosis of urticaria

Wheals or angioedema can also occur in conditions other than AU and CSU (Table 4).

A key aspect in the differential diagnosis of wheals/angioedema is their appearance. Unlike the wheals associated with AU or CU, other urticarial-like lesions may be more hardened, discolored, or darkened, last longer than 24 hours in most cases, and resolve with residual marks, typically hyperpigmentation. These lesions often cause pain or burning, with little or no itching, and angioedema is typically absent. Systemic symptoms such as arthralgia, fever, malaise, and weight loss may be associated and should be further investigated.²⁵

Isolated, recurrent angioedema evokes multiple differential diagnoses, and warning signs include the absence of response to H1 antihistamines, corticosteroids, and epinephrine (suggesting a bradykinin-mediated mechanism); the presence of similar cases in other family members (hereditary angioedema); and the presence of other symptoms or diseases, particularly lymphoproliferative disorders and collagen diseases (acquired angioedema). Association with medication use should always be considered in cases of isolated recurrent angioedema, especially with angiotensin-converting enzyme inhibitors (bradykinin-mediated mechanism) and NSAIDs (histamine-mediated mechanism). Table 5 lists the main diagnoses to be considered in cases of isolated recurrent angioedema.²⁶

Other conditions that may involve edema and should be considered in the differential diagnosis of angioedema include infections (cellulitis), Melkersson-Rosenthal syndrome, contact dermatitis, thyroid diseases, and dermatomyositis.²⁶

Table 4Differential diagnoses of urticarial lesions²⁵⁻²⁸

Condition	Pathophysiology	Secondary associations	Indicative features	Investigation
Cutaneous mastocytosis	Genetic	Systemic mastocytosis	Darier's sign may be present	Skin biopsy for mast cell infiltrate. Serum for c-KIT D816V analysis
Erythema multiforme	Hypersensitivity	Infections and drugs (less common)	Target lesion with a central dusky area	Inflammatory markers PCR for HSV or mycoplasma. Skin biopsy for keratinocyte necrosis
Urticarial vasculitis	Inflammatory	Autoimmune diseases. Lymphoproliferative diseases. Infections. Drugs	Bruised lesions that heal with ecchymotic hyperpigmented marks	Inflammatory markers. Serum complements. Screening for autoimmune, infectious, and lymphoproliferative diseases. Skin biopsy for leukocytoclastic vasculitis and neutrophilic predominance
Erythema marginatum	Genetic	Hereditary angioedema	Often manifests as a prodrome of angioedema exacerbation	Serum C4 Serum C1 esterase inhibitor (qualitative and quantitative). Genetic study for patients with normal C1 inhibitor (F12 variants, others)
Urticarial dermatitis	Inflammatory	None	Pruritic, erythematous plaques and papules lasting longer than 24 hours	Skin biopsy for dermal edema and spongiosis or minimal lichenoid reaction
Bullous pemphigoid	Autoimmune	None	Tense blisters form on the urticarial base	Direct immunofluorescence for linear IgG deposition along the basement membrane. Indirect immunofluorescence for IgG deposition along the basement membrane
Polymorphic eruption of pregnancy	Inflammatory	None	Small itchy papules and plaques start in stretch marks and spread to the periumbilical area	Clinical diagnosis, no tests needed.
Autoinflammatory syndromes	Genetic	Amyloidosis	Urticarial rash lasting > 24 hours accompanied by systemic inflammation (recurrent fever, joint pain, weight loss, etc.) or articular, perda de peso, etc.)	Nonspecific skin biopsy, predominance of neutrophilic urticaria. Consider genetic evaluation in children. Laboratory tests according to the suspected syndrom

Assessment of urticaria activity, impact, and control

An accurate assessment of clinical status, disease activity, and progression is crucial for the adequate understanding and management of CU to help reduce its impact on several domains of patients' lives and improve their overall well-being. Therefore, in 2011, the GA²LEN recommended the use of the Patient Report Outcomes Measures (PROMs) for the assessment of CU in daily clinical practice and as a primary outcome in clinical studies.²⁹ It is recommended that patients be evaluated regarding disease activity, impact, and control during each medical visit.³⁰

CU severely compromises the quality of life of patients due to its unpredictable, debilitating, and uncomfortable symptoms, which can persist for years.³¹

Currently, there are insufficient data to validate the use of laboratory biomarkers alone to identify and measure disease activity. Thus, the use of PROMs is critical in the assessment and monitoring of patients, as well as to provide objective data to help guide decision-making on the best treatment option.^{29,31,32}

There are six instruments used to assess CU, namely: Urticaria Activity Score summed over 7 days (UAS7), Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), Urticaria Control Test (UCT), Angioedema Activity Score (AAS), Angioedema Quality of Life Questionnaire (AE-QoL), and Angioedema Control Test (AECT). These instruments are either validated or in the process of being validated for use in Brazilian Portuguese (Table 6).³³⁻³⁸

The main tool for assessing urticaria activity is the UAS7, a questionnaire based on the prospective evaluation by patients of their symptoms (itching and wheals) over 7 consecutive days. The total score is the sum of the 7 days, and it ranges from 0 to 42. The UAS7 allows the categorization of disease severity as follows: 0 = urticaria-free; 1-6 = well-controlled urticaria; 7-15 = mild urticaria; 16-27 = moderate urticaria; and 28-42 = severe urticaria.³³ A UAS7 score of ≤ 6 is considered adequate, but it should be preferably close to 0, which is the treatment target for patients with CSU.¹

Although the UAS7 has proven to be a useful tool and has become the gold standard for measuring disease activity in patients with CSU, it has some limitations: it does not account for angioedema, does not evaluate CIndU, and does not assess disease control. In addition, it relies on the patient's commitment to correctly fill in the information.³²

The UCT was specifically developed to assess CU control status, addressing the limitations of the UAS7. It is a retrospective questionnaire that evaluates urticaria control based on patient perception over the previous 4 weeks. The total score ranges from 0 to 16, with higher scores indicating better control, and has a cut-off point of 12, meaning that a score of 12 or higher indicates that the disease is under control.³¹ The UCT assesses both CSU and CIndU and also takes into account angioedema. It is easy to use in clinical practice and can be administered during routine medical visits.^{35,39}

The CU-Q2oL is another tool that effectively measures the impact of CU on quality of life. The questionnaire consists of 23 questions regarding the 2 weeks prior to the consultation. Each question has five response options, ranging from 1 (not at all) to 5 (very much), with a total score ranging from 23 to 115, where a higher score indicates a worse quality of life. The CU-Q2oL has been validated in Brazilian Portuguese.^{34,40} Some limitations include that it only evaluates CSU and not CIndU, is validated only for adults, lacks severity categorization, and does not include specific questions about the impact of angioedema.³²

The AAS is a simple tool that can determine disease activity in patients with recurrent angioedema. It consists of 5 questions about the occurrence of angioedema in the last 24 hours that patients should complete daily. The questions cover symptom duration, main complaints, limitations in activities of daily living, effects on physical appearance, and symptom severity, in addition to indirectly assessing the interval between episodes. The score ranges from 0 to 3 for each question, with a maximum total score of 15, which reflects severe angioedema activity.⁴¹

Patients should complete the AAS for at least 28 days because angioedema may be more episodic than urticaria. Patients with CSU who present with both wheals and angioedema should be instructed on the differences between these lesions, as errors in evaluation may lead to an inaccurate assessment of angioedema activity.⁴¹

The AE-QoL is the first validated tool to measure the impact of recurrent angioedema on quality of life. It includes 17 questions, each with 5 response options ranging from 1 (never) to 5 (very frequently), with a total score ranging from 17 to 85. A higher score indicates greater impairment in health-related quality of life. The questionnaire was validated in Brazilian Portuguese.^{36,37} The main limitations of the AE-QoL

include its length, which can hinder its use in daily practice; it only provides information on angioedema and should be complemented by urticaria-specific tools; and patients may confuse angioedema with wheals, compromising the assessment.³²

The AECT is the first tool developed to assess disease control in patients with any type of recurrent angioedema. It consists of 4 questions related to the frequency of symptoms, quality of life, disease unpredictability, and treatment, with a score ranging from 0 to 16. A score of 16 represents total control, while a score of ≥ 10 and < 10 indicates good control

and lack of control, respectively. Because the AECT was only recently developed, it is currently in the process of being validated in Brazil.³⁸

Treatment

Treatment goals

The main goal of CU treatment is to achieve complete control of symptoms whenever possible, allowing patients to enjoy the best possible quality of life and perform activities of daily living without impairment or limitations.¹ The treatment should follow

Table 5

Nonhistaminergic recurrent angioedema²⁶

Condition	Pathophysiology	Secondary associations	Indicative features	Investigation
Hereditary angioedema	Genetic	Erythema marginatum	Family history	Serum C1 esterase inhibitor (qualitative and quantitative). Serum C4. Genetic study for patients with normal C1 inhibitor (<i>F12</i> variants, others)
Acquired angioedema	Complement consumption	Lymphoproliferative disorders. Solid tumors. Autoimmune. Medications: ACE inhibitors	Angioedema unresponsive to conventional treatment. Associated systemic symptoms	Serum C1 esterase inhibitor (qualitative and quantitative). Serum C4. Serum C1q
Eosinophilic angioedema (Gleich syndrome)	Interleukin-5	Hypereosinophilic syndrome	Weight gain, significant eosinophilia, unilateral facial edema involving the neck, and painful limb edema	Skin biopsy showing eosinophilic infiltrate. ESR, CRP, LDH, serum albumin, C3, and C4

Table 6

Instruments for urticaria assessment

CSU			
Clinical presentation	Wheals	Wheals and angioedema	Angioedema
Disease activity	UAS7	UAS7 and AAS	ASA
Disease control	UCT	UCT and AECT	AECT
Quality of life	CU-Q2oL	CU-Q2oL and AE-Q2oL	AE-Q2oL

AAS = Angioedema Activity Score, AECT = Angioedema Control Test, AE-Q2oL = Angioedema Quality of Life Questionnaire, CSU = chronic spontaneous urticaria, CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire, UAS7 = Urticaria Activity Score summed over 7 days, UCT = Urticaria Control Test.

the basic principles of “treating as much as needed and as little as possible,” as long as symptoms remain under control. Urticaria is considered controlled when the UCT score is ≥ 12 and/or the UAS7 is ≤ 6 , while a UCT score of 16 and a USAS7 score of 0 means absence of symptoms.⁴² Once disease control is achieved, reduction of treatment should be considered to reduce the therapeutic burden and to assess spontaneous remission. Treatment should continue until urticaria is in complete remission, and regular patient reassessment is important (Figure 4).

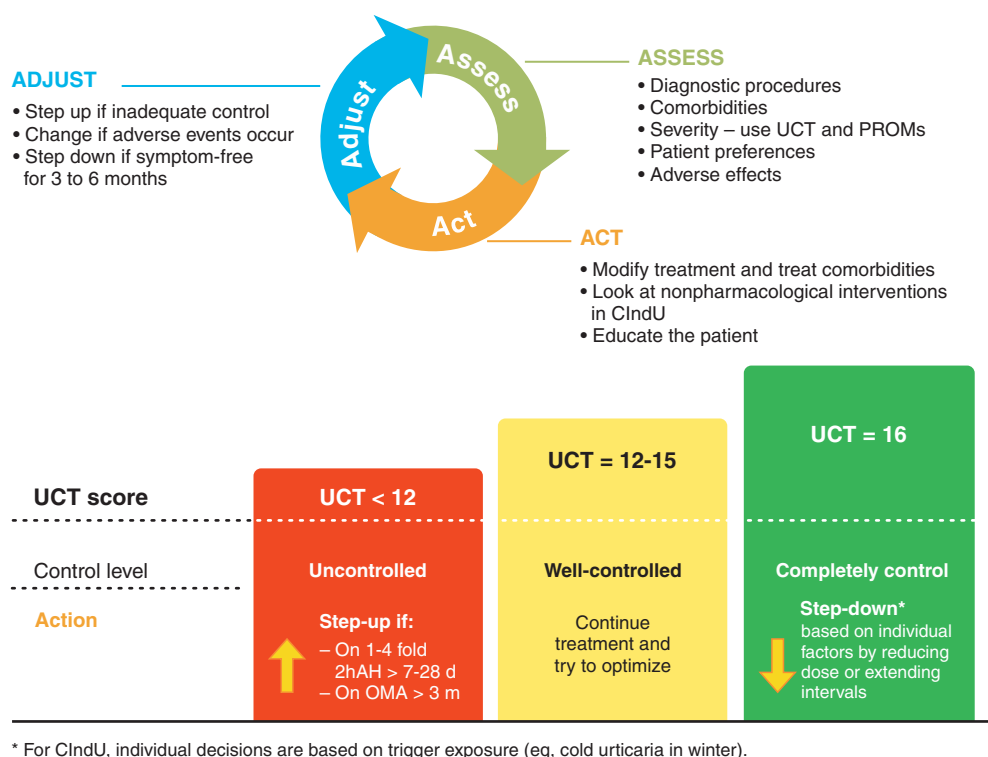
First-line treatment: second-generation nonsedating antihistamines

Second generation nonsedating antihistamines are recommended as first-line treatment for all types of urticaria. Updosing up to a fourfold is recommended in patients with urticaria refractory to a standard dose.

Second-generation H1-antihistamines are the first-line treatment for both AU and CU, with an excellent safety profile across all age groups, causing minimal to no sedation and free from anticholinergic effects.^{43,44}

Compared to first-generation H1-antihistamines, second-generation H1-antihistamines have anti-inflammatory effects by inhibiting the release of cytokines from mast cells and basophils, have a longer half-life, and are less soluble in lipids, meaning they are far less likely to cross the blood-brain barrier.⁴⁵ In addition, first-generation antihistamines are not recommended due to their safety profile, which includes anticholinergic and sedative effects, as well as interactions with alcohol and other medications such as analgesics and hypnotics. They also reduce REM sleep, learning ability, and impair performance in activities of daily living such as driving.^{1,46} In general, the half-life of first-generation H1-antihistamines in the central nervous system is longer than in peripheral blood, meaning their adverse effects last longer than their antihistaminic effect.⁴⁶

There is evidence supporting the use of most second-generation H1-antihistamines in the treatment of urticaria, although no well-designed studies have directly compared the efficacy and safety of different medications. Research has demonstrated the benefit and safety of bilastine,

**Figure 4**

Management decisions and treatment adjustments for urticaria

CIndU = chronic induced urticaria, d = days, m = months, PROMs = Patient-Reported Outcome Measures, OMA = omalizumab, 2hAH = second-generation H1-antihistamine, UCT = Urticaria Control Test.

Adapted from Zuberbier et al.¹

cetirizine, levocetirizine, desloratadine, ebastine, fexofenadine, and rupatadine at doses up to 4 times the standard dose.¹

For AU, the recommended treatment duration with second-generation H1-antihistamines is 2 to 3 weeks. However, more severe cases may require higher doses of antihistamines than those licensed, along with a course of systemic corticosteroids, such as prednisone or prednisolone, at a dose of 1 mg/kg/day for 7 to 10 days.^{1,47} In all types of CU, second-generation H1-antihistamines should be maintained

long enough to achieve complete symptom control until the patient enters remission.¹

The treatment should start with the licensed dose of second-generation H1-antihistamines. If symptom control is inadequate, the dose can be increased up to 2 or 4 times the standard. A period of 2 to 4 weeks is generally enough to observe the benefits of the prescribed dose (Figure 5). There is no evidence that combining different antihistamines provides better urticaria control. It is important to note that using higher doses of the same antihistamine has

been shown to be superior to combining different antihistamines for itching control.^{1,48,49}

Approximately 61% of patients with CSU do not respond to the licensed dose of second-generation H1-antihistamines, and of these, 63% do not benefit from higher doses. These patients will require second-line therapy with the anti-IgE monoclonal antibody omalizumab.^{1,3,50}

Second-line treatment: omalizumab

Omalizumab is recommended as an add-on therapy for patients with CU who are refractory to fourfold doses of second-generation H1-antihistamines.

Omalizumab is the first biologic therapy licensed for the treatment of adults and adolescents (≥ 12 years) with CSU who are unresponsive to second-generation H1-antihistamines.¹ It is a recombinant humanized monoclonal antibody (IgG1) that binds to the C ϵ 3 domain of free IgE, the site of high-affinity

IgE receptor (Fc ϵ RI) binding on the surface of mast cells and basophils, thus preventing the release of inflammatory mediators.^{50,51}

Although the exact mechanism of action of omalizumab is not fully understood, by binding to circulating IgE molecules, it prevents them from attaching to high-affinity receptors on mast cells and basophils. This inhibits mast cell activation and the release of proinflammatory mediators, as well as the recruitment of eosinophils to affected areas. In patients responsive to omalizumab, these cells return to the periphery, normalizing eosinophil and basophil levels and reversing the eosinopenia and basopenia observed in active disease. Additionally, by binding to circulating IgE, omalizumab reduces IgE receptor expression on the surface of mast cells and basophils, further decreasing cell activity. Consequently, patients with autoallergic CSU (Type I) are likely to respond more quickly to omalizumab (early responders), while patients with autoimmune

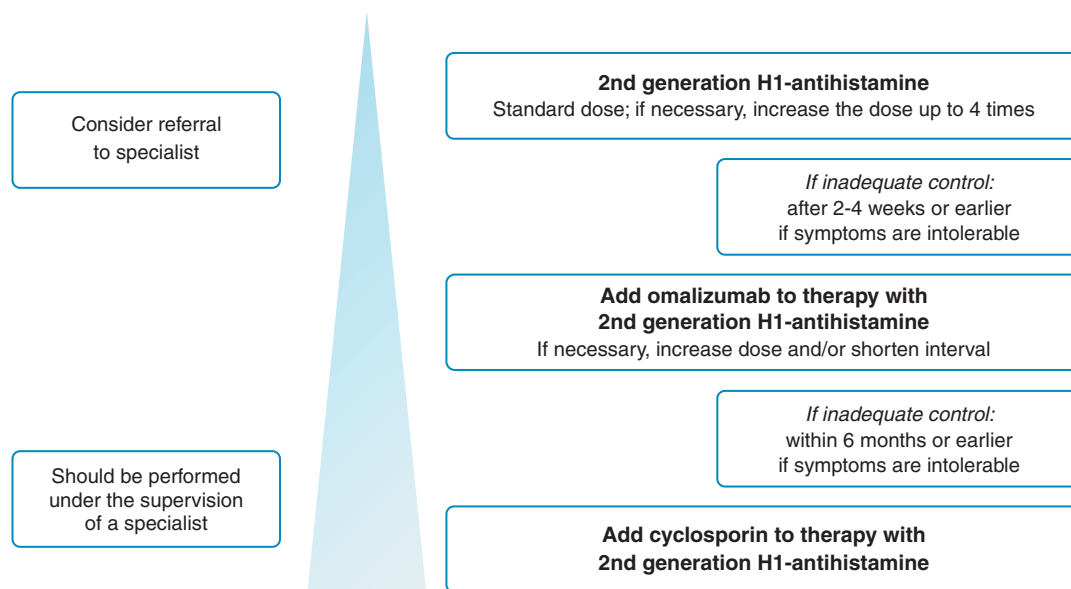


Figure 5

Treatment algorithm for urticaria

Adapted from Zuberbier et al.¹

CSU (Type IIb) are likely to be late responders, as their response is more dependent on the reduction of high-affinity receptor expression on the membranes of mast cells and basophils. This process is slower for mast cells, taking approximately 70 days to achieve a reduction comparable to that of individuals without the disease.⁵²

Omalizumab is available as an injection solution in a single-dose vial (150 mg/vial) or a single-dose prefilled syringe (75 mg and 150 mg). The recommended dose is 300 mg every 4 weeks administered subcutaneously in the deltoid region, lower abdomen, or the thigh. Patients with no history of anaphylaxis may self-administer or have a caregiver administer the medication from the fourth dose onwards, under medical recommendation. Dosing is independent of serum IgE and body weight.¹

Routine laboratory monitoring is not required before initiating treatment with omalizumab for CSU. However, measuring baseline levels of total serum IgE is recommended, as levels below 40 IU/mL may suggest a suboptimal treatment response.^{53,54}

Currently, responders to omalizumab are classified into 2 groups: fast responders, ie, those who achieve symptom control within 4 to 6 weeks; and late responders, ie, those who achieve symptom control only after 12 to 16 weeks.⁵⁵ Therefore, nonresponse to omalizumab should not be determined before a minimum of 6 months of treatment.⁵⁴ However, approximately 30% of patients remain symptomatic with licensed doses of omalizumab after more than 6 months of treatment.⁵³

Optimal management of patients with CSU refractory to omalizumab has not been established. The latest international guidelines suggest gradually increasing the dose to 450 mg/4 weeks and, if necessary, to 600 mg/2 weeks, based on disease activity and control. Higher doses are not recommended due to a lack of clinical evidence. Another option is to reduce the dosing interval to 2 weeks.⁵⁰

There are no biomarkers for urticaria remission, and the total duration of omalizumab treatment for CSU has not been well-defined. After complete symptom control, treatment with omalizumab should be discontinued to assess if the disease is in remission. Thus, after complete CSU control (UCT = 16) for at least 6 months, the decision to discontinue treatment should be individualized.

Strategies for discontinuing omalizumab therapy in CSU include:

1. Immediate discontinuation after complete symptom control, with continuous patient monitoring and retreatment if the disease recurs.
2. Gradually extending the dosing interval weekly until an 8-week interval is reached, followed by discontinuation.

Omalizumab is a safe medication with few side effects, the most common being pain at the injection site, headache, and arthralgia.^{56,57} Very rare cases of anaphylaxis have been reported, mostly occurring within the first 3 months of treatment.^{58,59} Therefore, the first 3 doses should be administered in a clinic, but home administration is an option from the fourth dose onward.⁵³

Omalizumab is not currently licensed for the treatment of CIndU. However, multiple publications, including a systematic review of over 40 studies with several investigator-initiated randomized controlled trials, have demonstrated that most patients with CIndU gain complete or partial control of symptoms with omalizumab.⁶⁰ The highest efficacy was observed for cold urticaria, symptomatic dermographism, solar urticaria, heat urticaria, delayed pressure urticaria, and cholinergic urticaria.⁶⁰ There is limited evidence for vibratory, aquagenic, and contact urticaria, likely due to their rarity.⁶⁰ Unlike CSU, the omalizumab dose for CIndU has not been completely determined, with some studies showing a good response with 150 mg/4 weeks, while others indicate that higher doses may be more effective.^{60,61} More controlled clinical trials are needed to clarify this further.

Third-line treatment: cyclosporine A

Cyclosporine A is recommended as an add-on therapy for patients with CU who do not respond to high doses of second-generation H1-antihistamines and omalizumab.

Cyclosporine A (CsA) inhibits the activity of calcineurin, which impairs the production of IL-2, IL-3, IL-4, tumor necrosis factor alpha, and other inflammatory cytokines, thereby inhibiting activated T lymphocytes. Because IL-4 is involved in IgE production, CsA may inhibit IgE-mediated release of histamine and reduce mast cell degranulation.⁶²

CsA can be used for the treatment of severe CSU that is refractory to antihistamines and omalizumab (Figure 6). Although its use in urticaria is off-label, there is high-quality evidence supporting this indication, with an overall response rate of 65%.⁶³

The recommended dose is 3 to 5 mg/kg/day, and adverse effects are dose- and time-dependent and have been reported in more than 50% of patients treated with moderate doses (4 to 5 mg/kg/day).⁴⁷ The main side effects that require monitoring include hypertension, peripheral neuropathy, and increased serum creatinine.⁶⁴ CsA should not be used for prolonged periods or in high doses, as there is a risk of malignancies, such as non-melanoma skin cancer, and a higher incidence of infections.⁶⁴

There is no consensus on the best treatment strategy—whether to start with a lower dose and increase it if necessary or to begin with a high dose and reduce it according to the degree of symptom control. However, based on the authors' experience, it is safer to start with lower doses, which can be increased if there is no satisfactory response.

It should be noted that there are no direct comparisons evaluating the efficacy of CsA vs omalizumab. However, a retrospective analysis of patients treated with either CsA or omalizumab showed that CsA is less effective in controlling CSU symptoms.⁶⁵ For this reason, and especially due to the potential risk of serious adverse effects, CsA is recommended only in patients who do not respond to omalizumab.¹

A recent study conducted in Turkey found that patients who responded to CsA were more likely to have elevated CRP, a family history of urticaria, positive autologous serum skin tests, eosinopenia, basopenia, elevated ESR, higher anti-TPO IgG, lower total IgE, and more severe disease activity and poorer disease control—features associated with CSU^{aiTIIb}.⁶⁶

Absolute and/or relative contraindications to CsA include hypersensitivity reactions, concomitant malignancy (except for non-melanoma skin cancer), uncontrolled hypertension, kidney disease, uncontrolled infection, and pregnancy/lactation.⁶⁴

Before starting treatment, patients should be assessed for clinical and laboratory parameters that help identify potential contraindications. Similarly, these parameters are useful in monitoring for potential side effects related to CsA use, such as hypertension and kidney or liver dysfunction.^{65,67}

Patients eligible for CsA should have their blood pressure measured on two separate occasions and undergo laboratory tests, including serum urea and creatinine levels, differential blood count, magnesium, lipids, potassium, uric acid, and liver function tests.

During treatment, these tests should be performed monthly, as well as whenever the dose is adjusted.⁶⁷

Systemic corticosteroids for the treatment of urticaria

Long-term use of systemic corticosteroids is not recommended in the treatment of urticaria.

Short-term use of systemic corticosteroid may be considered for the management of exacerbation of chronic urticaria.

Topical corticosteroids should not be used in urticaria.

Corticosteroids (COs) have widespread effects in many organ systems. In the immune system, they may act as anti-inflammatory or immunosuppressants, depending on the dose. The most well-known mechanism involves CO binding to its intracellular receptor, which modulates transcription by either repressing or activating several genes. This classic mechanism occurs a few hours after administration of systemic COs. Recent studies reported that COs have induced faster responses in clinical practice. However, this non-genomic and faster mechanism is not yet fully understood but is suspected to involve receptor interaction with other signaling pathways or even CO binding to other membrane receptors.^{68,69}

The first-line treatment for urticaria in emergency care is second-generation H1-antihistamines. In more severe cases, with widespread wheals and/or angioedema, they may be combined with systemic COs. Although this combination is commonly used, robust evidence of its efficacy is limited, as some studies have not shown systemic COs to be effective in AU.^{70,71} Upon discharge from emergency care, second-generation H1-antihistamines should be prescribed as the treatment of choice, in doses ranging from 1 to 4 times per day as needed. Oral COs may be added for 7 to 10 days at a dose of 0.5 to 1 mg/kg/day (20 to 60 mg of prednisone or prednisolone in adults). The combination of oral COs with low doses of second-generation H1 antihistamines is not recommended but may be considered in patients who do not respond to fourfold increases in the standard antihistamine dose. In addition, repeated courses of COs should be avoided.^{9,70}

In CU, systemic COs may be used for short periods to manage exacerbations. Long-term use of COs should be avoided due to the significant risks outweighing potential benefits. Prolonged use

of corticosteroids is associated with severe side effects, including hypothalamic-pituitary-adrenal axis suppression, osteoporosis with an increased risk of fractures, metabolic and cardiovascular disorders such as diabetes, eye diseases, and a higher risk of infections.^{1,72}

Other treatments for urticaria

Currently, no additional therapies are recommended for CSU. However, if a patient does not respond to the therapeutic options suggested by the treatment algorithm described above, alternative options may be considered. These include immunosuppressants such as methotrexate (MTX), azathioprine, mycophenolate mofetil (MMF), and hydroxychloroquine. These treatments are off-label for use in CSU, and studies on these medications are small, uncontrolled, and provide low-quality evidence for their use.⁷³ In randomized clinical trials, MTX did not show efficacy as an add-on therapy to antihistamines. Azathioprine was effective in refractory cases, while MMF, in less robust studies, showed improvement in symptoms as well as reduction in itching and wheals in patients resistant to antihistamines and corticosteroids. Similarly, hydroxychloroquine was shown to reduce symptoms and improve quality of life.^{73,74}

Dapsone is a sulfone antibiotic that has shown some effectiveness in CSU treatment. Studies demonstrated a positive response after 3 months of treatment with dapsone and cetirizine. The effects of dapsone have been reported to last up to 1 year, with significant reduction in itching and severity of symptoms. Other therapies, such as autologous serum therapy and intravenous immunoglobulin (IVIG), have shown mixed results. However, randomized clinical trials are necessary to validate the efficacy of IVIG in reducing urticaria activity.⁷⁴

The identification of different molecular pathways in the pathophysiology of CSU has allowed for the development of more targeted therapies. Biologics have emerged as a promising class in this setting. One example is omalizumab, a drug with anti-IgE properties, which has proven efficacy and widespread use in CSU. Other biologics, such as dupilumab and barzolvolimab, along with new medications such as Bruton tyrosine kinase inhibitors (fenebrutinib and remibrutinib), have emerged as potential treatments and are currently under investigation in randomized clinical trials. Soon, there will be more therapeutic options for patients with refractory CSU.⁷⁴

Treatment of special populations

Children

The treatment of CU in children follows the same algorithm recommended for adults, with second-generation H1-antihistamines being the medication of choice, dosed according to body weight and age. If symptom control is insufficient after 2 to 4 weeks of treatment, it is recommended to increase the licensed dose up to a fourfold.¹

Although increasing the dose requires caution, the effectiveness of this approach has been demonstrated in pediatric populations, with rates of symptom control ranging from 35% to 92%.⁷⁵⁻⁷⁷ There are only a few randomized placebo-controlled studies that have tested the safety of increasing the standard dose of second-generation H1-antihistamines up to a fourfold in children, but most have shown similar safety profiles across different dose groups.⁷⁸⁻⁸⁰

The choice of which second-generation H1-antihistamine to use in children should take into consideration the child's age and weight, as well as drug formulation, as not all medications are available in solution, drops, or syrup forms. The lowest licensed age for use also varies, starting at 6 months. Second-generation H1-antihistamines recommended and available in Brazil for the pediatric population include bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine (Table 7). It should be noted that patients using increased doses of loratadine should have their liver function monitored regularly.¹ First-generation H1-antihistamines are not recommended for use in children, as they cross the blood-brain barrier, leading to disruption of REM sleep and impaired school learning, as well as potentially causing paradoxical excitability, weight gain, and constipation.^{1,62} Long-term CO use is not recommended due to side effects, and short courses should only be used as a very restricted measure and dosed according to weight.¹

In cases refractory to antihistamines, anti-IgE therapy (omalizumab) 300 mg every 4 weeks is recommended and licensed for children with CSU aged 12 or older, as well as for adults.¹ Although there is a lack of controlled studies on the efficacy and safety of omalizumab in children with CU under 12 years old, studies and case series involving this age group have shown good treatment response, with little to no reported adverse events. These studies have shown complete symptom control in 46% to 81% of cases, partial control in 10% to 46%, and a mean treatment

response time of 4 weeks to 3 months. Dosing ranged from 75 mg to 450 mg per month.⁸²⁻⁸⁶ Even though this is an off-label recommendation, omalizumab may be used in refractory CSU in children over 6 years old at doses of 150 mg to 300 mg. Increasing the dose or shortening dosing intervals should be considered for partial responders.

For cases refractory to antihistamines and omalizumab, CsA is indicated. Some studies with children have shown CsA to be both effective and safe and to help reduce chronic CO use. The recommended dose varies from 3 to 4 mg/kg/day given twice daily and can be gradually reduced once urticaria remains controlled for 1 to 3 months. In pediatric studies, complete symptom resolution occurred between 2 days and 3 months from the start of treatment, with little to no adverse events.^{87,88}

Most side effects of CsA are related to increased doses and long-term treatment, including hypertension, elevated creatinine, gastrointestinal symptoms, headaches, hirsutism, infections, and paresthesia. Therefore, patients should be assessed for adverse events at least every 4 weeks and the CsA dose should be adjusted once urticaria is controlled to avoid prolonged use.⁸⁹

As in adults, not all children will achieve good symptom control with the recommended treatment options in the algorithm. Staubach et al. reported the cases of 2 children with inadequate response to CsA who were successfully treated with off-label dupilumab 300 mg. The authors suggest that in children with high levels of IgE with inadequate response to omalizumab and CsA, dupilumab may be an option, with doses adjusted according to weight at 200 mg or 300 mg every 2 weeks.⁹⁰

There is insufficient evidence to recommend the use of other immunosuppressants in children with CU. For example, the efficacy of MTX in CSU is uncertain and its use in children has not been investigated.⁹¹ Considering the autoimmune mechanisms of urticaria, there is also no clear evidence that treating autoimmune thyroid diseases impacts the natural course of CU in children. However, hormone replacement therapy is indicated in clinical practice and may have positive effects on CU.⁹²

Although there is limited data on the use of high doses of second-generation H1-antihistamines, omalizumab, and CsA in children with CU, current evidence indicates that treatment following the algorithm is effective and safe in this population

when administered with caution, respecting age-appropriate doses and monitoring for adverse events.

Pregnant and lactating women

CU mostly affects women of reproductive age, and pregnancy may exacerbate disease activity.^{93,94}

During pregnancy, CU tends to improve in half of the patients and worsen in one-third. Some may experience exacerbations, especially in the first and third trimesters, indicating a predominance of Th1 response and proinflammatory signals that activate mast cells. Relevant risk factors for worsening urticaria during pregnancy include mild disease before pregnancy and not being on treatment during pregnancy. Half of the patients whose CU improved during pregnancy reported worsening after giving birth, while half of the patients with worsening CU during pregnancy reported no difference after giving birth.⁹³

The international guideline for urticaria recommends the same standard treatment for pregnant and lactating women with CU: start with the licensed dose of second-generation H1-antihistamines, increase the dose up to a fourfold if there is no response, and add omalizumab for refractory patients.¹

There have been no reports of congenital defects in pregnant women using second-generation H1-antihistamines. Loratadine or cetirizine should be preferred, with possible extrapolation to desloratadine, bilastine, and levocetirizine. These medications are excreted in breast milk in low concentrations. First-generation H1-antihistamines should be avoided during both pregnancy and breastfeeding.¹ It is important to discuss the risks and benefits of treatment with patients, as there is no safety data for increasing the dose of second-generation H1-antihistamines in pregnant and lactating women, but untreated urticaria can be dangerous, with exacerbations of CU being an independent risk factor for preterm birth.^{95,96}

Omalizumab is a safe and effective option for pregnant women, women planning to become pregnant, and lactating women with CSU. There is no evidence that the use of this medication increases the risk of adverse events in pregnant women or their infants.^{1,94,97,98} Only minimal concentrations of omalizumab are transferred into breast milk, with no reports of complications to the baby during breastfeeding.⁹⁹

Table 7Standard dosage of second-generation antihistamines for the treatment of urticaria in children⁸¹

Name	Presentation	Standard dose (as per label)
Cetirizine	Drops (10 mg/mL)	2 to 6 years: 5 drops every 12 hours or 10 drops 1 times/day 6 to 12 years: 10 drops every 12 hours > 12 years: 20 drops 1 times/day
	Oral solution (1 mg/mL)	2 to 6 years: 2.5 mL every 12 hours 6 to 12 years: 5 mL every 12 hours or 10 mL 1 times/day > 12 years: 10 mL 1 times/day
	Tablet (10 mg/tablet)	> 12 years: 1 tablet/day
Levocetirizine	Drops (5 mg/mL)	2 to 6 years: 5 drops every 12 hours > 6 years: 20 drops 1 times/day
	Orodispersible tablet (5 mg/tablet)	> 6 years: 1 tablet/day
Fexofenadine	Oral solution (6 mg/mL)	6 months to 2 years (up to 10.5 kg): 2.5 mL every 12 hours 2 to 11 years (> 10.5 kg): 5 mL every 12 hours
	Tablet (60 mg/tablet) (120 mg/tablet) (180 mg/tablet)	> 12 years: 60 mg/tablet every 12 hours 120 mg/tablet 1 times/day 180 mg/tablet 1 times/day
Desloratadine	Drops (1.25 mg/mL)	6 to 11 months: 16 drops 1 times/day 1 to 5 years: 20 drops 1 times/day 6 to 11 years: 40 drops 1 times/day > 12 years: 80 drops 1 times/day
	Oral solution (0.5 mg/mL)	6 to 11 months: 2 mL 1 times/day 1 to 5 years: 2.5 mL 1 times/day. 6 to 11 years: 5 mL 1 times/day > 12 years: 10 mL 1 times/day
	Tablet (5 mg/tablet)	> 12 years: 1 tablet/day
Loratadine	Oral solution (1 mg/mL)	2 to 12 years: < 30 kg: 5 mL 1 times/day > 30 kg: 10 mL 1 times/day
	Tablet (10 mg/tablet)	> 12 anos: 1 cp 1 vez/dia
Rupatadine	Tablet (10 mg/tablet)	> 12 years: 1 tablet 1 times/day
Bilastine	Oral solution (2.5 mg/mL)	6 to 11 years: 4 mL 1 times/day > 12 years: 8 mL 1 times/day
	Tablet (20 mg/tablet)	> 12 years: 1 tablet 1 times/day

More studies are needed to establish the long-term safety of CSU treatment in this special population.⁹⁴

Older adults

The World Health Organization and the United Nations define “older person,” respectively, as those aged between ≥ 60 years and ≥ 65 years. In recent years, people are living longer due to advances in both technology and modern medicine.¹⁰⁰ CU is one of the most common pruritic conditions in older adults, with prevalence ranging from 0.2% to 2.8%. Among all patients with CU, 4.1% to 5.5% are in the older age group.¹⁰⁰

Mean age at diagnosis of CU in this population was 72 ± 5.9 years, and mean referral time to a specialist was 22.8 ± 53 months from the onset of symptoms.¹⁰¹ CSU was the most common subtype among older people, while symptomatic dermographism was the most common form of CIndU. Furthermore, compared with the adult population, older patients showed a lower rate of atopy, a higher prevalence of age-related comorbidities such as metabolic syndrome, autoimmune disorders, and malignancies, a lower rate of associated angioedema, and lower rates of positive autologous serum skin tests.¹⁰⁰

Regarding comorbidities, Lapi et al. reported that the risk of developing CU is related to multiple factors. Gastrointestinal diseases were the most common comorbidity, alongside coronary artery disease, cerebrovascular disease, metabolic syndrome, autoimmune diseases, thyroid disorders, psychiatric problems, and malignancies, all reported at high rates in older adults with CU.¹⁰⁰

Currently, the diagnostic and therapeutic procedures for CU in older patients are the same as those recommended for other age groups.¹⁰² Therefore, treatment of CU in older patients tends to follow the same guidelines for the general population.¹⁰⁰

The aging process may affect pharmacokinetics and pharmacodynamics, resulting in different treatment responses.¹⁰² Polypharmacy increases the risk of drug interactions that may cause medication safety problems, as well as the risk of low treatment adherence, which in turn can cause suboptimal therapeutic efficacy and lead to poor clinical outcomes.¹⁰³ Therefore, the selection of medication and dose for older patients should be considered carefully due to possible drug interactions or adverse effects.¹⁰⁴

Second-generation H1-antihistamines are recommended as first-line treatment for CU in older patients, with standard doses typically being sufficient to achieve clinical control in most patients.¹⁰⁰ Increasing the standard dose up to a fourfold has also shown good efficacy.¹⁰⁰ However, older patients with multiple comorbidities or kidney/liver dysfunction may require dose adjustments depending on the choice of antihistamine. Bilastine was shown to be safe in these patients.¹⁰⁴

For patients who do not respond to antihistamine treatment, successful symptom control has been achieved with omalizumab.¹⁰⁰ In refractory cases, other diagnoses related to underlying medical conditions should be considered.¹⁰⁰ However, it should be noted that the differential diagnosis of CU may be more challenging in older adults due to the higher likelihood of other age-specific diseases.¹⁰²

There are no well-defined markers to predict the risk of urticaria recurrence after omalizumab discontinuation in older patients with CSU. However, baseline serum IgG anti-TPO levels and the IgG anti-TPO/total IgE ratio may serve as predictors of CSU recurrence after discontinuation of omalizumab in older patients.¹⁰⁵

Conclusion

Urticaria is a common and heterogeneous inflammatory skin disease that presents acutely or chronically. Although its chronic form does not have high mortality rates, it significantly affects the quality of life and well-being of patients. Knowledge of the differential diagnoses of urticaria helps reduce the rates of misdiagnosis, leading to adequate management of the condition. The treatment algorithm recommended by international guidelines leads to urticaria control in most patients, but there remains a subset with refractory disease. Several ongoing studies aim to further understand the pathophysiology of urticaria to allow the development of new medications.

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;77:734-66.

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. doi:10.5935/2526-5393.20190052.
3. Kolkhir P, Giménez-Arnau AM, Kulthanan K, Peter J, Metz M, Maurer M. Urticaria. *Nat Rev Dis Primer*. 2022;8:61.
4. Balp M-M, Lopes Da Silva N, Vietri J, Tian H, Ensina LF. The Burden of Chronic Urticaria from Brazilian Patients' Perspective. *Dermatol Ther*. 2017;7:535-45.
5. Andrade Coelho Dias G, Cunha Coelho F, Filippo P, Lacerda Pedrazzi D, Nogueira Arraes AC, Perello MI, et al. Clinical experience of a chronic urticaria referral university center. *Eur Ann Allergy Clin Immunol*. 2020;52:74.
6. De Souza ACMCF, Dortas Junior SD, Azizi GG, França AT, Lupi O, Valle SOR. Chronic urticaria: profile from a reference center. *An Bras Dermatol*. 2022;97:511-12.
7. Borriello F, Iannone R, Marone G. Histamine Release from Mast Cells and Basophils. In: Hattori Y, Seifert R (eds). *Histamine and Histamine Receptors in Health and Disease*. Springer International Publishing: Cham, 2017. p. 121-39.
8. Asero R, Ferrer M, Kocaturk E, Maurer M. Chronic Spontaneous Urticaria: The Role and Relevance of Autoreactivity, Autoimmunity, and Autoallergy. *J Allergy Clin Immunol Pract*. 2023;11:2302-8.
9. Sabroe RA. Acute urticaria. *Immunol Allergy Clin North Am*. 2014;34:11-21.
10. Solé D, Ivancevich JC, Borges MS, Coelho MA, Rosário NA, Arduzzo LRF, et al. Anaphylaxis in Latin America: a report of the online Latin American survey on anaphylaxis (OLASA). *Clinics*. 2011;66:943-7.
11. Jares EJ, Sánchez-Borges M, Cardona-Villa R, Ensina LF, Arias-Cruz A, Gómez M, et al. Multinational experience with hypersensitivity drug reactions in Latin America. *Ann Allergy Asthma Immunol*. 2014;113:282-9.
12. Modena B, White AA, Woessner KM. Aspirin and Nonsteroidal Antiinflammatory Drugs Hypersensitivity and Management. *Immunol Allergy Clin North Am*. 2017;37:727-49.
13. Rutnin N, Kulthanan K, Tuchinda P, Jongjarearnprasert K. Drug-induced urticaria: causes and clinical courses. *J Drugs Dermatol JDD*. 2011;10:1019-24.
14. Fok JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. *Allergy*. 2021;76:2965-81.
15. Metz M, Altrichter S, Buttgerit T, Fluhr JW, Fok JS, Hawro T, et al. The Diagnostic Workup in Chronic Spontaneous Urticaria-What to Test and Why. *J Allergy Clin Immunol Pract*. 2021;9:2274-83.
16. Kaplan A, Lebowitz M, Giménez-Arnau AM, Hide M, Armstrong AW, Maurer M. Chronic spontaneous urticaria: Focus on pathophysiology to unlock treatment advances. *Allergy*. 2023;78:389-401.
17. Kolkhir P, Muñoz M, Asero R, Ferrer M, Kocatürk E, Metz M, et al. Autoimmune chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2022;149:1819-31.
18. Schoepke N, Asero R, Ellrich A, Ferrer M, Gimenez-Arnau A, EH Grattan C, et al. Biomarkers and clinical characteristics of autoimmune chronic spontaneous urticaria: Results of the PURIST Study. *Allergy*. 2019;74:2427-36.
19. Metz M, Altrichter S, Buttgerit T, Fluhr JW, Fok JS, Hawro T, et al. The Diagnostic Workup in Chronic Spontaneous Urticaria – What to Test and Why. *J Allergy Clin Immunol Pract*. 2021;9:2274-83.
20. Sánchez J, Sánchez A, Cardona R. Prevalence of Drugs as Triggers of Exacerbations in Chronic Urticaria. *J Investig Allergol Clin Immunol*. 2019;29:112-7.
21. Bansal CJ, Bansal AS. Stress, pseudoallergens, autoimmunity, infection and inflammation in chronic spontaneous urticaria. *Allergy Asthma Clin Immunol*. 2019;15:56.
22. Sánchez J, Sánchez A, Cardona R. Dietary Habits in Patients with Chronic Spontaneous Urticaria: Evaluation of Food as Trigger of Symptoms Exacerbation. *Dermatol Res Pract*. 2018;2018: 6703052.
23. 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;71:780-2.
24. Fukunaga A, Washio K, Hatakeyama M, Oda Y, Ogura K, Horikawa T, et al. Cholinergic urticaria: epidemiology, physiopathology, new categorization, and management. *Clin Auton Res*. 2018 Feb;28(1):103-13.
25. Fok JS, Katelaris CH. Urticaria and mimickers of urticaria. *Front Allergy*. 2023;4:1274031.
26. Bernstein JA, Ziaie N, Criado R, Criado PR, Rea S, Davis M. Chronic Urticaria and Angioedema: Masqueraders and Misdiagnoses. *J Allergy Clin Immunol Pract*. 2023;11:2251-63.
27. Davis MDP, Van Der Hilst JCH. Mimickers of Urticaria: Urticarial Vasculitis and Autoinflammatory Diseases. *J Allergy Clin Immunol Pract*. 2018;6:1162-70.
28. Sekerel BE, Ilgun Gurel D, Sahiner UM, Soyer O, Kocaturk E. The many faces of pediatric urticaria. *Front Allergy*. 2023;4:1267663.
29. Baiardini I, Baido F, Bindslev-Jensen C, Bousquet PJ, Brzoza Z, Canonica GW, et al. Recommendations for assessing patient-reported outcomes and health-related quality of life in patients with urticaria: a GA(2) LEN taskforce position paper. *Allergy*. 2011;66:840-4.
30. 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 Imunol*. 2018;2(2):209-24. doi:10.5935/2526-5393.20180021.
31. Moestrup K, Ghazanfar MN, Thomsen SF. Patient-reported outcomes (PROs) in chronic urticaria. *Int J Dermatol*. 2017;56:1342-48.
32. Weller K, Siebenhaar F, Hawro T, Altrichter S, Schoepke N, Maurer M. Clinical Measures of Chronic Urticaria. *Immunol Allergy Clin North Am*. 2017;37:35-49.
33. Stull D, McBride D, Tian H, Gimenez Arnau A, Maurer M, Marsland A, et al. Analysis of disease activity categories in chronic spontaneous/idiopathic urticaria. *Br J Dermatol*. 2017;177:1093-101.
34. Dias GAC, Pires GV, Valle SOR, França AT, Papi JA, Dortas SD, et al. Cross-cultural adaptation of the Brazilian-Portuguese version of the chronic urticaria quality-of-life questionnaire - CU-Q2oL. *Allergy*. 2011;66:1487-93.
35. Dortas Junior SD, Valle SOR, Weller K, Maurer M, Lupi O. Validity, reliability, and interpretability of the Brazilian urticaria control test. *Allergy Asthma Proc*. 2020;41:e61-e66.
36. de-Aquino BM, Lacerda AE, Marcelino FC, da-Silva BG, Nunes ICC, Solé D, et al. Tradução e adaptação transcultural para o idioma português (Brasil) do instrumento 'Angioedema Activity Score'. *Arq Asma Alerg Imunol*. 2018;2(3):351-6. doi:10.5935/2526-5393.20180042.
37. 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;67:1289-98.

38. Weller K, Donoso T, Magerl M, Ayyören-Pürsün E, Staubach P, Martinez-Saguer I, et al. Validation of the Angioedema Control Test (AECT) – A Patient-Reported Outcome Instrument for Assessing Angioedema Control. *J Allergy Clin Immunol Pract.* 2020;8:2050-2057.e4.
39. 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;133:1365-1372.e6.
40. 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-QoL). *Allergy.* 2005;60:1073-78.
41. 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;68:1185-92.
42. Weller K, Zuberbier T, Maurer M. Chronic urticaria: tools to aid the diagnosis and assessment of disease status in daily practice. *J Eur Acad Dermatol Venereol JEADV.* 2015;29(Suppl 3):38-44.
43. Kubo N, Senda M, Ohsumi Y, Sakamoto S, Matsumoto K, Tashiro M, et al. Brain histamine H1 receptor occupancy of loratadine measured by positron emission tomography: comparison of H1 receptor occupancy and proportional impairment ratio: H1 RECEPTOR OCCUPANCY OF LORATADINE. *Hum Psychopharmacol Clin Exp.* 2011;26:133-9.
44. Sharma M, Bennett C, Cohen SN, Carter B. H1-antihistamines for chronic spontaneous urticaria. *Cochrane Database Syst Rev.* 2014 Nov 14;2014(11):CD006137.
45. Lippert U, Möller A, Welker P, Artuc M, Henz BM. Inhibition of cytokine secretion from human leukemic mast cells and basophils by H1- and H2-receptor antagonists. *Exp Dermatol.* 2000;9:118-24.
46. Church MK, Maurer M, Simons FER, Bindslev-Jensen C, van Cauwenberge P, Bousquet J, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy.* 2010;65:459-66.
47. Maurer M, Zuberbier T, Metz M. The Classification, Pathogenesis, Diagnostic Workup, and Management of Urticaria: An Update. In: Traidl-Hoffmann C, Zuberbier T, Werfel T (eds). *Allergic Diseases – From Basic Mechanisms to Comprehensive Management and Prevention.* Springer International Publishing: Cham; 2021. p. 117-33.
48. Guillén-Aguinaga S, Jáuregui Presa I, Aguinaga-Ontoso E, Guillén-Grima F, Ferrer M. Updosing non-sedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. *Br J Dermatol.* 2016;175:1153-65.
49. Zuberbier T. Pharmacological rationale for the treatment of chronic urticaria with second-generation non-sedating antihistamines at higher-than-standard doses. *J Eur Acad Dermatol Venereol JEADV.* 2012;26:9-18.
50. Giménez Arnau AM, Valero Santiago A, Bartra Tomás J, Jáuregui Presa I, Labrador Horrillo M, Miquel Miquel FJ, et al. Therapeutic Strategy According to Differences in Response to Omalizumab in Patients With Chronic Spontaneous Urticaria. *J Investig Allergol Clin Immunol.* 2019;29:338-48.
51. Easthope S, Jarvis B. Omalizumab: Drugs. 2001;61:253-60.
52. Kaplan AP, Giménez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. *Allergy.* 2017;72:519-33.
53. Agache I, Akdis CA, Akdis M, Brockow K, Chivato T, Del Giacco S, et al. EAACI Biologicals Guidelines – Omalizumab for the treatment of chronic spontaneous urticaria in adults and in the paediatric population 12-17 years old. *Allergy.* 2022;77:17-38.
54. Türk M, Carneiro-Leão L, Kolkhir P, Bonnekoh H, Buttgerit T, Maurer M. How to Treat Patients with Chronic Spontaneous Urticaria with Omalizumab: Questions and Answers. *J Allergy Clin Immunol Pract.* 2020;8:113-24.
55. Ferrer M, Boccon-Gibod I, Gonçalves M, Inalöz HS, Knulst A, Lapeere H, et al. Expert opinion: defining response to omalizumab in patients with chronic spontaneous urticaria. *Eur J Dermatol.* 2017;27:455-63.
56. Saini SS, Bindslev-Jensen C, Maurer M, Grob J-J, Bülbül Baskan E, Bradley MS, et al. Efficacy and Safety of Omalizumab in Patients with Chronic Idiopathic/Spontaneous Urticaria Who Remain Symptomatic on H1 Antihistamines: A Randomized, Placebo-Controlled Study. *J Invest Dermatol.* 2015;135:67-75.
57. Giménez-Arnau AM. Omalizumab for treating chronic spontaneous urticaria: an expert review on efficacy and safety. *Expert Opin Biol Ther.* 2017;17:375-85.
58. Omalizumab [Internet]. DrugBank. Available from: <https://www.drugbank.ca/drugs/DB00043>. Accessed Feb 06 2024.
59. Xolair: EPAR-Product Information [Internet]. Last update: 21/12/2023. Available in: https://www.ema.europa.eu/en/documents/product-information/xolair-epar-product-information_en.pdf. Accessed Feb 06 2024.
60. Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, et al. Omalizumab treatment in patients with chronic inducible urticaria: A systematic review of published evidence. *J Allergy Clin Immunol.* 2018;141:638-49.
61. McSweeney SM, Christou EAA, Maurer M, Grattan CE, Tziotziou C, McGrath JA. Physical urticaria: Clinical features, pathogenesis, diagnostic work-up, and management. *J Am Acad Dermatol.* 2023;89:324-37.
62. Chang J, Cattelan L, Ben-Shoshan M, Le M, Netchiporouk E. Management of Pediatric Chronic Spontaneous Urticaria: A Review of Current Evidence and Guidelines. *J Asthma Allergy.* 2021;14:187-99.
63. Khan DA. Alternative agents in refractory chronic urticaria: evidence and considerations on their selection and use. *J Allergy Clin Immunol Pract.* 2013;1:433-440.e1.
64. Kessel A, Toubi E. Cyclosporine - A in severe chronic urticaria: the option for long-term therapy. *Allergy.* 2010;65:1478-82.
65. Savic S, Marsland A, McKay D, Arden-Jones MR, Leslie T, Somenzi O, et al. Retrospective case note review of chronic spontaneous urticaria outcomes and adverse effects in patients treated with omalizumab or ciclosporin in UK secondary care. *Allergy Asthma Clin Immunol.* 2015 Jul 21;11(1):21.
66. Kocatürk E, Baskan EB, Küçük ÖS, Özdemir M, Örnek S, Can PK et al. Omalizumab versus cyclosporin-A for the treatment of chronic spontaneous urticaria: can we define better-responding endotypes? *An Bras Dermatol.* 2022;97:592-600.
67. Vena GA, Maurer M, Cassano N, Zuberbier T. Alternative treatments for chronic spontaneous urticaria beyond the guideline algorithm. *Curr Opin Allergy Clin Immunol.* 2017;17:278-85.
68. Cain DW, Cidrowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol.* 2017;17:233-47.
69. Levin ER, Hammes SR. Nuclear receptors outside the nucleus: extranuclear signalling by steroid receptors. *Nat Rev Mol Cell Biol.* 2016;17:783-97.
70. Alcântara CTD, Raeder DFT, Campinhos FL, Brandão LS, Campos RDA, Franca AT, et al. Practical guide to acute urticaria. *Arq Asma Alerg Imunol.* 2022;6:214-24.
71. Palungwachira P, Vilaisri K, Musikatavorn K, Wongpiyabovorn J. A randomized controlled trial of adding intravenous corticosteroids to H1 antihistamines in patients with acute urticaria. *Am J Emerg Med.* 2021;42:192-7.

72. Doumen M, Pazmino S, Bertrand D, Westhovens R, Verschueren P. Glucocorticoids in rheumatoid arthritis: Balancing benefits and harm by leveraging the therapeutic window of opportunity. *Joint Bone Spine*. 2023;90:105491.
73. Kocaturk E, Saini SS, Rubeiz CJ, Bernstein JA. Existing and Investigational Medications for Refractory Chronic Spontaneous Urticaria: Safety, Adverse Effects, and Monitoring. *J Allergy Clin Immunol Pract*. 2022;10:3099-116.
74. Yosipovitch G, Biazus Soares G, Mahmoud O. Current and Emerging Therapies for Chronic Spontaneous Urticaria: A Narrative Review. *Dermatol Ther*. 2023;13:1647-60.
75. Gabrielli S, Le M, Netchiporouk E, Miedzybrodzki B, Baum S, Greenberger S, et al. Chronic urticaria in children can be controlled effectively with up dosing second-generation antihistamines. *J Am Acad Dermatol*. 2020;82:1535-7.
76. Ensina LF, Bastos PGA, de Lacerda AE, de Araujo CA, Camelo-Nunes I, Solé D. Comments on Balp et al. *Pediatr Allergy Immunol*. 2018 Sep;29(6):669-70.
77. Balp MM, Weller K, Carboni V, Chirilov A, Papavassilis C, Severin T, et al. Reply to Ensina et al. *Pediatr Allergy Immunol*. 2018 Sep;29(6):670-1.
78. Hide M, Suzuki T, Tanaka A, Aoki H. Efficacy and safety of rupatadine in Japanese adult and adolescent patients with chronic spontaneous urticaria: A double-blind, randomized, multicenter, placebo-controlled clinical trial. *Allergol Int*. 2019 Jan;68(1):59-67.
79. Gimenez-Arnau A, Pujol RM, Ianos S, Kaszuba A, Malbran A, Poop G, et al. Rupatadine in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicentre study. *Allergy*. 2007;62:539-46.
80. Nelson HS, Reynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2000 May;84(5):517-22.
81. Consultas: Bulário Eletrônico ANVISA - Agência Nacional de Vigilância Sanitária. [Internet]. Available from: <https://consultas.anvisa.gov.br/#/bulario/>. Accessed Sep 02 2023.
82. Al-Shaikhly T, Rosenthal JA, Ayars AG, Petroni DH. Omalizumab for chronic urticaria in children younger than 12 years. *Ann Allergy Asthma Immunol*. 2019 Aug;123(2):208-10.
83. Corral-Magaña O, Gil-Sánchez JA, Bover-Bauzá C, Martínez-Cepas P, Montis-Palos MC, Martín-Santiago A. Chronic urticaria in children under 15 years of age: Clinical experience beyond the clinical trials. *Pediatr Dermatol*. 2021;38:385-9.
84. Song X-T, Chen Y-D, Yu M, Liu B, Zhao Z-T, Maurer M. Omalizumab in children and adolescents with chronic urticaria: A 16-week real-world study. *Allergy*. 2021;76:1271-3.
85. Briand C, Tetart F, Soria A, Staumont-Sallé D, Sterling B, Boralevi F, et al. Omalizumab in cold urticaria in children: Retrospective case series of 13 patients, review of the literature. *Ann Dermatol Venerol*. 2021;148: 269-71.
86. Japiassu LG, Bastos PGA, Araújo CA, Camelo-Nunes IC, Solé D, Ensina LF. Omalizumabe no tratamento da urticária crônica espontânea em pacientes pediátricos. *Arq Asma Alerg Imunol*. 2018;2:s78.
87. Neverman L, Weinberger M. Treatment of chronic urticaria in children with antihistamines and cyclosporine. *J Allergy Clin Immunol Pract*. 2014;2:434-8.
88. Boubouka CD, Charissi C, Kouimintzis D, Kalogeromitros D, Stavropoulos PG, Katsarou A. Treatment of autoimmune urticaria with low-dose cyclosporin A: A one-year follow-up. *Acta Derm Venereol*. 2011;91:50-4.
89. Kulthanan K, Chaweekulrat P, Komoltri C, Hunnangkul S, Tuchinda P, Chularojanamontri L, et al. Cyclosporine for Chronic Spontaneous Urticaria: A Meta-Analysis and Systematic Review. *J Allergy Clin Immunol Pract*. 2018;6:586-99.
90. Staubach P, Peveling-Oberhag A, Lang BM, Zimmer S, Sohn A, Mann C. Severe chronic spontaneous urticaria in children - treatment options according to the guidelines and beyond - a 10 years review. *J Dermatol Treat*. 2022;33:1119-22.
91. 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;45:101.
92. Kolkhir P, Metz M, Altrichter S, Maurer M. Comorbidity of chronic spontaneous urticaria and autoimmune thyroid diseases: A systematic review. *Allergy*. 2017;72:1440-60.
93. Kocatürk E, Podder I, Zenclussen AC, Kasperska Zajac A, Elieh-Ali-Komi D, Church MK, et al. Urticaria in Pregnancy and Lactation. *Front Allergy*. 2022;3:892673.
94. Liao S-L, Yu M, Zhao Z-T, Maurer M. Case Report: Omalizumab for Chronic Spontaneous Urticaria in Pregnancy. *Front Immunol*. 2021;12:652973.
95. Podder I, Dhabal A, Chakraborty SS. Efficacy and Safety of Up-dosed Second-generation Antihistamines in Uncontrolled Chronic Spontaneous Urticaria: A Review. *J Clin Aesthetic Dermatol*. 2023;16:44-50.
96. Kocatürk E, Al-Ahmad M, Krause K, Gimenez-Arnau AM, Thomsen SF, Conlon N, et al. Treatment patterns and outcomes in patients with chronic urticaria during pregnancy: Results of PREG-CU, a UCARE study. *J Eur Acad Dermatol Venereol*. 2023;37:356-64.
97. Vieira dos Santos R, Locks Bidese B, Rabello de Souza J, Maurer M. Effects of omalizumab in a patient with three types of chronic urticaria. *Br J Dermatol*. 2014;170:469-71.
98. 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;27:326-7.
99. Saito J, Yakuwa N, Sandaiji N, Uno C, Yagishita S, Suzuki T, et al. Omalizumab concentrations in pregnancy and lactation: A case study. *J Allergy Clin Immunol Pract*. 2020;8:3603-4.
100. Kulthanan K, Rujitharanawong C, Munprom K, Trakanwittayarak S, Phumariyapong P, Prasertsook S, et al. Prevalence, Clinical Manifestations, Treatment, and Clinical Course of Chronic Urticaria in Elderly: A Systematic Review. *J Asthma Allergy*. 2022;15:1455-90.
101. Khaliliya R, Confino-Cohen R, Lachover-Roth I, Meir-Shafir K, Cohen-Engler A, Rosman Y. Chronic Urticaria in Elderly-New Insights. *J Allergy Clin Immunol Pract*. 2023;11:1290-8.
102. Patruno C, Fabbrocini G, Cillo F, Torta G, Stingeni L, Napolitano M. Chronic Urticaria in Older Adults: Treatment Considerations. *Drugs Aging*. 2023;40:165-77.
103. Netti 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;120:318-23.
104. Cho Y-T, Chan TC, Lee C-H, Chou W-Y, Hsiao P-F, Chen Y-J, et al. Taiwanese dermatological association consensus for the definition, classification, diagnosis, and management of urticaria: A 2021 update. *J Formos Med Assoc Taiwan Yi Zhi*. 2022;121:1191-203.
105. Oztup N, Demir S, Unal D, Beyaz S, Terzioğlu K, Olgac M, et al. Predictive factors of recurrence after omalizumab cessation in the elderly with urticaria: A real-life study. *Allergy Asthma Proc*. 2022;43:519-28.

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Reactions to iodinated contrast media – practical aspects

Reações aos meios de contraste iodados – aspectos práticos

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ABSTRACT

Introduced in the 1950s, iodinated contrast media (ICM) remain among the most commonly prescribed drugs in radiology and have been widely used following new formulations with increased resolution and reduced toxicity. While adverse reactions to ICM are not uncommon, they are underreported and severe reactions are not always recorded. Guidelines for the management of reactions to ICM vary across different international societies, giving rise to several controversies. This paper discusses the main aspects of adverse reactions to ICM and investigation using *in vivo* assays to identify safe alternatives for future procedures. It also addresses the indications for premedication.

Keywords: Iodinated contrast media, hypersensitivity reactions, skin tests, premedication.

RESUMO

Desde a sua introdução na década de 1950, os meios de contraste iodados (MCI) têm estado entre os fármacos mais frequentemente prescritos na radiologia e vêm sendo amplamente utilizados após as novas formulações, com melhor resolução e menor toxicidade. As reações adversas a esses agentes não são incomuns, mas são subnotificadas e nem sempre há registro das reações graves. As diretrizes para manejo de pacientes com reação aos contrastes variam entre as diferentes sociedades internacionais, trazendo à discussão diversas controvérsias. Nesse artigo discutiremos sobre os principais aspectos relacionados às reações adversas aos MCI, sobre a investigação através dos testes *in vivo* em busca de alternativas seguras em caso de procedimentos futuros e também abordaremos as indicações da pré-medicação.

Descritores: Meios de contraste iodados, reações de hipersensibilidade, testes cutâneos, pré-medicação.

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Introduction

Contrast media (CM) are solutions used to increase image definition in radiology, improving diagnostic accuracy and monitoring of various diseases. The most frequent types are iodinated CM (ICM) for X-ray and tomography examinations, gadolinium-based CM for magnetic resonance examinations, in addition to dyes such as patent blue, isosulfan blue, methylene blue, and fluorescein.

More than 70 million doses of ICM are administered annually worldwide, making adverse reactions to these agents increasingly relevant.^{1,2} Adverse reactions to CM include toxic reactions (generalized itching, sensation of heat, flushing, nausea, metallic taste) and hypersensitivity reactions. Hypersensitivity reactions may be allergic or non-allergic and, according to the chronology and clinical picture, are classified as immediate (i.e. those occurring up to 1 hour [or up to 6 hours] after administration) or delayed reactions (i.e. from 1 hour to a few days after exposure).^{3,4} Skin tests are highly recommended to identify allergic hypersensitivity reactions and determine alternative agents, and the provocation test can be used to confirm tolerance.³

How are iodinated contrast media classified?

The chemical structure of ICM consists of a benzene ring linked to at least 3 iodine atoms

responsible for radiopacity. Side chains are modified with hydroxyl groups and other molecules and define the properties of each CM (Figure 1).⁵ ICM can be classified according to 3 properties: the charge of the iodine molecule (ionic or non-ionic), the molecular structure (monomeric or dimeric), and the osmolality of the contrast solution (hyperosmolar, hypo-osmolar or iso-osmolar) (Figure 2).⁶

The ionization capacity of ICM is directly related to the frequency and severity of adverse reactions.⁶ Non-ionic and lower osmolality ICM are associated with a lower incidence of reactions.

Are reactions to iodinated contrast media common?

In the past, high-osmolality ICM were associated with a higher incidence of immediate reactions due to direct histamine release without the involvement of an immune mechanism. After low-osmolality ICM were introduced in the market, the incidence of immediate reactions decreased, but evidence of reactions induced by an immune mechanism has been increasing, especially delayed reactions.⁶

Currently, immediate or delayed reactions to ICM occur at a frequency of 0.5% to 3% of infusions, and are usually mild to moderate. Mortality is low, ranging from 1 to 2 per 100,000 administrations.^{3,4,7}

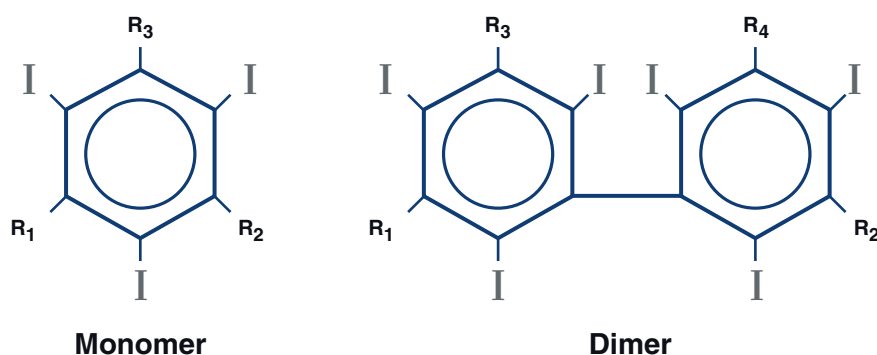


Figure1
Chemical structure of iodinated contrast media

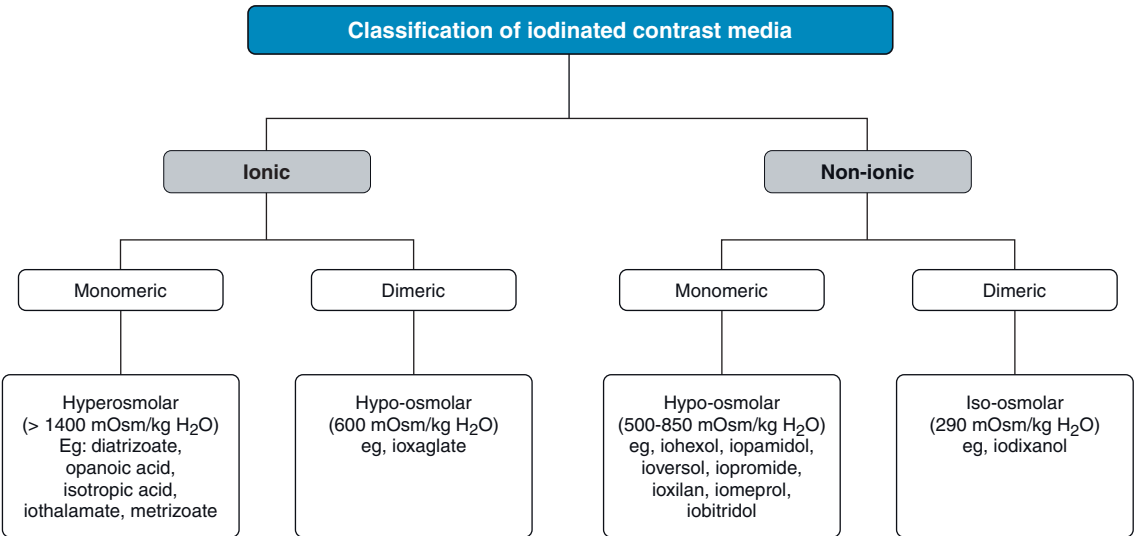


Figure 2
Classification of iodinated contrast media according to ionization capacity, molecular structure, and osmolarity⁶

What are the main risk factors?

Previous reactions to contrast-enhanced exams are the main risk factor for new reactions, increasing the risk by approximately 5 times for re-exposure to the same CM.^{2,4,7,8} An immediate hypersensitivity reaction is not a risk factor for a delayed reaction and vice versa. Immediate hypersensitivity reactions to CM are substantially less frequent in intra-arterial and extravascular (e.g., gastrointestinal, genitourinary) administration.³ Other less significant risk factors for immediate and delayed reactions are shown in Table 1.⁶

It should be noted that a history of allergy to crustaceans, mollusks, and fish, as well as contact dermatitis due to products containing iodine, are not risk factors for ICM reactions.⁶

There is no evidence that people with systemic mastocytosis have a higher risk of immediate hypersensitivity reactions to ICM than the general

Table 1
Risk factors for immediate and delayed hypersensitivity reactions

Previous reaction to ICM
Repeated administration of ICM
Renal failure
Female sex
Drug allergy
Cardiopulmonary disease
IL-2 treatment
Atopy
Use of beta-blockers, ACE inhibitors or proton pump inhibitors (immediate reactions)

ICM = iodinated contrast medium, IL-2 = interleukin 2, ACEI = angiotensin-converting enzyme inhibitors.
Adapted from Rosado-Ingelmo, et al.⁶.

population,^{3,4} but due to the variety of anaphylaxis triggers in mastocytosis, the basal serum tryptase of patients with anaphylaxis to ICM should be measured as a screening method.⁴

How are reactions classified?

Adverse reactions to CM can be classified as toxic or hypersensitive. The former are associated with the chemical properties of the media, are dose and infusion rate dependent, and include vasovagal reaction, convulsions, arrhythmias and toxicity in some organs, especially the kidneys.^{4,6,7} Hypersensitivity reactions occur independently of the dose and infusion rate and may occur in response to small amounts of contrast. They are classified based on the chronology, involved mechanism, or phenotype. According to onset time after contrast infusion, they are divided into immediate or delayed hypersensitivity reactions, and the lesion type should also be considered.^{4,6,7}

Although immediate hypersensitivity reactions may have an immunological mechanism (IgE-mediated), non-immunological mechanisms (direct histamine release or non-immunological complement activation) are more common, especially among high-osmolarity ICM. The clinical manifestations of immediate hypersensitivity reactions are urticaria and/or angioedema, either isolated or associated with bronchospasm, vomiting and/or hypotension, which characterizes anaphylaxis. Seventy percent of immediate hypersensitivity reactions occur within 5 minutes of infusion, and the greater the number of organs affected and/or severity of the reaction, the greater the possibility of an IgE-mediated reaction.^{2,4}

Immune-mediated (T-cell) immediate hypersensitivity reactions are based on the structure of the ICM, and their spectrum ranges from maculopapular exanthema, fixed drug eruption, drug-related symmetrical intertriginous and flexural exanthema, and late-onset urticaria to severe cutaneous reactions, such as drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Uncomplicated maculopapular exanthema is the most common adverse reaction to dimeric nonionic ICM, being implicated in > 50% of cases.^{4,9}

Who should be investigated?

Because previous reactions to contrast-enhanced exams are the main risk factor for new immediate or

delayed reactions, it is important to investigate patients with suspected hypersensitivity reactions. Nonspecific reactions, such as generalized pruritus, burning sensation, transient erythema, flushing, skin reaction at the injection site, atopy, asthma, allergy to other medications, food allergy, patients classified as allergic to iodine (eg, crustaceans, povidone, and mollusks) are not indicated for ICM allergy investigation when there is no history of reaction to them.^{4,6}

Investigation: when, how, and where?

The ideal time for investigating immediate hypersensitivity reactions or delayed hypersensitivity reactions should be 2 to 6 months after the reaction and at least 6 months after a drug reaction with eosinophilia and systemic symptoms and sequential reactivation of herpes virus. Studies show that sensitivity decreases from 50% to 18% 6 months after the reaction test.³

For immediate hypersensitivity reactions, a skin prick test with undiluted ICM 300-320 mg/ml and immediate reading in 20 minutes is recommended. If negative, proceed with an intradermal test at 1/10 dilution. Use the involved ICM whenever possible.^{3,4}

In delayed hypersensitivity reactions, delayed-reading (48/72 h) intradermal tests (1/10) and patch tests (undiluted ICM) are the initial approach (Table 2). Do not perform intradermal testing for drug reactions with eosinophilia and systemic symptoms, fixed drug eruptions, or bullous reactions due to the risk of reactivation. Testing with an alternative ICM is mandatory if these tests are positive or if the incriminating ICM is unknown (Figures 3 and 4).^{3,4}

In vitro tests (basophil activation test and lymphoproliferative test) are not standardized and are still unavailable outside of clinical research. Provocation tests are controversial due to their risk, but can be performed to rule out mild delayed reactions, offer alternatives, assess the risks and benefits, and exclude contraindications.⁴ It is important to note that tests must always be performed in a prepared environment (hospital or level 3 office) by a team trained to handle reactions.

Is there cross-reactivity between iodinated contrast media?

The frequency of cross-reactions between ICM vary in different studies (20%-75%) and are not related to iodine, excipient, or ionic charge. They are more common in late reactions with ICM that have the N-(2,3-dihydroxypropyl) carbamoyl side chain.^{3,6,11,12}

Safe alternatives for re-exposure must be selected with caution due to the possibility of cross-reactivity between different products.¹³

The role of cross-reactions between different ICMs was highlighted in an article by Lerondeau et al. and confirmed by Schrijvers et al., who classified ICMs

into 3 groups (A, B and C) based on the frequency of cross-reactivity between agents in the same group and the low cross-reactivity between the 3 groups (Table 3).^{12,14} Therefore, sensitized patients should be tested with an alternative ICM from a different subgroup than the offending ICM.¹²

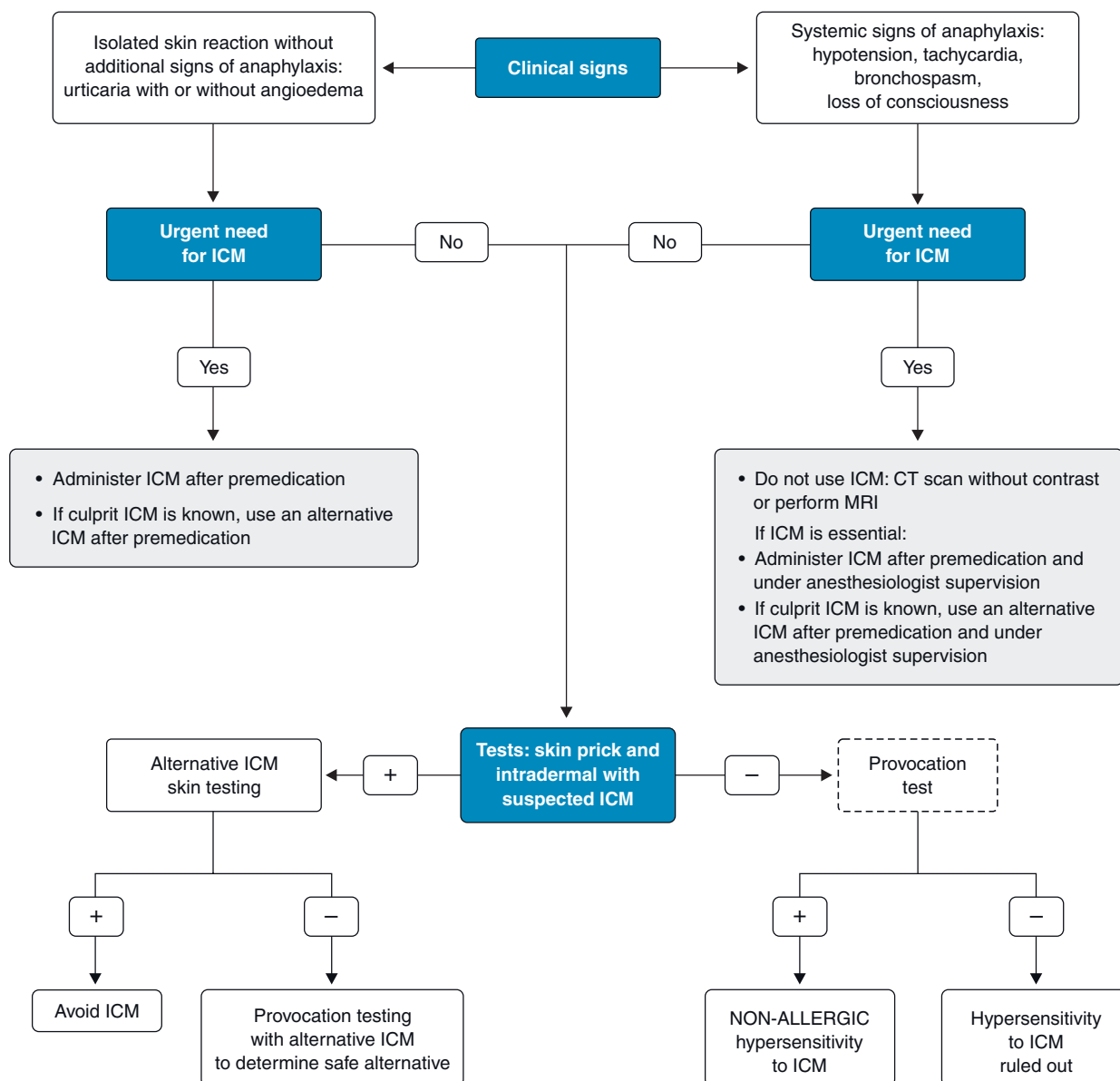


Figure 3

Algorithm for diagnosing and managing immediate hypersensitivity reactions to iodinated contrast media

ICM = iodinated contrast media, CT = computed tomography, MRI = magnetic resonance imaging, Positive skin tests = > 3 mm.

Adapted from Torres, et al.⁴

When should premedication be used?

Routine premedication for patients with allergic or undetermined reactions to ICM is a common practice and is endorsed by some American associations. However, European guidelines advise against it, emphasizing the importance of investigation, considering both the risk of breakthrough reactions in patients with a history of severe reactions, as well as

the false sense of security from using it. Exchanging ICM within the same hypo-osmolar group or using premedication for mild-to-moderate immediate reactions is recommended. However, no evidence exists that premedication is efficacious for moderate or severe IgE-mediated reactions. In such cases, performing a skin test and using an alternative ICM with a negative test is safer. Premedication is not indicated for delayed reactions.

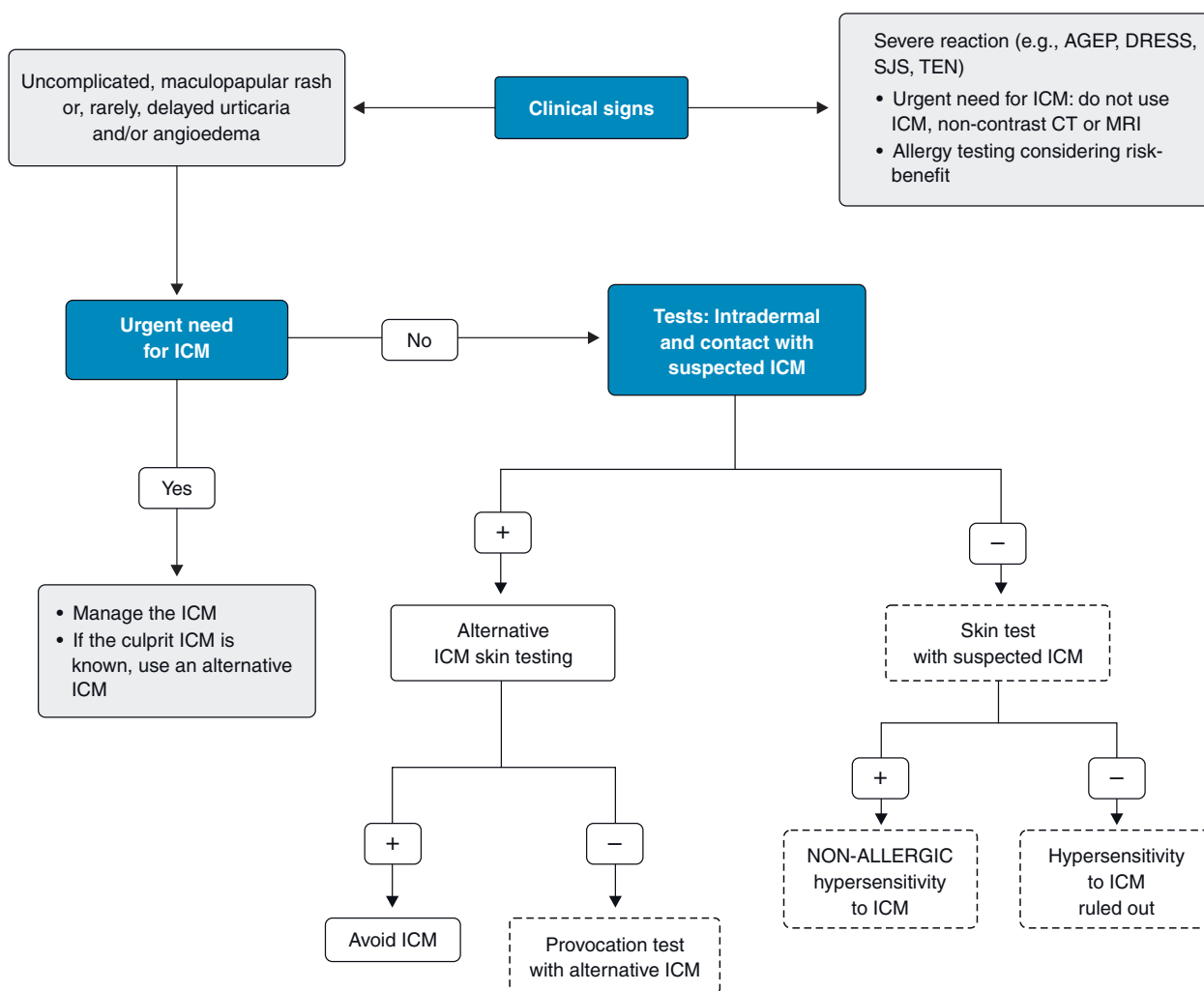


Figure 4

Algorithm for diagnosis and management of non-immediate hypersensitivity reactions to iodinated contrast media

ICM = iodinated contrast media, CT = computed tomography, MRI = magnetic resonance imaging, DRESS = drug reaction with eosinophilia and systemic symptoms, AGEP = acute generalized exanthematous pustulosis, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis.

Adapted from Torres, et al.⁴.

Table 2
Concentrations used in skin tests for iodinated contrast media

Test	Concentration ^a	Reading	
		Immediate reaction	Delayed reaction
Skin prick test	Undiluted	20 min	
Intradermal test	1/10 dilution ^b	20 min	20 min, 48 h, 72 h
Patch test	Undiluted		20 min, 48 h, 72 h

^a Undiluted iodinated contrast media at a concentration of 300-320 mg/mL. In more severe reactions, intradermal tests should be performed with higher dilutions.

^b In non-severe delayed reactions, if the result of the intradermal test at 1/10 dilution is negative, the test can be repeated using the undiluted ICM, but in this case, if there is a reaction in the 20-minute reading, it should be interpreted as an irritant⁴.

Adapted from Brockow¹⁰.

The most widely used and referenced protocol in the literature for premedication recommends diphenhydramine as an antihistamine (Table 4).^{4,6,8,15} However, since this medication is not available in oral form in Brazil, we suggest using a second generation H1 antihistamine.

No evidence exists that protocols lasting < 4-5 hours (oral or IV) are efficacious, but they may be considered in emergency situations when there are no alternatives. In these cases, methylprednisolone 40 mg or hydrocortisone 200 mg IV are used immediately and every 4 hours until the administration

Table 3
Cross-reactivity between iodinated contrast media

Group A	Group B	Group C
Iodixanol	Ioxaglate	Amidotrizoate
Iopamidol	Iobitridol	
Iomeprol		
Iohexol		
Ioversol		
Iopromide		
Ioxitalamate ^a		

^a The only iodinated contrast medium in group A without the N-(2,3-dihydroxypropyl) carbamoyl side chain.

Adapted from Lerondeau B, et al.¹².

Table 4

Suggested premedication protocols for immediate reactions according to age group

Adults	Prednisone 50 mg, oral dose, 13 h, 7 h and 1 h before the procedure. If oral administration is unfeasible, opt for IV methylprednisolone^a 40 mg at the same time intervals AND Diphenhydramine^b 50 mg, oral or IV, administered 1 h before the procedure.
Children	Prednisone 0.5 to 0.7 mg/kg per dose up to 50 mg per oral dose, 13 h, 7 h, and 1 h before the procedure. If oral administration is unfeasible, opt for IV methylprednisolone^a 0.5 mg/kg, up to a maximum of 40 mg per dose AND Diphenhydramine^b 1.25 mg/kg, ≤ 50 mg, oral or IV, administered 1 h before the procedure.

IV = intravenous.

^a Option: Hydrocortisone 200 mg IV.^b Oral diphenhydramine is not available in Brazil, therefore a 2nd generation H1 antihistamine is suggested.Adapted from Wang C, et al.⁸

of ICM and diphenhydramine 50 mg IV 1 hour before using the ICM.⁸

Conclusions

The approach to patients with contrast reactions is challenging. Clinical history and in vivo tests are the cornerstones of diagnosis, but in vitro tests are not yet widely available. A previous reaction to an ICM is the main risk factor for future reactions. The frequent lack of description of the involved ICM and the time elapsed between the reaction and the investigation hinder this entire process. When tests are positive, skin tests with an alternative CM should be performed, since cross-reactions may occur. Provocation tests may be indicated after risk-benefit assessment. Premedication may be indicated for mild-to-moderate reactions, but not for delayed or severe immediate reactions.

References

- Schönmann C, Brockow K. Adverse reactions during procedures: Hypersensitivity to contrast agents and dyes. *Ann Allergy Asthma Immunol*. 2020 Feb;124(2):156-64.
- Tasker F, Fleming H, McNeill G, Creamer D, Walsh S. Contrast media and cutaneous reactions. Part 1. Immediate hypersensitivity reactions to contrast media and gadolinium deposition. *Clin Exp Dermatol*. 2019;44(8):839-43.
- Brockow K. Diagnosing and Managing Patients with Reactions to Radiocontrast Media. *Curr Treat Options Allergy*. 2021;8:210-21.
- Torres MJ, Trautmann A, Böhm I, Scherer K, Barbaud A, Bavbek S, et al. Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity. *Allergy*. 2021 May;76(5):1325-39.
- Dutra BG, Bauab Jr T (eds.). Meios de contraste: conceitos e diretrizes. Manual da Sociedade Paulista de Radiologia e Diagnóstico por Imagem. 1st ed. São Caetano do Sul, Difusão Editora; 2020. p. 1-226.
- Rosado Ingelmo A, Doña Diaz I, Cabañas Moreno R, Moya Quesada MC, García-Avilés C, García Nuñez I, et al. Clinical Practice Guidelines for Diagnosis and Management of Hypersensitivity Reactions to Contrast Media. *J Investig Allergol Clin Immunol*. 2016;26(3):144-55.
- Brockow K, Sánchez-Borges M. Hypersensitivity to contrast media and dyes. *Immunol Allergy Clin North Am*. 2014 Aug;34(3):547-64.
- American College Radiology, ACR Committee on Drugs and Contrast Media. Wang C, Ash D (eds.). Manual on Contrast Media. ACR; 2023. p.1-140.
- Tasker F, Fleming H, McNeill G, Creamer D, Walsh S. Contrast media and cutaneous reactions. Part 2: Delayed hypersensitivity reactions to iodinated contrast media. *Clin Exp Dermatol*. 2019 Dec;44(8):844-60.
- Brockow K. Medical algorithm: Diagnosis and treatment of radiocontrast media hypersensitivity. *Allergy*. 2020 May;75(5):1278-80.
- Gamboa P, Sánchez de Vicente J, Galán C, Jáuregui I, Seguro A, García-Lirio E, et al. Non-immediate hypersensitivity reactions to iomeprol: Diagnostic value of skin tests and cross-reactivity with other iodinated contrast media. *Allergy*. 2022 Dec;77(12):3641-7.
- Lerondeau B, Trechot P, Waton J, Poreaux C, Luc A, Schmutz JL, et al. Analysis of cross-reactivity among radiocontrast media in 97 hypersensitivity reactions. *J Allergy Clin Immunol*. 2016 Feb;137(2):633-635.e4.

13. Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadonna P, et al.; European Network of Drug Allergy and the EAACI interest group on drug hypersensitivity. Skin testing in patients with hypersensitivity reactions to iodinated contrast media - a European multicenter study. *Allergy*. 2009 Feb;64(2):234-41.
14. Schrijvers R, Breynaert C, Ahmedali Y, Bourrain JL, Demoly P, Chiriac AM. Skin Testing for Suspected Iodinated Contrast Media Hypersensitivity. *J Allergy Clin Immunol Pract*. 2018;6(4):1246-54.
15. Schopp JG, Iyer RS, Wang CL, Petscavage JM, Paladin AM, Bush WH, et al. Allergic reactions to iodinated contrast media: premedication considerations for patients at risk. *Emerg Radiol*. 2013 Aug;20(4):299-306.

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Food allergens on food product labels: unification of nomenclature

Alérgenos alimentares em rótulos de produtos alimentícios: uma unificação da nomenclatura

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ABSTRACT

The prevalence of food allergies has grown considerably in recent decades. Patient education on label reading and identification of allergens in food products is essential, even after the publication of RDC No. 26/2015, which established the labeling requirements for the main food allergens. A major difficulty is the use of multiple terminologies to name a food ingredient, in addition to the lack of a compilation of these nomenclatures into a single list. In this study, we developed an unified list of the nomenclatures of the 4 main food allergens based on preexisting lists for use in clinical practice and in future projects involving identification of food allergens through artificial intelligence tools.

Keywords: Food hypersensitivity, allergens, food labeling.

RESUMO

A prevalência das alergias alimentares vem crescendo de forma significativa nas últimas décadas. A educação do paciente na leitura de rótulos e identificação dos alérgenos nos produtos alimentícios é fundamental, mesmo após a publicação da RDC nº 26/2015, que estabeleceu os requisitos de rotulagem dos principais alérgenos alimentares. Uma das maiores dificuldades é a utilização de numerosas terminologias diferentes que são utilizadas para nomear um ingrediente alimentício, além de não haver uma compilação destas nomenclaturas em uma única listagem. Neste trabalho, foi realizada uma listagem unificada das nomenclaturas dos quatro principais alérgenos alimentares com base nas listas preexistentes, a fim de uso na prática clínica e em projetos futuros envolvendo identificação dos alérgenos alimentares através de ferramentas de inteligência artificial.

Descritores: Hipersensibilidade alimentar, alérgenos, rotulagem de alimentos.

Food allergies have shown an increasing prevalence in recent decades. In Brazil, it is estimated that approximately 8% of children up to 2 years old and 2% of adults may have some type of food allergy^{1,2}. Currently, the cornerstone of food allergy management is avoidance of the allergenic food.

In this context, proper reading of nutrition facts labels and the identification of allergenic proteins by patients and caregivers is essential. In 2014, the

campaign “Põe no Rótulo” (“Put It on the Label”) was launched to raise public awareness about food allergies and promote actions toward standardizing the labeling of food allergens³. In 2015, the Brazilian Health Regulatory Agency (ANVISA) issued Resolution No. 26/2015, establishing requirements for mandatory labeling of the major allergens implicated in food allergies⁴, providing clearer and more accessible information to the public. However, recent studies

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show that, even after the publication of the ANVISA resolution, many labels still fail to comply, either due to missing allergen declarations or spelling errors. A study conducted in Bahia, Brazil, in 2023⁵ found that 27% of the analyzed food labels did not comply with Resolution No. 26/2015. A study conducted in Minas Gerais, Brazil, in 2022⁶ analyzed product labels and found that 35% were noncompliant, with the majority (91.4%) failing to declare allergens. These studies highlight the ongoing need for consumer education and active engagement in reading nutrition fact labels.

One of the major challenges in this regard is the extensive list of terms used to name food ingredients. The nomenclature may not only refer to the allergenic food itself but also to derivatives or proteins of the allergenic food. Additionally, technical or scientific terms are often used to refer to allergens, making it harder for consumers to understand and identify them.

Several lists have been published on national and international websites and in consensus guidelines, aiming to cover the main nomenclatures for allergenic foods⁷⁻¹⁰. However, a quick search shows that these lists are often incomplete. Tables 1, 2, 3, and 4 present a unified and revised listing of the 4 major food allergens that feature a variety of nomenclatures on product labels (milk, egg, wheat, and soy). Other allergens listed in the ANVISA resolution (such as peanuts, tree nuts, shrimp, and fish) were not included, as their nomenclature tends to be more straightforward on nutrition facts labels, appearing as the name of the food itself rather than under alternative terms.

A more comprehensive list would allow for the standardization of the incomplete lists currently published, with the aim of facilitating their use in clinical practice for educating patients with food allergies. Furthermore, our group has been developing a mobile application powered by artificial intelligence algorithms that can read nutrition facts labels, identify the presence of allergens, and inform the user, to assist in the care of individuals with food allergies¹¹. For the development of this tool, it is crucial to use the most complete list possible to improve the sensitivity of the method in detecting allergens.

Table 1
Nomenclature for cow's milk found on labels

Milk (whole, semi-skimmed, skimmed, powdered, condensed, evaporated)
Anhydrous milk fat
Butter
Butter esters
Butter fat
Butter oil
Buttermilk
Caramelized milk (or <i>dulce de leche</i>)
Casein
Casein hydrolysate
Caseinate (calcium, potassium, ammonium, magnesium, sodium)
Cream
Curds
Dairy blend
Dairy compound
Dairy protein
Delactosed or demineralized whey
Diacetyl
Ghee
Half-and-half
Hydrolyzed milk protein
Hydrolyzed whey protein
Lactalbumin
Lactalbumin hydrolysate
Lactalbumin phosphate
Lactic acid starter culture
Lactic acid starter culture in milk or whey
Lactoferrin
Lactoglobulin
Lactose
Lactulone
Lactulose
Microparticulate whey protein
Milk fat
Milk protein concentrate
Milk protein hydrolysate
Nougat
Petit-suisse
Rennet casein
Sour milk solids
Yogurt
Yogurt hydrolysate

Table 2

Nomenclature for egg found on labels

Egg (chicken, duck, goose, turkey, quail, raw, boiled, fried, poached, omelet)
 Albumin (or albumen)
 Avidin
 Cystatin
 Dried egg whites
 Egg albumin
 Egg solids
 Egg white
 Egg yolk
 Flavoprotein
 Lecithin
 Livetin
 Livoprotein
 Low-density lipoprotein
 Lysozyme
 Ovalbumin
 Ovoglobulin
 Ovoglycoprotein
 Ovomacroglobulin
 Ovomucin
 Ovomuroid
 Ovestatin
 Ovotransferrin
 Vitellin

Table 3 (*continuation*)

Nomenclature for wheat found on labels

Kamut wheat
 Kibbeh (or kibe or kubbeh)
 Matzoh, matzoh meal (or matzo, matzah, matza)
 Seitan (or gluten meat)
 Semolina
 Triticale
 Wheat beer
 Wheat bran
 Wheat flakes
 Wheat flour
 Wheat germ
 Wheat germ oil
 Wheat gluten
 Wheat semolina
 Wheat sprouts
 Wheat starch
 Wheatgrass
 Whey protein isolate
 Whole wheat flour
 Whole wheat grains
 Whole wheat grains

Table 3

Nomenclature for wheat found on labels

Wheat
 Atta (or *chakki atta*)
 Bread crumbs
 Bread pudding
 Buckwheat
 Bulgur (or burghul, spelt)
 Cereal extract
 Cereal flour
 Chlorophyll
 Couscous
 Durum
 Einkorn
 Emmer
 Enriched all-purpose flour
Fu wheat
 Gluten
 Hydrolyzed wheat bran

Table 4

Nomenclature for soy found on labels

Soy
 Beta-amylase
 Conglycin
 Conglycinin
 Edamame
 Fermented soybean paste
 Globulins
 Glycinin
 Hemagglutinin
 Hydrolyzed vegetable protein
 Isoflavone
 Lecithin
 Lipoxigenase
 Miso
Natto
Shoyu
 Soy extract
 Soy protein isolate

Table 4 (continuation)

Nomenclature for soy found on labels

Soy sauce
Sufu
Tamari
Tao-cho
Tao-si
Taotjo
Tempeh
Teriyaki
Textured soy protein
Textured vegetable protein
Tofu
Trypsin inhibitor
Urease
Vegetable broth
Vegetable fat
Vegetable protein
Yuba

References

1. Associação Brasileira de Alergia e Imunologia, ASBAI. Alergia Alimentar é o tema central da Semana Mundial [Internet]. 2019. Available from: <https://asbai.org.br/alergia-alimentar-e-o-tema-central-da-semana-mundial/>. Accessed jan 06 2024.
2. Solé D, Silva LR, Cocco RR, Ferreira CT, Sarni RO, Oliveira LC, et al. Consenso Brasileiro sobre Alergia Alimentar: 2018 - Parte 1 - Etiopatogenia, clínica e diagnóstico. Documento conjunto elaborado pela Sociedade Brasileira de Pediatria e Associação Brasileira de Alergia e Imunologia. Arq Asma Alerg Imunol. 2018;2(1):7-38.
3. poenorotulo.com.br [Internet]. Brasil: Põe no Rótulo [citado em 2014]. Available from: <https://www.poenorotulo.com.br/sobre>. Accessed jan 06 2024.
4. Brasil, Ministério da Saúde, Agência Nacional de Vigilância Sanitária, ANVISA. Resolução da Diretoria Colegiada – RDC nº 26, de 02 de julho de 2015. Diário Oficial da União (02 de julho de 2015). Available from: https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2015/rdc0026_26_06_2015.pdf. Accessed jan 06 2024.
5. Martins LTS. Rotulagem de alimentos alergênicos: análise das informações. Revista Higiene Alimentar;37(296): e1113, Jan-Jun, 2023. doi: 10.37585/HA2023.01rotulagem.
6. Oliveira Andrade M, Alves DT, Nascimento WCA. Avaliação da rotulagem de alimentos e da conformidade quanto à declaração obrigatória de alergênicos. Alim: Cien Tecn M Amb. 2022; 3(1):14-25. Available from: <https://revistascientificas.ifrrj.edu.br/index.php/alimentos/article/view/2221>.
7. Yonamine, GH, Pinotti, R. Alergia alimentar: alimentação, nutrição e terapia nutricional. 1st ed. Barueri: Manole; 2020. 504 p.
8. Food Allergy Research & Education (FARE) [Internet], Estados Unidos. Available from: <https://www.foodallergy.org/living-food-allergies/food-allergy-essentials/common-allergens>. Accessed jan 06 2024.
9. poenorotulo.com.br [Internet]. Brasil: Cartilha da Alergia Alimentar [Citado em 2014]. Available from: https://www.poenorotulo.com.br/_files/ugd/4f5582_f1dccdd773a14076b0fd271b534427fc.pdf?index=true. Accessed jan 06 2024.
10. Canadá, Governo do Canadá. Allergens and gluten sources labelling [Internet]. Available from: <https://www.canada.ca/en/health-canada/services/food-allergies-intolerances/avoiding-allergens-food/allergen-labelling.html>. Accessed jan 06 2024.
11. Gadelha GA. Processamento de Linguagem Natural aplicado na identificação de alérgenos em rótulos alimentares [course conclusion paper]. Porto Alegre: Curso de Informática Biomédica: Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA); 2023.

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Efficacy and safety of house dust mite sublingual immunotherapy in children and adolescents with allergic rhinitis

Eficácia e segurança da imunoterapia sublingual para ácaros em crianças e adolescentes com rinite alérgica

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ABSTRACT

Objective: To describe the efficacy and safety of house dust mite sublingual immunotherapy (SLIT) in patients with allergic rhinitis (AR) over a 12-month period. **Methods:** This is a prospective, open-label study of children and adolescents aged 4 to 18 years with AR/asthma according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, followed up at the outpatient clinics of the Hospital de Clínicas affiliated with the Federal University of Paraná, southern Brazil. All patients received SLIT drops (750 UBE/day) for *Dermatophagoides pteronyssinus* (DP) and *Blomia tropicalis* (BLO) at a concentration of 5000 UBE/mL for 12 months. Symptom and medication scores (RTSS) were assessed and skin prick tests for aeroallergens were performed from January 2022 to January 2023. **Results:** Twenty participants with an AR diagnosis for at least 4 years (range, 2-10) were included. The mean SLIT adherence rate was 89%. The mean DP wheal diameter reduced from 7.0 (SD 2.9) to 4.2 (SD 2.1) mm after 12 months ($p=0.0002$), while the median BLO wheal diameter reduced from 3.7 to 3.0 mm ($p=0.0001$). Patients showed a reduction in rescue medication use, symptom score, and combined symptom and medication scores ($p<0.05$). The mean visual analog scale score reduced from 9.3

RESUMO

Objetivo: Descrever a eficácia e segurança da imunoterapia com alérgenos sublingual (SLIT) com ácaros em pacientes com rinite alérgica durante um período de 12 meses. **Métodos:** Estudo experimental aberto, prospectivo que envolveu crianças e adolescentes de 4 a 18 anos com rinite alérgica/asma segundo as diretrizes *Allergic Rhinitis and its Impact on Asthma* (ARIA), acompanhados nos ambulatórios do Hospital de Clínicas da Universidade Federal do Paraná. Todos os pacientes receberam gotas (750 UBE/dia) de SLIT para *Dermatophagoides pteronyssinus* (DP) e *Blomia tropicalis* (BLO) na concentração de 5.000 UBE/mL durante 12 meses. Foram aplicados escores de medicação (RTSS), testes cutâneos para aeroalérgenos entre janeiro de 2022 e janeiro de 2023. **Resultados:** Vinte participantes com pelo menos 4 (variação de 2 a 10) anos de diagnóstico de RA. A adesão média à SLIT foi de 89%. Houve redução no diâmetro médio da pápula DP de $7 \pm 2,9$ mm para $4,2 \pm 2,1$ mm após 12 meses ($p = 0,0002$), bem como na mediana do diâmetro médio da pápula BLO de 3,7 mm a 3 mm ($p = 0,0001$). Os pacientes apresentaram redução no consumo de medicamentos de resgate, no escore de sintomas e no escore combinado de sintomas e medicamentos ($p < 0,05$). A

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(SD 0.7) to 5.2 (SD 1.4) ($p < 0.05$). There was no difference in asthma control ($p = 0.16$). The rate of mild adverse effects was low and did not differ throughout the study ($p = 0.62$). There were no anaphylactic reactions. **Conclusion:** SLIT may provide short-term benefits to patients with AR, reducing the need for medication and improving nasal symptoms. SLIT was well tolerated and safe, with no serious adverse events.

Keywords: Allergen-specific immunotherapy, sublingual immunotherapy, allergic rhinitis.

pontuação da escala visual analógica reduziu de $9,3 \pm 0,7$ para $5,2 \pm 1,4$ ao final do estudo ($p < 0,05$). Não houve diferença no controle da asma ($p = 0,16$). A taxa de efeitos adversos leves foi baixa e não diferiu ao longo do estudo ($p = 0,62$), e não houve reações anafiláticas. **Conclusão:** A SLIT pode trazer benefícios em curto prazo em pacientes com RA, reduzindo a necessidade de medicação e melhorando os sintomas nasais. Foi bem tolerada e segura, sem eventos adversos graves.

Descritores: Imunoterapia alérgeno-específica, imunoterapia sublingual, rinite alérgica.

Introduction

Allergic rhinitis (AR), with or without associated conjunctivitis, is a common disease that affects between 10 and 40% of the population worldwide and has a significant impact on patients' quality of life. In some countries, more than 50% of adolescents have symptoms of AR.¹⁻³ In Brazil, it affects approximately 20% of the pediatric population.⁴

Although it is not a serious disease, AR has a significant socioeconomic impact. Direct costs include expenditures on medical care, tests, and medications, while indirect costs include reduced productivity and absenteeism at school and work. Among children, the disease also affects quality of life significantly, and can cause irritability and decreased cognitive performance.^{1,5,6} Long-term chronic nasal obstruction leads to changes in facial growth pattern, as well as functional complications and aesthetic issues.⁷

The main recommendations for patients with AR are avoidance of allergens, drug therapy for symptom management (mainly antihistamines and topical nasal corticosteroids), and, for patients with difficult-to-control disease, specific immunotherapy.^{1,5,8} Subcutaneous injection of immunotherapeutics has been used for decades. The exact mechanism of action is not fully understood but includes changes in serum antibody levels and cellular immunity, including a shift from a Th2 to a Th1 response, among other regulatory mechanisms. The realization that the rich vascular bed located under the tongue could serve as a novel approach for allergen delivery led to the development of rapidly disintegrating tablets or aqueous extracts that could be efficiently absorbed by this route⁹⁻¹¹.

The immunomodulation resulting from this treatment has been shown to induce immune

tolerance, with a significant reduction in symptoms and need for medication.¹²

The decision to start allergen-based immunotherapy should rely on clinical assessment and physical examination findings, with supplemental in vivo or in vitro testing as appropriate to identify sensitivity to specific relevant allergens, as well as a detailed discussion on treatment goals, risk versus benefit, and long-term commitment to a treatment plan. Because sublingual allergen immunotherapy (SLIT) involves long-term daily therapy, it requires patient or caregiver commitment to help maximize adherence.^{12,13}

Control of AR symptoms remains satisfactory in the long term even after completion of immunotherapy, reducing or, in some cases, even altogether eliminating the need for medication. Therefore, this therapy can be considered potentially capable of inducing complete disease remission.¹³

The Allergic Rhinitis and its Impact on Asthma (ARIA), European Academy of Allergy, Asthma and Immunology (EAACI), Brazilian Association of Allergy and Immunology (ASBAI), and American Academy of Allergy, Asthma and Immunology (AAAAI) guidelines all recognize immunotherapy performed with allergen extracts as a valid form of treatment, as long as the extracts are of high quality (preferably standardized) and care is taken when selecting the antigen mix, since some allergens may contain proteolytic enzymes capable of inactivating other components of the mixture.^{1,2,5,9}

The primary objective of this study is to ascertain whether SLIT constitutes an effective and safe therapy for pediatric patients with allergic rhinitis, with or

without conjunctivitis. Our secondary objectives were to assess the safety of SLIT and the degree of skin reaction before and after immunotherapy.

Methods

This open-label, prospective experimental study was conducted from January 2022 through December 2023. The study protocol was approved by the Research Ethics Committee of Universidade Federal do Paraná (opinion no. 74790323.6.0000.0096).

Data were obtained from the medical records of patients with persistent moderate/severe allergic rhinitis and/or rhinoconjunctivitis who underwent SLIT with *Dermatophagoides pteronyssinus* (DP) and *Blomia tropicalis* (BLO) extract for 12 months at the Outpatient Pediatric Allergy and Immunology Clinic, Hospital de Clínicas da UFPR (CHC-UFPR). The diagnosis of AR followed the ARIA guideline recommendations.

The sample comprised children and adolescents aged 4 to 18 years with moderate-severe allergic rhinitis/rhinoconjunctivitis, with or without comorbid asthma (mild or moderate, with $FEV_1 > 80\%$ of baseline), exclusively sensitized to DP and BLO, and in whom pharmacotherapy plus specific environmental control measures had not been sufficient to control symptoms.

Patients with serious diseases of the immune system (such as autoimmune conditions), active infections (such as tuberculosis), heart disease, severe high blood pressure (even if controlled), severe kidney disease, severe atopic dermatitis, malignancies, or psychiatric diseases that would preclude full consent were excluded, as were those taking beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, or immunosuppressants.

Patients (or their guardians) kept a daily record of symptoms and medication use during the follow-up period. Mean scores were calculated for the assessment instruments administered during monthly study visits. Records of patients meeting the aforementioned criteria were retrieved from a database and analyzed according to the following variables: sex (male or female), age (in years), underlying disease that led to SLIT, presence of concomitant asthma, total IgE measurement, visual analogue scale (VAS) score (assessed at all visits), results of skin prick testing (SPT) with DP and BLO extracts (carried out at the start of treatment and after 12 months of treatment), adherence (assessed according to the clinician's

judgment), medications required to control symptoms, symptom score, treatment-emergent adverse events, and clinical progress (after 12 months of treatment). The safety of SLIT in participants and their severity of skin reaction to house dust mites DP and BLO were recorded by comparing the mean wheal diameter on SPT before and after 12 months of SLIT. The frequency of adverse effects related to SLIT was ascertained with a questionnaire administered during study visits. Treatment adherence was assessed subjectively by the treating physician.

Clinical findings, symptom progression, adverse effects, concomitant medication, SPT results, and treatment adherence were reported descriptively and subsequently analyzed.

A simple ARIA-standard VAS was used to score the severity of rhinitis symptoms such as nasal congestion, itching, sneezing, and discharge, as well as conjunctival symptoms. In addition to the general perception of such symptoms' effect on quality of life, they are jointly measured on a ruler-type scale marked with figures and patients are asked to point out which point along this ruler best matches their current status, ranging from zero (completely asymptomatic) to 10 (awful, completely uncontrolled symptoms).

Symptom scores and medication scores were assigned according to symptom severity and the need for medication use respectively, as recorded in diaries kept by the patient or their guardians; these diaries were reviewed at regular intervals by the investigators. Visits were scheduled every three months starting from the SLIT induction phase. SPTs for DP and BLO were performed using standardized allergen extracts, positive control, and negative control. One drop of each allergen was applied to the volar surface of the forearm and the skin was pricked with a lancet. After 15 minutes, the reaction was read; a wheal diameter greater than or equal to 3 mm was considered positive. SPTs were used to monitor SLIT efficacy at the start of treatment and at 12-month follow-up. Reduction in wheal size was used as a secondary parameter to assess treatment efficacy. Allergen extracts were provided by FDA Allergenic Pharmaceuticals, Rio de Janeiro, Brazil.

The liquid extract administered in this study consisted of a standardized mixture of equal proportions of DP and BLO extracts at a concentration of 5,000 biological allergy units (BAU)/mL.

The study medication was titrated incrementally every day for 5 days (induction phase) up to a

maximum maintenance dose of 750 BAU/day for 12 months. Again, the extract was provided by FDA Allergenic Pharmaceuticals, Rio de Janeiro, Brazil (Table 1).

After enrollment, participants received vials of the SLIT extract, which were administered at home by the patient or guardian. Every 21 days, the parents or guardians of the participants collected the new vials in person at the study center.

The induction dose was 1 sublingual drop of the standardized DP/BLO extract for 5 days, followed by 3 sublingual drops daily for 12 months. The first dose was administered by a physician at the study center, and patients were kept for 1 hour under observation.

At a series of follow-up visits and at the end of treatment (or at the end-of-study visit), the following data were recorded: changes in SLIT treatment (dose modification, early discontinuation, etc.); changes in medications taken for symptom control; symptom progression; and any adverse events. Patient adherence and satisfaction, as perceived by the treating physician, were also recorded at each follow-up visit. Events such as failure to attend prearranged follow-up appointments and delay in collecting SLIT refills were deemed indicative of treatment non-adherence.

Primary outcome

The primary parameter for evaluating efficacy was a combination of the symptom score (SS) and use of rescue medication score (MS), the so-called Combined Symptom and Medication Score (CSMS), as proposed in the 2014 European Academy of Allergy and Clinical Immunology (EAACI) Position Paper on standardization of clinical outcomes used in allergen immunotherapy trials.¹⁴ The CSMS was calculated with the following formula:

$$\text{CSMS} = \text{SS}/6 \text{ (0-3)} + \text{MS} \text{ (0-3)} = 0-6$$

where: SS was the sum score from 0 to 3 (absent, mild, moderate, or severe) of four nasal symptoms (itchy nose, runny nose, blocked nose, and sneezing) and two conjunctival symptoms (itchy eyes and watery eyes). The maximum possible SS is 18; and MS was the sum score based on daily rescue medication use: topical nasal corticosteroid (1 or 2 sprays – 1 or 2 points, respectively) and loratadine (3 points), as shown in Table 2.

Loratadine (10 mg) was only indicated when nasal corticosteroids alone were not sufficient to control symptoms. Information on medications was recorded daily in a journal of rescue medication use.

Table 1

SLIT treatment regimen with *Dermatophagoides pteronyssinus* (DP) and *Blomia tropicalis* (BLO) extracts

Concentration	Phase	Dose	Frequency	Der p 1, M phase	Blo t 5, M phase	Dose (BAU), M phase
5,000 BAU/mL	I	1 drop	QD for 5 days	0.6 µg/day	22.5 ng/day	750 BAU/day
	M	3 drops	QD for 12 months			
5,000 BAU/mL	I	1 drop	QD for 5 days	0.6 µg/day	22.5 ng/day	750 BAU/day
	M	3 drops	QD for 12 months			

Table 2

European Academy of Allergy and Clinical Immunology (EAACI) Task Force Recommendation for standardization of clinical outcomes used in efficacy trials of with allergen immunotherapy

A) Symptom score		
Nasal symptoms	(Score 0-3)	0 = no symptoms 1 = mild symptoms ^a 2 = moderate symptoms ^b 3 = severe symptoms ^c
	Itchy nose	0-3a
	Sneezing	0-3
	Runny nose	0-3
	Blocked nose	0-3
Conjunctival symptoms	Itchy eyes	0-3
	Watery eyes	0-3
Total daily symptom score (dSS)		0-3 (max score is 18÷6=3)
B) Medication score		
	Intranasal corticosteroids QD	1 point
	Intranasal corticosteroids BID	2 points
	Oral antihistamine QD	3 points
Total daily medication score (dMS)		0-3 (max score is 3)
C) Combined symptom and medication score		
CSMS	dSS (0-3) + dMS (0-3)	0-6

^a Sign/symptom clearly present, but minimal awareness; easily tolerated.

^b Definite awareness of sign/symptom that is bothersome but tolerable.

^c sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping.

Adapted from EAACI Position Paper, Pfaar, et al.¹⁹.

To assess safety, participants or their guardians recorded a daily journal of any emergent local and systemic adverse effects.

Safety outcomes were assessed by the number of patients who experienced any treatment-related adverse events (TRAEs) leading to treatment discontinuation.

Adverse events (AE) were evaluated and categorized according to the World Allergy Organization (WAO) definition¹⁵ as follows:

Local AEs: oral itching, swelling of the lips or tongue, and nausea/abdominal pain/diarrhea.

Systemic AEs: urticaria, exacerbation of rhinitis and/or asthma, angioedema, and hypotension.

Eight follow-up visits were prearranged at the start of treatment. Patients who were overdue more than 15

days for a study visit or SLIT refill were excluded from the study, as this was deemed indicative of treatment nonadherence by the participant as perceived by the treating physician.

For statistical analysis, categorical variables were presented as frequency distributions and proportions. The chi-square test was used to compare proportions. Continuous variables were expressed as means and standard deviations or medians and ranges as appropriate.

Student's *t* test was used to compare means, and the Wilcoxon test to compare medians. Statistical analyses were carried out in Stat Plus version 5.9.5.0 software (Analyst Soft Inc., USA). A *p*-value < 0.05 was considered to rule out the null hypothesis.

Results

Data from 20 patients aged 4 to 18 years diagnosed with persistent moderate-severe AR induced by house dust mites, with symptoms ranging from 2 to 10 years in duration, were analyzed.

Baseline demographic data and clinical characteristics of the population of children and adolescents on SLIT are presented in Table 3.

All patients who had comorbid asthma were sensitized to DP and BLO, and all had normal lung function.

At 1-year follow-up, IgE and eosinophil levels did not show significant changes during SLIT ($p = 0.6$).

The mean diameter of the DP wheal did show a reduction after 12 months. The median diameter of the BLO wheal showed the same behavior.

SPT with the allergen extract itself was also associated with a lessened reaction at the end of treatment (Table 3).

Asthma control was evaluated at two time points during this first year of treatment using the ACT (Asthma Control Test) as an assessment tool. The first assessment took place at induction ($ACT\ 20.5 \pm 2.1$) and the second after at least 6 months of SLIT ($ACT\ 21.1 \pm 2$). There was no significant difference between these two time points ($p = 0.16$).

No deaths, cases of anaphylactic shock, or other life-threatening events were reported during the study.

Table 4 shows a summary of treatment safety. No serious TRAE was reported in this study.

Ten TRAEs occurred in the study group over the 12-month follow-up: five cases of oral symptoms or pruritus at the application site, two of lip angioedema, and three of worsening allergic symptoms/asthma exacerbation. The total TRAE rate was 15% at induction, 15% in the first month of SLIT, 5% in the third month, 10% in the sixth month, and 5% at the last (12-month) assessment, respectively.

Table 3

Demographic distribution of study patients undergoing sublingual immunotherapy (SLIT)

Characteristics	Pre	Post	p
Male sex	10 (50%)		
BMI	19.3 $\pm$ 1.5		
Age at initiation of SLIT, mean $\pm$ SD in years	10.3 $\pm$ 2.8		
Moderate/severe rhinitis	20 (100%)		
Duration of symptoms in years, median (range)	4 (2-10)		
Asthma	20 (100%)		
FEV ₁ , % of predicted	109.1 $\pm$ 13.5		
Total IgE, geometric mean in KU/L	493.9	438.8	0.6
Eosinophils/mm ³ , median (range)	385 (130-1,110)	350 (108-720)	0.6
Wheal diameter with <i>Dermatophagoides pteronyssinus</i> extract, mean $\pm$ SD in mm	7 $\pm$ 2.9	4.2 $\pm$ 2.1	0.0002
Wheal diameter with <i>Blomia tropicalis</i> extract, median (range) in mm	3.7 (3-15)	3 (0-7)	0.0001
Wheal diameter with SLIT extract, mean $\pm$ SD in mm	3.8 $\pm$ 1.6	2.7 $\pm$ 1.8	0.02
Wheal diameter with histamine 10 mg/mL, mean $\pm$ SD in mm	5.7 $\pm$ 1.7	5.1 $\pm$ 2.1	0.03

Table 4

Assessment of adverse events

Variable	Induction	1 month	3 months	6 months	12 months	p
Local TRAE	3 (15%)	1 (5%)	1 (5%)	1 (5%)	1 (5%)	0.62
Systemic TRAE	0	2 (10%)	0	1 (5%)	0	0.7

TRAE = treatment-related adverse events.

There was no significant difference in TRAE between the time points of assessment ($p > 0.05$).

Primary outcome analysis after one year of SLIT showed that patients had significant improvements in MS, SS, and CSMS (Figures 1, 2, and 3).

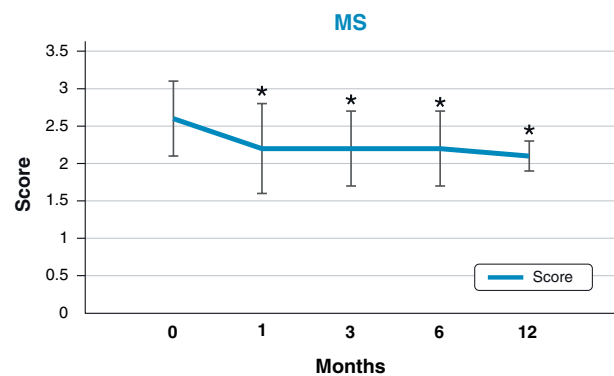
The average treatment adherence in the 12-month follow-up period was higher than 89%, which is expected for SLIT. The maximum tolerated delay in attending scheduled interview visits or collecting medication refills was 15 days (Figure 4).

The VAS score decreased from baseline to the end of the follow-up period ($p < 0.05$) (Figure 5).

Discussion

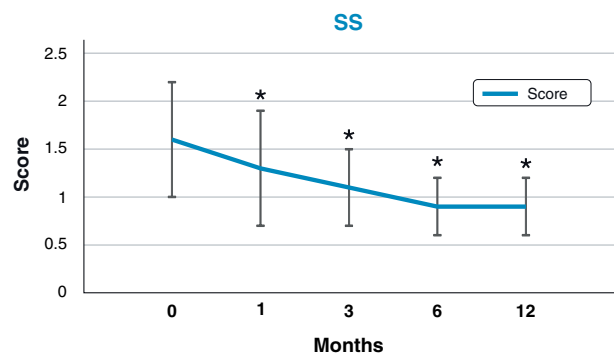
Allergen immunotherapy (AIT) is an immune-based, disease-modifying treatment option for IgE-mediated allergies such as allergic rhinoconjunctivitis and allergic asthma. However, studies on the long-term efficacy of SLIT for AR, especially in pediatric patients, are still scarce.

Previous studies have demonstrated the effectiveness of SLIT in relieving AR symptoms and reducing medication use.¹⁶ Total symptom score, total medication score, and VAS have been recommended as possible outcomes for assessing efficacy in SLIT studies. Most meta-analyses on SLIT in children have proven its efficacy in reducing symptom scores and medication use compared to placebo groups in allergic respiratory diseases.¹⁷ In the present study, we found significant decreases in MS, SS, and CSMS compared to baseline, proving the effectiveness of SLIT in our

**Figure 1**

Comparison of rescue medication scores between baseline and months 1, 3, 6, and 12

* $p < 0.05$. Data expressed as means and standard deviations.

**Figure 2**

Comparison of symptom scores between baseline and months 1, 3, 6, and 12

* $p < 0.05$. Data expressed as means and standard deviations.

cohort, which is in agreement with other studies,¹⁷ and further supporting the short-term clinical benefits of SLIT for patients with house dust mite-induced AR.

Although it has not been used in practice as a good biomarker of response, the mean wheal diameter on DP and BLO skin prick testing reduced significantly after treatment, showing a rapid reduction in allergic sensitization by SLIT.

AIT has among its mechanisms of action very early desensitization effects, modulation of T- and B-cell responses and related antibody isotypes, as well as inhibition of eosinophil, basophil, and mast cell migration into tissues and release of their respective mediators.²⁵ In the present study, the 12-month period of observation was too short to observe such reductions; further investigation is required to corroborate and supplement our findings.

Allergen-specific IgE shows an early rise and relatively late decline. These events occur in parallel with increases in IgG4, which rises continuously as treatment continues. After several months, the allergen-specific IgE/IgG4 ratio decreases. After a few months, reductions are seen in tissue mast cell and eosinophil populations, in release of their mediators, and in the late-phase response of the skin.²⁵

SLIT may be associated with milder AEs (mainly pruritus or oropharyngeal edema), while serious side effects are rare. However, reports of AEs after immunotherapy are very heterogeneous in the literature.

The World Allergy Organization (WAO) standardized grading system for local reactions after SLIT, or mild symptoms of systemic reactions, should be used in future immunotherapy trial protocols.¹⁸ In the present study, there were few local AEs and only three reports of systemic AEs, management of which did not require medication.

SLIT is self-administered and, therefore, many adverse effects likely go unreported.¹⁹ In the present study, symptom assessments for pediatric patients were conducted by their parents or guardians to ensure unified assessment.

The VAS method has been widely used to assess the overall severity of AR and is recommended as a secondary outcome in SLIT trials. Del Cuavillo et al. proposed a classification method to assess the severity of AR based on VAS scores, which are also mentioned in the Chinese guideline for the diagnosis and treatment of AR.^{20,21} In a retrospective study, patients who completed 3 and 4 years of SLIT showed

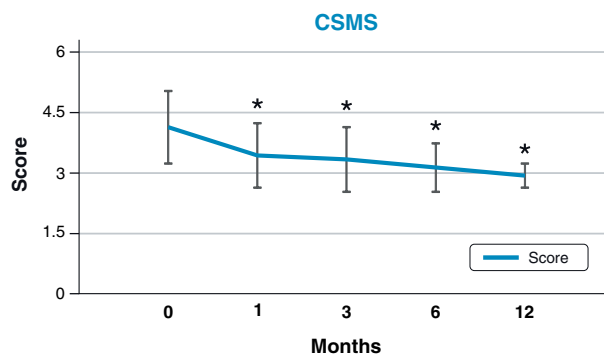


Figure 3

Comparison of combined symptom and medication scores between baseline and months 1, 3, 6, and 12

* $p < 0.05$. Data expressed as means and standard deviations.

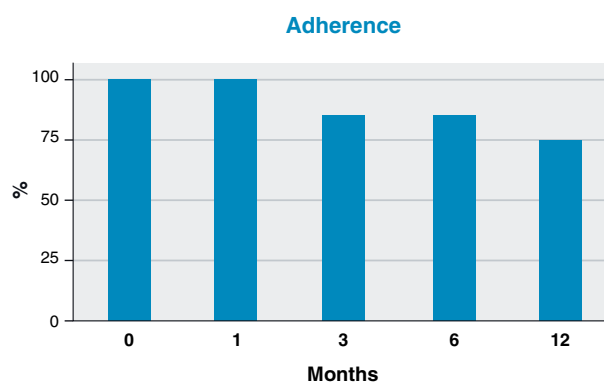


Figure 4

Comparison of percent adherence over 12 months of sublingual allergen immunotherapy (SLIT)

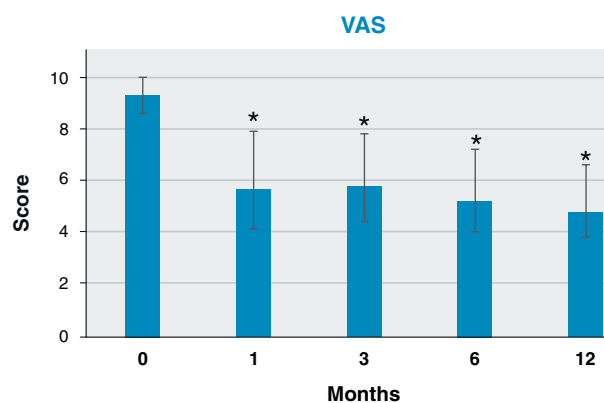


Figure 5

VAS scores of nasal and conjunctival symptoms at 12 months

VAS = visual analogue scale.

*Compared with baseline score, $p < 0.05$.

Data expressed as means and standard deviations.

a significant decrease in VAS scores compared with those who completed a 2-year course of SLIT.²¹ Our study was not placebo-controlled, but our results are consistent with the literature regarding improvement of nasal and conjunctival symptom scores.

A real-life retrospective study by Bahceciler et al. of 90 children undergoing SLIT suggested it results in short- and long-term avoidance of inhaled corticosteroid (ICS) use in patients with allergic asthma.²² Although several studies have evaluated the effectiveness of SLIT in preventing ICS use in patients with asthma, there is a dearth of studies on the efficacy of SLIT in patients with allergic asthma. In our study, we did not observe a significant symptom reduction in asthmatics over the two semesters analyzed, although their AR was moderate to severe, lung function was normal, and the ACT did not differ significantly across time points ($p = 0.16$).

We followed patients on SLIT for 12 months, but their treatment course did not end there; all are on a 3-4-year plan, which highlights the importance of long-term SLIT to maintain lasting effects. Lin et al. enrolled 500 participants to receive 1-3 years of SLIT and found that, in patients with AR, a 3-year course of SLIT was more effective than 1 year or 2 years.²³ Hamada et al. documented a significant decrease in nasal discharge, sneezing, nasal obstruction symptoms, and CSMS in patients receiving 4-5 years of SLIT compared with those receiving 1 year of SLIT,¹⁰ thus showing that clinical outcomes tend to be even more satisfactory with more prolonged courses of SLIT.

Because SLIT requires daily administration of the allergen for at least 3 years to achieve clinical efficacy, adherence is a major issue from the perspective of patients, providers, and payers. However, adherence to SLIT is characterized by widely variable discontinuation rates. Based on controlled and observational studies that provided information on adherence over different treatment times, overall discontinuation rates have been approximated for the first to third years of treatment for SCIT (subcutaneous immunotherapy) (22%, 34%, and 26% respectively) and SLIT (42%, 29%, and 27% respectively).¹⁷ In our study, no patient discontinued SLIT; however, there were cases of nonadherence.

In conclusion, the results obtained in this study suggest that SLIT should be administered for longer periods to allow assessment of broader outcomes. However, we also observed that SLIT is able to consistently provide short-term benefit in patients with moderate-severe AR, improving nasal symptoms,

reducing the need for medication, and improving quality of life—a disease-modifying effect. SLIT was well tolerated by all patients and there were no treatment-related anaphylaxis events.

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References

1. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol*. 2017;140(4):950-8.
2. Alvaro-Lozano M, Akdis CA, Akdis M, Alviani C, Angier E, Arasi S, et al. EAACI allergen immunotherapy user's guide. *Pediatr Allergy Immunol*. 2020;31(25):1-101.
3. Wilson DR, Torres Lima M, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy*. 2005;60(1):4-12.
4. Chong Neto HJ, Rosário CS, Rosário BA, Chong FH, Grasselli EA, Silva FC, et al. Allergic rhinitis in preschool children from southern Brazil. *Allergy*. 2014;69(4):545-7.
5. Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, et al. Rhinitis 2020: A practice parameter update. *J Allergy Clin Immunol*. 2020;146(4):721-67.
6. Devillier P, Fadel R, De Beaumont O. House dust mite sublingual immunotherapy is safe in patients with mild-to-moderate, persistent asthma: a clinical trial. *Allergy*. 2016;71(2):249-57.
7. Carvalho A, Sgnori DJ, Rosário Fº NA. Prevalência do padrão facial em crianças com rinite alérgica persistente. *Orthod SciPract*. 2020;13(51):90-7.
8. Aarestrup FM, Taketomi EA, Santos Galvão CES, Gagete E, Arruda ACNM, Alves GB, et al. Good clinical practice recommendations in allergen immunotherapy: Position paper of the Brazilian Association of Allergy and Immunology – ASBAI. *World Allergy Organ J*. 2022;15(10):100697.
9. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J*. 2014;7(1):6.
10. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol*. 2009;123(1):167-73.
11. Nolte H, Bernstein DI, Nelson HS, Kleine-Tebbe J, Sussman GL, Seitzberg D, et al. Efficacy of house dust mite sublingual immunotherapy tablet in North American adolescents and adults in a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2016;138(6):1631-8.
12. Aarestrup FM, Lira GV de AG, Taketomi EA, Gagete E, Rosário Filho NA, Rizzo MC, et al. Brazilian guidelines for allergen immunotherapy in the treatment of allergic rhinitis. *Rev Assoc Med Bras [Internet]*. 2023;69(5):e2023D695.
13. Radulovic S, Wilson D, Calderon M, Durham S. Systematic reviews of sublingual immunotherapy (SLIT). *Allergy*. 2011;66(6):740-52.

14. Pfaar O, Kleine-Tebbe J, Hörmann K, Klimek L. Allergen-specific immunotherapy: which outcome measures are useful in monitoring clinical trials? 2011. *Immunol Allergy Clin North Am*. 2011;31(2):289-309.
15. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Rivas MF, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. *World Allergy Organ J*. 2020;13(10):100472.
16. Lin SY, Erekosima N, Kim JM, Ramanathan M, Suarez-Cuervo C, Chelladurai Y, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *JAMA*. 2013;309(12):1278-88.
17. Canonica GW, Cox L, Pawankar R, BaenaCagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J*. 2014;7(1):6.
18. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). *Allergo J Int*. 2014;23(8):282-319.
19. Position paper: Immunotherapy with hymenoptera venoms. (EAACI) The European Academy of Allergology and Clinical Immunology. *Allergy*. 1993;48(14 Suppl):36-46.
20. Del Cuvillo A, Santos V, Montoro J, Bartra J, Davila I, Ferrer M, et al. Allergic rhinitis severity can be assessed using a visual analogue scale in mild, moderate and severe. *Rhinology*. 2017;55(1):34-38.
21. Chen S, Zeng X, Wang L, Chen B, Chen L, Wu S, et al. [Effects of house dust mite sublingual immunotherapy in children with allergic rhinitis and asthma]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2015 Aug;50(8):627-31. Chinese.
22. Bahceciler NN, Galip N, Babayigit A. Steroid sparing effect of sublingual immunotherapy: real life study in mono/polysensitized children with asthma. *Immunotherapy*. 2017;9(15):1263-9.
23. Lin Z, Liu Q, Li T, Chen D, Chen D, Xu R. The effects of house dust mite sublingual immunotherapy in patients with allergic rhinitis according to duration. *Int Forum Allergy Rhinol*. 2016;6(1):82-7.
24. Hamada S, Kobayashi Y, Sakamoto D, Shimamura A, Kuroda K, Kawachi R, et al. Long- term sublingual immunotherapy provides better effects for patients with Japanese cedar pollinosis. *Auris Nasus Larynx*. 2021;48(4):646-52.
25. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. *World Allergy Organ J*. 2015;8(1):17.

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Distinctive inflammasome activation in individuals allergic to Hymenoptera venoms

Resposta distintiva do inflamassoma aos venenos de himenópteros em indivíduos alérgicos

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ABSTRACT

Introduction: Previous studies have shown that different types of venoms, such as those from snakes, arachnids, and Hymenoptera insects, can activate the inflammasome complex, particularly through the NLRP3 receptor, as seen with the honeybee (*Apis mellifera*) venom component melittin. Furthermore, inflammasome activation has been linked to increased susceptibility to hypersensitivity. This study aimed to investigate inflammasome activation in individuals allergic to Hymenoptera venoms based on the hypothesis that allergic individuals may exhibit enhanced inflammasome activity in response to Hymenoptera venoms. **Methods:** Ten allergic individuals and 17 nonallergic healthy adults were recruited. Inflammasome activation was determined by immunofluorescence detection of activated caspase-1 using the FAM-FLICA kit and pyroptosis. Cytokine levels were measured by ELISA. **Results:** Allergic individuals exhibited constitutive inflammasome-derived cytokine release and an exaggerated inflammasome response to honeybee, wasp, and fire ant venoms in monocyte-derived macrophages, as evidenced by elevated interleukin-1 β levels and pyroptosis. **Conclusion:** These findings suggest that, in addition to the immunoglobulin E-mediated response, a proinflammatory profile may also contribute to hypersensitivity to insect venom.

Keywords: Inflammasome allergy, Hymenoptera venom, IL-1 β , pyroptosis, pyrin domain-containing 3 protein NLR family.

RESUMO

Introdução: Estudos anteriores mostraram que diferentes tipos de veneno, como os de cobras, aracnídeos e insetos *Hymenoptera*, podem induzir a ativação do complexo inflamatório, e especificamente do seu receptor NLRP3, como o componente melitina do veneno da abelha (*Apis mellifera*). Além disso, o complexo inflamatório pode aumentar a suscetibilidade à hipersensibilidade. Este estudo teve como objetivo caracterizar a ativação do inflamassoma em indivíduos alérgicos ao veneno de himenópteros a partir da hipótese de que a ativação do inflamassoma pode estar desregulada em indivíduos alérgicos e, portanto, contribuir para o traço alérgico. **Métodos:** Dez indivíduos alérgicos e 17 adultos saudáveis não alérgicos foram recrutados. A ativação do inflamassoma foi medida por imunofluorescência da caspase-1 ativada com o kit FAM-FLICA e pela piroptose. As citocinas foram medidas por ELISA. **Resultados:** Indivíduos alérgicos apresentam uma liberação constitutiva de citocinas derivadas do inflamassoma e uma hiper-resposta do inflamassoma aos venenos de abelha, vespa ou formiga "fire" em macrófagos derivados de monócitos, tanto em termos de liberação de IL-1 β quanto de piroptose. **Conclusão:** Os achados do estudo sugerem que um contexto pró-inflamatório pode influenciar a reação alérgica ao veneno de inseto além da resposta relacionada à IgE.

Descritores: Alergia ao inflamassoma, veneno de Hymenoptera, IL-1 β , piroptose, proteína 3 que contém domínio de pirina da família NLR.

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Introduction

Stings from Hymenoptera insects, such as honeybees, wasps, and fire ants, can trigger allergic reactions or even cause fatal anaphylaxis.¹ Although immunoglobulin E (IgE)-mediated type I hypersensitivity is recognized as a primary immediate reaction, the precise molecular mechanisms triggered by injected venom, as well as the subsequent innate immune response, remain poorly understood.

Previous studies have shown that different types of venom, such as those from snakes, arachnids, and Hymenoptera insects, can activate the inflammasome complex,² particularly through the NLRP3 receptor, as seen with the honeybee (*Apis mellifera*) venom component melittin.³ Moreover, activation of the inflammasome complex may increase susceptibility to hypersensitivity reactions.⁴⁻⁵ The inflammasome-dependent cytokine interleukin (IL)-18 has been associated with the development of allergic disorders,⁶ airway inflammation in asthma,⁷ eosinophilic activity,⁸ and the activation of Th2 cytokines.⁹

Considering these findings and the increasing body of evidence regarding the role of the NLRP3 inflammasome in allergic conditions,^{4-5,10} we hypothesized that allergic individuals may exhibit enhanced inflammasome activity in response to Hymenoptera venom.

Patients and methods

Study participants

All participants, including patients and healthy donors (HDs), provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional ethics committees (CAEE no. 55881222.0.0000.0068 and no. 52647921.8.0000.5467). We recruited 10 allergic individuals from the Allergy and Clinical Immunology Clinic at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (FMUSP), Brazil, and 17 healthy nonallergic adults (HD) from the general community at the Institute of Biomedical Sciences of Universidade de São Paulo, Brazil (Table 1).

In vitro assays and inflammasome analysis

Peripheral blood monocyte-derived macrophages (MDMs) were obtained from volunteers as described elsewhere.¹¹ They were treated with venom extracts

from *Apis mellifera*, *Polybia paulista*, and *Solenopsis invicta*, with or without priming with lipopolysaccharide (*E. coli* O111:B4 strain; Sigma-Aldrich/Merck) for 3 hours. Dose- and time-response are shown in Figure 1. ATP (Sigma-Aldrich/Merck) was added at the end of the stimulation period. MDMs were pretreated with the NLRP3 inhibitor MCC-950 (InvivoGen) when applicable. Inflammasome activation was determined by immunofluorescence staining of activated caspase-1 using the FAM-FLICA kit (Immunochemistry Technologies), alongside measurements of IL-1 β release and pyroptosis.

Cytokine quantification

Cytokine levels were determined using commercial ELISA kits (R&D Systems; Biolegend).

Pyroptosis analysis

Propidium iodide (PI; Thermo Fisher Scientific) uptake was measured using real-time fluorometric analysis (Synergy instrument; BioTek Instruments) or immunofluorescence staining. Lactate dehydrogenase (LDH) release was quantified using a commercial kit (ThermoFisher Scientific). Cleavage of gasdermin D (GSDMD) was assessed via western blot analysis.

Data analysis

The public dataset GSE92866 (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE92866>) was reanalyzed using the GEO2R software (<https://www.ncbi.nlm.nih.gov/geo/>) and the EnrichR platform (<https://maayanlab.cloud/Enrichr/>).

Student's *t*-test or ANOVA was employed to compare two or more groups (or variables). Categorical variables were evaluated using Fisher's exact test, and Spearman's correlation analysis was performed.

Results

Allergic individuals (*n*=12) from the public database GSE92866 exhibited enrichment of proinflammatory genes and pathways compared with HD (*n*=12) (Figure 2A-B), suggesting that a proinflammatory profile may contribute to hypersensitivity. Accordingly, allergic patients exhibited significantly elevated plasma levels of IL-6 and IL-18 compared with HD (Figure 2C-D), strongly suggesting constitutive and systemic inflammasome activation in allergic donors.

Table 1

Clinical data from Hymenoptera allergic patients

ID	Sex (F/M)	Age (years)	Insect	Atopy	Degree of anaphylaxis	Total serum IgE (UI/mL)	Allergic crisis at sampling
1	M	42	<i>Apis mellifera</i>	None	–	9	No
2	M	33	<i>Apis mellifera</i>	Allergic rhinitis	III	387	No
3	M	46	<i>Apis mellifera</i>	Allergic rhinitis	IV	N/A	No
4	F	40	<i>Apis mellifera</i>	Food allergy	III	N/A	Yes
5	M	30	<i>Polybia paulista</i>	None	IV	N/A	No
6	M	54	<i>Polybia paulista</i>	Asthma	III	116	No
7	M	10	<i>Solenopsis invicta</i>	Allergic rhinitis, asthma, and atopic dermatitis	III	1563	Yes
8	F	23	<i>Solenopsis invicta</i>	Allergic rhinitis	III	87.7	Yes
9	M	5	<i>Solenopsis invicta</i>	Allergic rhinitis, asthma, and food allergy	III	519	No
10	M	13	<i>Solenopsis invicta</i>	Allergic rhinitis, asthma, and atopic dermatitis	III	1832	No

IgE = immunoglobulin E; M = male; F = female; N/A = not available.

Clinical data obtained at the Ambulatório de Alergia e Imunologia Clínica from Hospital das Clínicas e Faculdade de Medicina, Universidade de São Paulo (HC-FMUSP).

In vitro assays showed that insect venoms induced rapid and pronounced release of IL-1 β (Figure 2E-G), but not IL18 (undetectable), and tumor necrosis factor (TNF) (Figure 2H-J) in MDMs from HD and allergic donors. IL-1 β , but not TNF, was significantly elevated in allergic individuals compared with HD (Figure 2H-J). Honeybee venom caused the most severe membrane damage in MDMs, occurring more rapidly

in allergic donors than HD (Figure 2K-P). Wasp and fire ant venoms caused moderate damage in MDMs, which was also more pronounced in allergic donors than HD.

These findings suggest venom-associated inflammasome activation, as supported by the correlation between IL-1 β levels and PI uptake (Figure 3A). The venoms rapidly activated caspase-1,

leading to loss of membrane permeability (Figure 3B-C), indicative of pyroptosis. Western blot analysis revealed that ant and wasp venoms, but not honeybee venom, enhanced cleavage of GSDMD (Figure 3D-E). LDH release was elevated in all venom-treated MDM

cultures (Figure 3F). The NLRP3 inhibitor MCC-950 significantly reduced IL-1 β levels and PI uptake induced by all venoms, underscoring the central role of NLRP3 inflammasome activation in response to Hymenoptera venoms (Figure 3G-H).

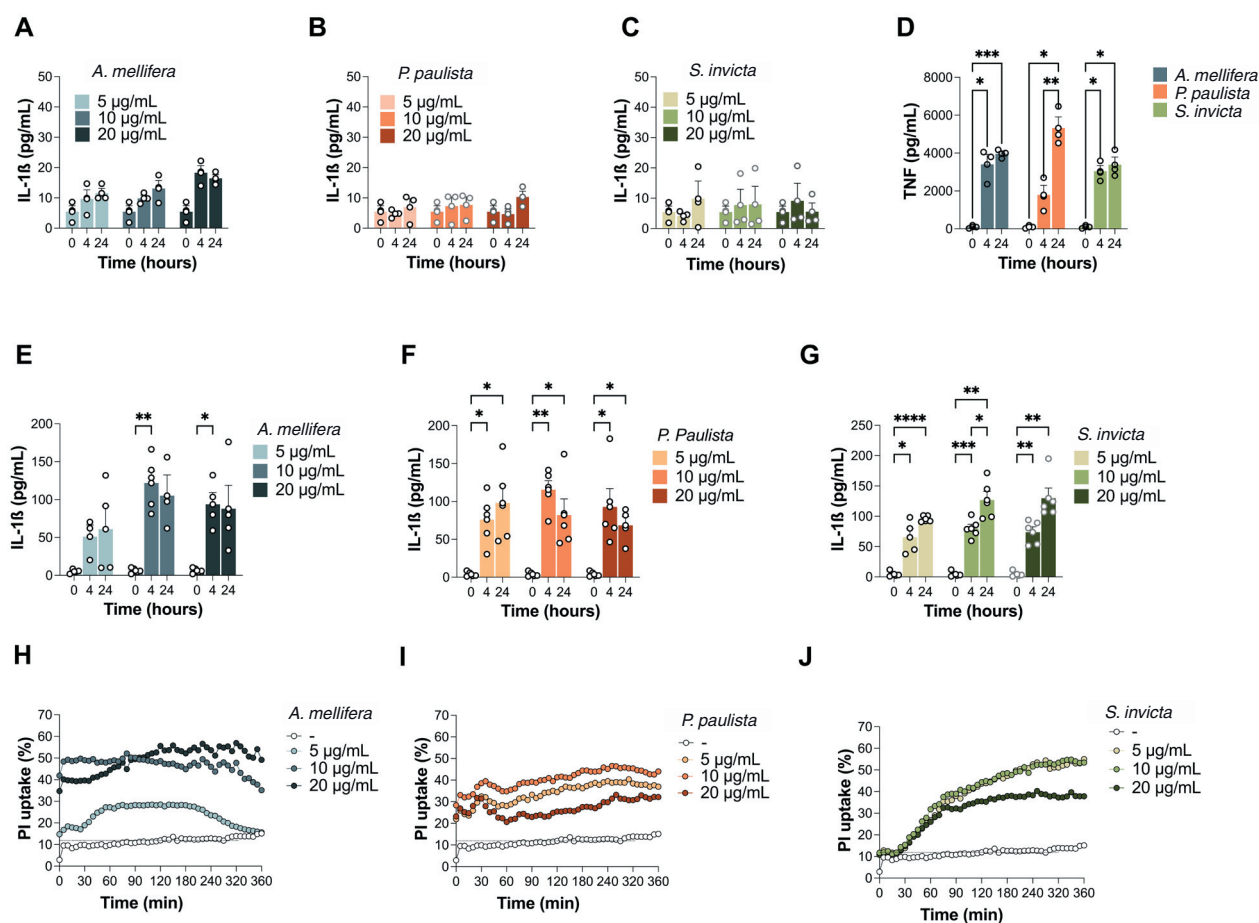


Figure 1

Standardization of stimulation time and concentration of Hymenoptera venoms

Monocyte-derived macrophages (MDMs) from healthy donors (8×10^4 cells) were stimulated for 4 or 24 hours with 5, 10, and 20 μ g/mL of venom extracts from (A) *Apis mellifera* (n=6), (B) *Polybia paulista* (n=5), and (C) *Solenopsis invicta* (n=6) without lipopolysaccharide priming. Interleukin (IL)-1 β levels were measured by ELISA. MDMs (8×10^4 cells) were also stimulated for 1, 4, or 24 hours with 5, 10, and 20 μ g/mL of venom extracts from (E) *Apis mellifera* (n=6), (F) *Polybia paulista* (n=5), and (G) *Solenopsis invicta* (n=6) after priming with lipopolysaccharide (1 μ g/mL) for 3 hours. IL-1 β levels were measured by ELISA. (D) Tumor necrosis factor (TNF) concentrations were determined by ELISA in the supernatants of MDMs stimulated with 10 μ g/mL of each venom for 1 and 4 hours. For propidium iodide (PI) uptake, approximately 2.5×10^4 MDMs were stimulated with 5, 10, and 20 μ g/mL of venom extracts from (H) *Apis mellifera* (n=4), (I) *Polybia paulista* (n=4), and (J) *Solenopsis invicta* (n=4) for 4 hours. 2.5 μ g/mL of PI per well was added before the start of real-time fluorometric readings. The kinetics of PI incorporation are reported. Two-way ANOVA, followed by multiple post-test comparisons, was applied to compare cytokine production between the 3 experiments. Differences were considered statistically significant when $p < 0.05$.

ns= nonsignificant; * = $p < 0.05$; ** = $p < 0.01$.

Discussion

Understanding and managing the immune response to Hymenoptera venom allergy is crucial for at-risk individuals. While Th2 response and IgE production typically characterize type-1 hypersensitivity reactions, our findings suggest that atopic individuals

also exhibit enhanced inflammasome activation, even during asymptomatic periods. This aligns with other medical hypothesis⁶⁻⁸ and previous genetic studies that have associated NLRP3 activation with type-1 hypersensitivity, such as aspirin and food allergies and asthma.^{4-5,10}

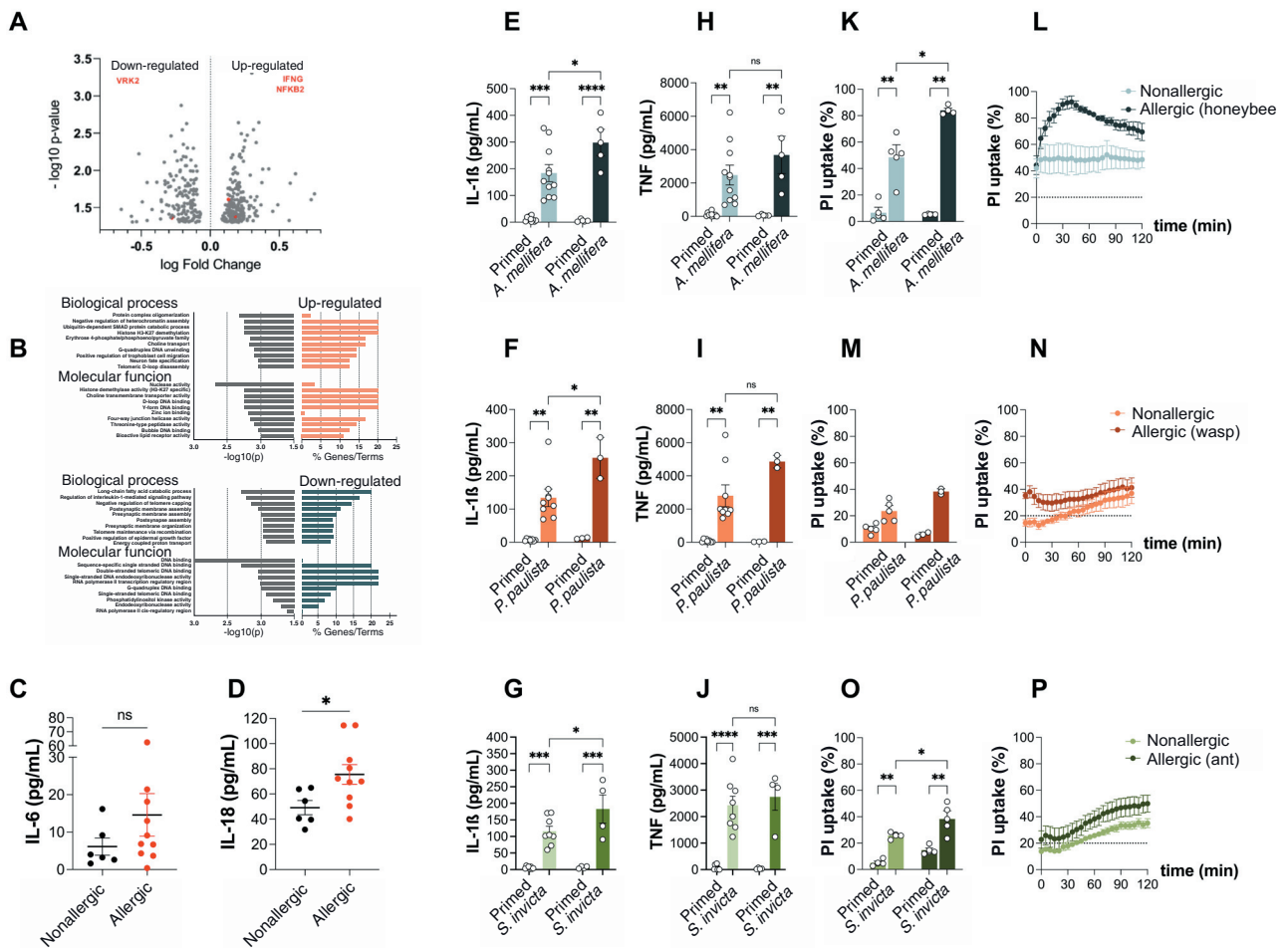


Figure 2
Inflammasome activation by Hymenoptera venoms in allergic and nonallergic donors

(A-B) Reanalysis of the GSE92866 database. (A) Differentially expressed genes (DEGs) between allergic patients and nonallergic individuals are shown in a volcano plot. Genes with fold change (FC) > 1.5 and $p < 0.05$ were considered DEGs. DEGs of interest are depicted in red. (B) Gene ontology enrichment analysis identified gene sets characteristic of allergic patients. Up-regulated pathways are shown in the upper graph, while down-regulated pathways are shown in the bottom graph. (C-D) Plasma concentrations of interleukin (IL)-6 and IL-18 were measured by ELISA in allergic ($n=10$) and nonallergic ($n=17$) donors. Monocyte-derived macrophages (MDMs) from allergic ($n=10$) and nonallergic ($n=17$) donors were primed with lipopolysaccharide ($1 \mu\text{g/mL}$) for 3 hours and then treated with *Apis mellifera*, *Polybia paulista*, and *Solenopsis invicta* venoms ($10 \mu\text{g/mL}$) for 4 hours. IL-1 β (E-G) and tumor necrosis factor (TNF) (H-J) release was measured in MDM supernatants from both groups by ELISA. Propidium iodide (PI) uptake was measured over 120 minutes after venom treatment, with the percentage of PI-positive cells reported at 60 minutes (K, M, O) and throughout 120 minutes in real-time (L, N, P).

Two-way ANOVA, followed by multiple post-test comparisons, was applied to compare cytokine production and PI uptake between the 3 experiments. Differences were considered statistically significant when $p < 0.05$.

ns = nonsignificant; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; **** = $p < 0.0001$.

Venoms from several Hymenoptera insects, including wasps and ants in addition to honeybees,³ lead to inflammasome activation and may serve as initial triggers for the development of type-1 hypersensitivity. Ant and wasp venoms, but not

honeybee venom, significantly enhanced cleavage of GSDMD, which is in agreement with earlier studies on honeybee venom.³ This suggests that distinct molecular mechanisms underlie venom-induced inflammasome activation.

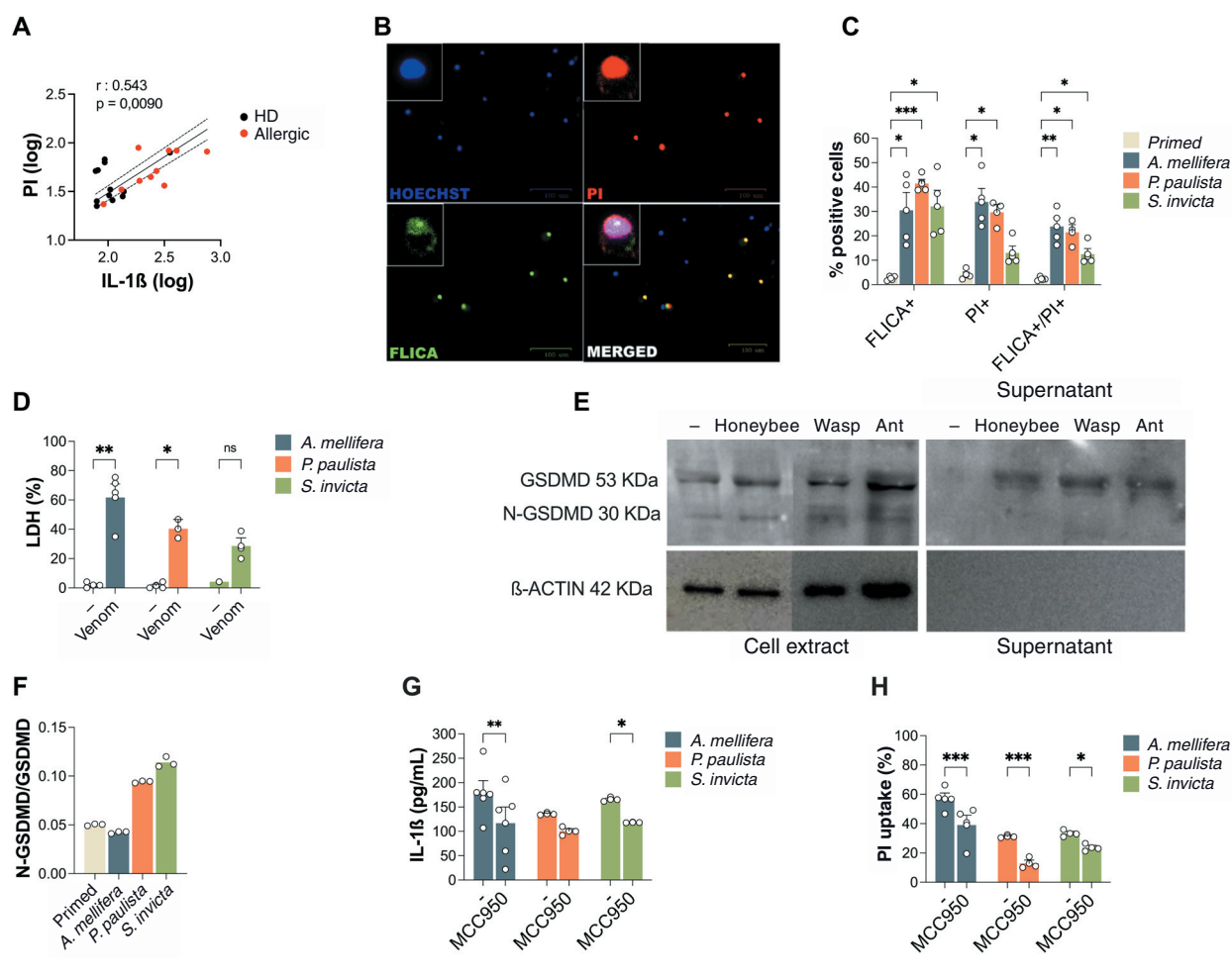


Figure 3

Hymenoptera venoms activate the inflammasome complex and promote pyroptosis

Monocyte-derived macrophages (MDMs) from healthy donors ($n=10$) were primed with lipopolysaccharide (1 $\mu\text{g/mL}$) for 3 hours and then treated with *Apis mellifera*, *Polybia paulista*, and *Solenopsis invicta* venoms (10 $\mu\text{g/mL}$) for 4 hours. Activation of caspase-1 was assessed using the FAM-FLICA kit. Interleukin (IL)-1 β and lactate dehydrogenase (LDH) release was measured in the supernatants, and propidium iodide (PI) uptake was measured after 60 minutes of venom treatment. Cells were lysed for western blot analysis. (A) Correlation analysis was performed between IL-1 β levels and PI uptake in venom-treated MDMs, with Spearman's r and p -values reported. (B) Immunofluorescence images (100 $\times$ magnification) show active caspase-1-positive (green) and PI-positive (red) cells, with nuclei stained using Hoechst (blue) in untreated and wasp venom-treated MDMs. (C) Total counts of MDMs positive for activated caspase-1 and PI in 3 fields/experiments for each venom are reported. (D) LDH release was measured using the LDH Activity Assay Kit (ThermoFisher Scientific) and expressed as the percentage of Triton-X100 lysed cells. (E) A representative western blot shows GSDMD cleavage (55 kDa) into N-GSDMD (33 kDa), with β -actin as the loading control. (F) Data from 3 western blots are reported as mean fluorescence intensity (MFI) for GSDMD and N-GSDMD, normalized to β -actin MFI. MDMs from healthy donors ($n=10$) were primed with lipopolysaccharide (1 $\mu\text{g/mL}$) for 3 hours, then treated with the NLRP3 inhibitor MCC-950 (10 μM) before exposure to the venoms (10 $\mu\text{g/mL}$) for 4 hours. (G) IL-1 β release was measured in cell supernatants, while (H) propidium iodide (PI) uptake was measured after 60 minutes of venom treatment. (F) Two-way ANOVA, followed by multiple post-test comparisons, was applied to compare cytokine production and PI uptake. Differences were considered statistically significant when $p < 0.05$.

ns = nonsignificant; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; **** = $p < 0.0001$.

Honeybee and wasp venoms contain at least 2 compounds known to trigger NLRP3 activation, phospholipase A2² and hyaluronidases,¹² along with bee melittin.³ Ant venom consists of water-soluble hyaluronidases and phospholipases, as well as water-insoluble alkaloids that have cytotoxic and hemolytic properties,^{2,12} which may activate NLRP3 via cell membrane damage.

Conclusions

Although further mechanistic studies are necessary, our findings provide novel insights into the role of inflammasome activation in atopic individuals. In addition to the classical Th2-related cytokines, our results suggest that proinflammatory markers may help in the characterization of type-1 hypersensitivity. These results strongly support the involvement of the NLRP3 inflammasome in allergic disease and indicate that specific NLRP3 inflammasome inhibitors may be potential therapeutic targets for allergic diseases.

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References

1. Brown TC, Tankersley MS. The sting of the honeybee: an allergic perspective. *Ann Allergy Asthma Immunol*. 2011 Dec;107(6):463-70; quiz 471.
2. Palm NW, Medzhitov R. Role of the inflammasome in defense against venoms. *Proc Natl Acad Sci U S A*. 2013 Jan 29;110(5):1809-14. doi: 10.1073/pnas.1221476110.
3. Martín-Sánchez F, Martínez-García JJ, Muñoz-García M, Martínez-Villanueva M, Noguera-Velasco JA, Andreu D, et al. Lytic cell death induced by melittin bypasses pyroptosis but induces NLRP3 inflammasome activation and IL-1 β release. *Cell Death Dis*. 2017 Aug 10;8(8):e2984. doi: 10.1038/cddis.2017.390.
4. Hitomi Y, Ebisawa M, Tomikawa M, Imai T, Komata T, Hirota T, et al. Associations of functional NLRP3 polymorphisms with susceptibility to food-induced anaphylaxis and aspirin-induced asthma. *J Allergy Clin Immunol*. 2009 Oct;124(4):779-85.e6. doi: 10.1016/j.jaci.2009.07.044.
5. Queiroz GA, da Silva RR, Pires AO, Costa RDS, Alcântara-Neves NM, da Silva TM, et al. New variants in NLRP3 inflammasome genes increase risk for asthma and *Blomia tropicalis*-induced allergy in a Brazilian population. *Cytokine X*. 2020 Sep;2(3):100032. doi: 10.1016/j.cytok.2020.100032.
6. Nakanishi K, Tsutsui H, Yoshimoto T. Importance of IL-18-induced super Th1 cells for the development of allergic inflammation. *Allergol Int*. 2010 Jun;59(2):137-41. doi: 10.2332/allergolint.10-RAI-0208.
7. Kuroda-Morimoto M, Tanaka H, Hayashi N, Nakahira M, Imai Y, Imamura M, et al. Contribution of IL-18 to eosinophilic airway inflammation induced by immunization and challenge with *Staphylococcus aureus* proteins. *Int Immunol*. 2010 Jul;22(7):561-70. doi: 10.1093/intimm/dxq040.
8. Kandikattu HK, Upparahalli Venkateshaiah S, Mishra A. Synergy of Interleukin (IL)-5 and IL-18 in eosinophil mediated pathogenesis of allergic diseases. *Cytokine Growth Factor Rev*. 2019 Jun;47:83-98. doi: 10.1016/j.cytogfr.2019.05.003.
9. Kroeger KM, Sullivan BM, Locksley RM. IL-18 and IL-33 elicit Th2 cytokines from basophils via a MyD88- and p38 α -dependent pathway. *J Leukoc Biol*. 2009 Oct;86(4):769-78. doi: 10.1189/jlb.0708452.
10. Bruchard M, Rebé C, Derangère V, Togbé D, Ryffel B, Boidot R, et al. The receptor NLRP3 is a transcriptional regulator of TH2 differentiation. *Nat Immunol*. 2015 Aug;16(8):859-70. doi: 10.1038/ni.3202.
11. Souza De Lima D, Bomfim CCB, Leal VNC, Reis EC, Soares JLS, Fernandes FP, et al. Combining Host Genetics and Functional Analysis to Depict Inflammasome Contribution in Tuberculosis Susceptibility and Outcome in Endemic Areas. *Front Immunol*. 2020 Oct 21;11:550624. doi: 10.3389/fimmu.2020.550624.
12. Fitzgerald KT, Flood AA. Hymenoptera stings. *Clin Tech Small Anim Pract*. 2006 Nov;21(4):194-204. doi: 10.1053/j.ctsap.2006.10.002.

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Chronic spontaneous urticaria: correlation of basophil counts with disease control and response to anti-IgE therapy

Urticária crônica espontânea: correlação dos valores de basófilos com o controle da doença e a resposta à terapêutica anti-IgE

Helena Pereira¹, João Lopes¹, Isabel Carrapatoso¹, Ana Todo-Bom¹

ABSTRACT

This retrospective study aimed to investigate the relationship between peripheral blood basophil counts and response to treatment with omalizumab in patients with chronic spontaneous urticaria (CSU). Most patients included in the study had a normal basophil count, but a significant correlation was found between a low basophil count and daily use of antihistamines still required to control symptoms. This suggests the potential utility of basophil count as a prognostic marker of response to anti-IgE monoclonal antibody therapy in CSU.

Keywords: Urticaria, basophils, biomarkers, omalizumab.

RESUMO

Este estudo retrospectivo procurou investigar a relação entre os níveis de basófilos periféricos em doentes com urticária crônica espontânea (UCE) em tratamento com omalizumab e a sua resposta terapêutica. Dos pacientes incluídos, a maioria apresentou níveis normais de basófilos, mas uma correlação significativa foi encontrada entre valores baixos de basófilos e o uso diário de anti-histamínicos ainda necessários para controle sintomático, colocando a hipótese da potencial utilidade destes como marcador prognóstico na UCE na resposta à terapêutica monoclonal anti-IgE.

Descritores: Urticária, basófilos, biomarcadores, omalizumab.

Introduction

Chronic spontaneous urticaria (CSU) is characterized by the presence of wheals with or without angioedema, which occur daily or almost daily for more than 6 weeks.¹ Mechanisms that have a probable role in the pathogenesis of CSU include autoimmunity, autoallergy, complement pathway, coagulation pathway, and chronic infections.²⁻⁴ Despite the known prevalence and impact of CSU on patients' quality of life, this condition remains poorly understood, making effective management a clinical challenge.²

The underlying pathogenesis of CSU has been predominantly centered on the activation of skin mast cells through multiple potential mechanisms.¹ Although CSU is not triggered by specific environmental allergens, IgE antibodies play a role in sensitizing mast cells and basophils to respond to endogenous and exogenous stimuli. Autoantibodies directed against self-antigens, such as IgE or IgE receptors, may be involved in the activation of mast cells and basophils in CSU.^{2,5} It is widely accepted that mast cells become activated and subsequently release mediators, such

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as histamine, that elicit symptoms of itching, induce vasodilation, and recruit other immune cells to lesional skin sites.² Growing evidence suggests the involvement of IgE and IgE receptor (FcεRI) activation in the pathophysiology of CSU, as demonstrated by the efficacy of monoclonal IgG anti-IgE antibodies in mitigating or resolving skin symptoms. Updated guidelines currently recommend omalizumab, an anti-IgE monoclonal antibody, for patients with CSU refractory to the maximum daily dose of antihistamines for more than 4 weeks.¹

There is a keen interest in further elucidating the role of IgE-bearing cells in the manifestation of CSU, including mast cells and basophils. The exact contributions of basophils to disease are currently being explored owing to improvements in tools to isolate roles for basophils.

Basophils can produce histamine, leukotrienes, C4, and cytokines such as interleukin (IL)-4, IL-13, and IL-31 in response to IgE receptor activation.^{5,6} However, the role of basophils in CSU extends beyond that of mere effector cells; accumulating evidence suggests their involvement in orchestrating the chronicity of the disease.⁷ Basophils exhibit plasticity in their phenotypic and functional profiles, with studies demonstrating their ability to sustain mast cell activation and to promote T-cell polarization toward a Th2 cytokine profile, perpetuating the inflammatory cascade underlying CSU.^{5,8,9}

Therefore, we aimed to evaluate peripheral blood basophil counts in a cohort of patients with CSU receiving anti-IgE monoclonal antibody therapy and to investigate a possible correlation of basophil counts with disease control and response to anti-IgE therapy.

Methods

Study design

This single-center retrospective observational study was conducted in the Allergy and Clinical Immunology Department of a tertiary care hospital. All adult and pediatric patients receiving anti-IgE monoclonal antibody therapy for CSU for at least 12 months were included.

This paper was written considering ethical and legal principles and in accordance with the recommendations of the Declaration of Helsinki of the World Medical Association.

Outcomes

The following outcome measures were assessed:

- Pretreatment serum basophil counts and other serological markers (eosinophils, C3, C4, total IgE levels) in all patients with CSU receiving anti-IgE monoclonal antibody therapy.
- Correlation of basophil counts with response to anti-IgE treatment (omalizumab) using control scores – Urticaria Control Test (UCT) and Weekly Urticaria Activity Score (UAS7) – and with disease control based on need for medication other than omalizumab.

Statistical analysis

Data were analyzed using SPSS, version 27.0. The Kolmogorov-Smirnov test was used to analyze continuous variables. The chi-square test (χ^2) and Mann-Whitney U test were used to determine differences in the distribution of nominal and continuous variables, respectively. Statistical significance was considered at $p < 0.05$.

Results

A total of 26 patients were included, with a median age of 38.7 years (SD, 15.8; range 10-66 years). Most participants were female (76.9%). The median age at symptom onset was 24.8 years, and the mean (SD) duration of omalizumab treatment was 20.36 (10.54) months.

Angioedema occurred in 30.8% of patients, and the most common sites of involvement were the face (15.4%), lips and/or tongue (8.7%), upper or lower extremities (4.3%), and genitals (2.4%).

In our cohort of 26 patients with CSU, a subset still requires pharmacological intervention for symptom control. Currently, 11 patients (42.3%) are on standard anti-IgE treatment alone (ranging from every 4 weeks to every 8 weeks) and 15 (57.7%) need at least 1 antihistamine daily (median of 2.6 antihistamines daily). Four patients (15.4%) are receiving oral corticosteroids, while 2 patients (7.7%) are still maintained on cyclosporine therapy at a maximum dose of 3 mg/kg. More than one-third of patients (34.6%) had been on immunosuppressive therapy (cyclosporine or daily oral corticosteroids) before starting omalizumab treatment.

Five patients had concomitant inducible urticaria: 2 (7.7%) had delayed pressure urticaria, 2 (7.7%) had symptomatic dermatographism, and 1 (3.8%) had cholinergic urticaria.

Allergic rhinitis was the most common atopic comorbidity, affecting 10 patients (38.5%), followed by asthma in 6 patients (23.1%) and food allergies in 3 patients (11.5%).

Before treatment, 16 patients (61.5%) had a normal peripheral blood basophil count, 9 (34.6%) had a decreased basophil count, and 1 (3.8%) had an increased basophil count. Results are displayed in Table 1.

Basophil counts were slightly associated with IgE levels ($p=0.049$, $r=0.13$). No association was found between basophil counts and eosinophils, C3, C4,

Table 1

Patients' characteristics, laboratory values, and disease control scores

Pretreatment anti-IgE therapy basophil count	Normal	Decreased	Increased	p-value	Spearman coefficient, r
Patients (n)	16	9	1		
Sex (n)					
Female	12	7	1	0.312	0.15
Age, years					
Median (IQR)	39 (15-67)	34 (5-13)	23	0.971	-0.53
Angioedema (n)	5	2	1	0.457	0.48
Total IgE (kU/L)					
Median (IQR)	226 (66-983)	169 (91-630)	62	0.049*	0.13
Eosinophils (cells/ μ L)					
Median (IQR)	87.3 (25-620)	56.2 (15-520)	45	0.691	-0.03
C3 (mg/dL)					
Median (IQR)	122 (85-175)	113 (77-168)	111	0.125	-0.32
C4 (mg/dL)					
Median (IQR)	32 (22-45)	31 (18-41)	40	0.091	0.22
Atopy					
Asthma (n)	3	3	1	0.211	
Rhinitis (n)	5	5	0	0.394	
Food allergy (n)	2	0	0	0.934	
Daily antihistamines (n)	2 (0-4)	3 (0-4)	1	0.025*	0.837
UAS7 score					
Median (IQR)	7.1 (0-19)	5.4 (2-17)	5	0.670	0.32
UCT score					
Median (IQR)	14.3 (10-16)	14.7 (11-16)	14	0.521	0.07

UAS7 = Weekly Urticaria Activity Score; UCT = Urticaria Control Test.

* Statistical significance ($p<0.05$).

duration of anti-IgE therapy, or the latest patients' UAS7 and UCT scores (disease control).

Regarding atopy, there was no statistically significant association between pretreatment basophil counts and presence or severity of atopic comorbidities.

A statistically significant association was found between pretreatment peripheral blood basophil counts and the daily number of antihistamines still taken by the patients ($p=0.025$, $r=0.837$).

Discussion

The results showed that most patients (61.5%) had a normal peripheral blood basophil count before omalizumab treatment, whereas 34.6% had a decreased basophil count; only 1 patient had an increased pretreatment basophil count.

There was no significant association between basophil counts and other laboratory parameters such as eosinophils, C3, C4, duration of anti-IgE therapy, or disease control scores (UAS7 and UCT). Furthermore, basophil counts were not significantly associated with the presence or severity of atopic comorbidities, but they were slightly associated with IgE levels ($p=0.049$, $r=0.13$). However, an intriguing finding emerged from this study in that peripheral blood basophil counts were significantly associated with the daily number of antihistamines required to achieve disease control while on omalizumab treatment, where higher basophil counts correlated with greater reliance on antihistamines for symptom management. Alongside a strong correlation ($r=0.837$), these results underscore the potential utility of basophil count as a prognostic marker of treatment response and disease severity in CSU.

Decreased blood basophil counts have been correlated with increased symptoms of itching and hives in a subset of patients with CSU and antihistamine resistance.^{10,11} A longitudinal study of patients with CSU with repeated basophil and clinical symptom evaluations demonstrated that interval increases in circulating basophil numbers were correlated with reductions in patient-reported CSU symptoms as measured by control scores.¹²

In a large-scale study, blood samples from patients with antihistamine-refractory CSU enrolled in omalizumab phase III trials were examined at baseline and after 12 weeks of therapy. An omalizumab dose-

dependent improvement in clinical symptoms was observed that was mirrored by a similar pattern of increase in blood basophil counts.¹³

Recently, the use of antihistamine therapy has been reported to increase basophil numbers following symptom improvement.¹⁴ These studies support that improvement in skin symptoms is associated with reduced basophil migration to the skin and increased circulating basophil numbers, which may serve as a potential biomeasure of clinical improvement.

Study limitations

Despite its contributions, this study has several limitations that warrant consideration. Firstly, the relatively small sample size may limit the generalizability of the findings and increase the risk of type II errors. Additionally, the retrospective nature of the study design and reliance on pre-existing patient data may introduce biases and confounding factors that could impact the validity of the results. Furthermore, the study's focus on peripheral blood basophil counts overlooks the functional aspects of basophil activation and degranulation, which could provide deeper insights into their role in CSU pathogenesis and treatment response. Lastly, the cross-sectional design of the study precludes the establishment of causality and warrants further longitudinal investigations to validate the observed associations.

Conclusion

While the study did not find a direct correlation between basophil counts and disease control or response to anti-IgE monoclonal antibody therapy in patients with CSU, it identified a significant association between basophil counts and daily requirement of antihistamines while still on omalizumab. This highlights the potential of peripheral blood basophil count as a predictive marker for treatment response and disease severity in CSU. Further research is warranted to elucidate the mechanistic underpinnings of this association and validate its clinical utility in larger cohorts of patients with CSU. Ultimately, understanding the role of basophils in CSU pathogenesis and treatment response may pave the way for personalized treatment approaches and improved outcomes for patients with this condition.

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;77:734-66.
2. Bracken SJ, Abraham S, MacLeod AS. Autoimmune theories of chronic spontaneous urticaria. *Front Immunol*. 2019;10:627.
3. Zhu H, Liang B, Li R, Li J, Lin L, Ma S, et al. Activation of coagulation, anti-coagulation, fibrinolysis and the complement system in patients with urticaria. *Asian Pac J Allergy Immunol*. 2013;31:43-50.
4. Di Campli C, Gasbarrini A, Nucera E, Franceschi F, Ojetti V, Sanz Torre E, et al. Beneficial effects of *Helicobacter pylori* eradication on idiopathic chronic urticaria. *Dig Dis Sci*. 1998;43:1226-9.
5. Schroeder JT. Basophils beyond effector cells of allergic inflammation. *Adv Immunol*. 2009;101:123e61.
6. Raap U, Gehring M, Kleiner S, Rudrich U, Eiz-Vesper B, Haas H, et al. Human basophils are a source of - and are differentially activated by - IL-31. *Clin Exp Allergy*. 2017;47:499e508.
7. Fok, JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. *Allergy*. 2001;76(10):2965-81.
8. Oda Y, Fukunaga A, Washio K, Imamura S, Hatakeyama M, Ogura K, et al. Low Responsiveness of Basophils via FcεRI Reflects Disease Activity in Chronic Spontaneous Urticaria. *J Allergy Clin Immunol Pract*. 2019 Nov-Dec;7(8):2835-2844.e7.
9. Giménez-Arnau AM, DeMontojoye L, Asero R, Cugno M, Kulthanan K, Yanase Y, et al. The Pathogenesis of Chronic Spontaneous Urticaria: The Role of Infiltrating Cells. *J Allergy Clin Immunol Pract*. 2021;9(6):2195-208.
10. Grattan CE, Dawn G, Gibbs S, Francis DM. Blood basophil numbers in chronic ordinary urticaria and healthy controls: diurnal variation, influence of loratadine and prednisolone and relationship to disease activity. *Clin Exp Allergy*. 2003;33:337e41.
11. Magen E, Mishal J, Zeldin Y, Schlesinger M. Clinical and laboratory features of antihistamine-resistant chronic idiopathic urticaria. *Allergy Asthma Proc*. 2011;32:460e6.
12. Oliver ET, Sterba PM, Saini SS. Interval shifts in basophil measures correlate with disease activity in chronic spontaneous urticaria. *Allergy*. 2015;70:601e3.
13. Saini SS, Omachi TA, Trzaskoma B, Hultner HN, Rosen K, Sterba PM, et al. Effect of omalizumab on blood basophil counts in patients with chronic idiopathic/spontaneous urticaria. *J Invest Dermatol*. 2017;137:958e61.
14. Kishimoto I, Ma N, Takimoto-Ito R, Nakashima C, Otsuka A, Walls AF, et al. Decreased peripheral basophil counts in urticaria and mouse model of oxazolone-induced hypersensitivity, the latter suggesting basopenia reflecting migration to skin. *Front Immunol*. 2022;13:1014924.

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Icatibant in a pregnant woman with HAE-FXII: a case report

Uso do icatibanto em gestante com AEH-FXII: relato de caso

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ABSTRACT

Hereditary angioedema (HAE) due to pathogenic variants in the factor XII gene (HAE-FXII) is the most common type of HAE with normal C1 inhibitor (HAE-nC1INH). HAE-FXII is highly influenced by estrogen exposure. Patients with this condition tend to experience worsening of angioedema-related symptoms during periods of elevated estrogen, such as pregnancy. Currently, there is no approved treatment for HAE-FXII, and during pregnancy management can be even more challenging, since first-line drugs are not always available. We report the case of a pregnant woman with HAE-FXII who received a single dose of icatibant during an upper airway angioedema attack in the third trimester, with a favorable outcome for the patient and fetus.

Keywords: Hereditary angioedema, bradykinin B2 receptor antagonists, pregnancy, factor XII.

RESUMO

O angioedema hereditário (AEH) por variantes patogênicas no gene que codifica o Fator XII da coagulação (AEHFXII) é o tipo mais comum de AEH com inibidor de C1 normal (AEH-nC1INH). O AEH-FXII é altamente influenciado pela exposição ao estrogênio. Pacientes com esta condição tendem a ter piora do angioedema em períodos de elevação deste hormônio, como na gestação. Atualmente, não há tratamentos específicos aprovados para o manejo do AEH-FXII, e durante a gravidez o tratamento pode ser ainda mais desafiador, visto que os medicamentos recomendados como primeira linha nem sempre estão disponíveis. Neste relato, descrevemos o caso de uma gestante portadora de AEH-FXII que recebeu icatibanto em dose única durante crise de angioedema de vias aéreas superiores no terceiro trimestre, com desfecho favorável para a paciente e para o feto.

Descritores: Angioedema hereditário, antagonistas de receptor B2 da bradicinina, gravidez, fator XII.

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominantly inherited genetic disease that manifests as recurrent and unpredictable attacks of AE in subcutaneous tissue and mucous membranes. Gastrointestinal tract involvement leads to attacks of intense abdominal pain and can result in unnecessary surgical interventions. Death by asphyxia due to upper

airway edema is the most feared event, and more than 60% of patients with HAE have reported report ≥ 1 laryngeal AE event. Variants in SERPING1, the gene that encodes C1-INH inhibitor (C1-INH), result in HAE with C1-INH deficiency (HAE-C1INH), which can be type 1 when the defect is quantitative or type 2 when it is functional. HAE with normal C1-INH (HAE-nC1INH)

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is associated with variants in other genes; 7 types are currently described. No genetic defects have been identified in some patients with HAE, so in carriers the cause is unknown. HAE-nC1INH is considered rarer than HAE-C1INH, with the most common cause being variants in the F12 gene. HAE-FXII also has an autosomal dominant inheritance pattern.¹⁻³

C1-INH inhibits the contact and kallikrein-kinin systems at different points. The absence or dysfunction of this inhibitor results in a cascade of uninhibited activation and final release of bradykinin (BK). The release of BK results in increased vascular permeability and AE through binding to its B2 receptor (BDKRB2). Activation of the contact and kallikrein-kinin systems is initiated by converting activated factor 12 (FXII) to its active form, FXIIa. FXIIa cleaves prekallikrein into kallikrein, which induces the release of BK from high molecular weight kininogen. In HAE-FXII, FXII is more sensitive to activation by plasmin. In addition to HAE-FXII, other forms of HAE-nC1INH are also mediated by BK, but some forms of HAE-nC1INH are due to increased vascular fragility, as is the case of HAE-nC1INH due to a variant in the angiopoietin-1 gene.^{1,2,4}

Short- and long-term prophylaxis and effective treatments for flare-ups are only approved for patients with HAE-C1INH. In Brazil, the first-line drugs for flare-ups are BDKRB2 inhibitor, subcutaneous icatibant, and intravenous human plasma-derived C1-INH concentrate (pdC1-INH), while fresh frozen plasma is a second-line therapy that should only be used intravenously when first-line therapies are unavailable. Intravenous pdC1-INH is the first-line option for short-term prophylaxis, while the second-line options are attenuated androgens, such as danazol and oxandrolone. Although difficult to access, the first-line options for long-term prophylaxis are intravenous pdC1-INH, subcutaneous pdC1-INH, subcutaneous lanadelumab, and oral berotralstat, the latter 2 being kallikrein inhibitors. Due to the limited availability of first-line therapies for flare prophylaxis, attenuated androgens and tranexamic acid, which are second-line options, are still commonly used.^{2,5-7}

No specific treatments have been approved for HAE-FXII, and current therapeutic strategies are based on treatments that have been shown to be effective in patients with HAE-C1INH.⁸ HAE-FXII treatment also includes discontinuation of potential triggers, such as estrogen-containing contraceptives, hormone replacement therapy, and angiotensin-converting enzyme inhibitors.^{9,10}

Proper pregnancy planning in patients with HAE is important to minimize risk to the mother and fetus. During pregnancy, changes in the severity and frequency of attacks are unpredictable and may decrease or increase. In patients with HAE-FXII, symptoms tend to worsen under hyperestrogenism conditions, such as pregnancy. Angioedema attacks in pregnant women mainly affect the abdomen and extremities. Airway attacks are less frequent, but should be treated urgently, preferably with pdC1-INH.^{11,12}

Although the safety of icatibant therapy during pregnancy is unknown, it can be used in pregnant women when pdC1-INH is unavailable or when the action of pdC1-INH is doubtful for a given patient. For ethical reasons, there have been no randomized controlled studies on these drugs for HAE attacks during pregnancy. However, several observational studies have found that icatibant is safe and efficacious for treating attacks during pregnancy. Therefore, until more data are available, icatibant is not recommended as a first-line option during pregnancy, but it can be considered when first-line medication is unavailable or when the benefits outweigh the risks.¹³⁻¹⁵

Case report

A female patient had frequent attacks of severe abdominal pain since childhood, which worsened at 22 years of age. In addition to the abdominal manifestations, she had AE of the extremities and face. Initially, the episodes recurred every 2 to 3 months, either in association with trauma or spontaneously. Increasing symptom severity coincided with the beginning of combined contraceptive use. At the age of 24, she was diagnosed with HAE-FXII. Laboratory tests at the time revealed normal C4 and C1-INH values (Table 1), and genetic testing found the pathogenic variant in exon 9 of the F12 gene, p.Thr328Lys (c.983C>A) in heterozygosis. Although there was no family history, the asymptomatic father is a carrier of the same variant.

When HAE-FXII was diagnosed, the use of combined contraceptives containing estrogen was suspended and, as the patient had no desire to become pregnant at the time, she continued using contraceptives containing only progesterone. The patient then remained completely asymptomatic for approximately 10 years.

Intending to become pregnant, she discontinued contraception and had her first pregnancy at 34

years of age. At 12 weeks of gestation, the attacks resumed and increased in severity and frequency over time. Because access to pdC1-INH was denied, prophylactic treatment with tranexamic acid 500 mg/day was indicated, with partial and unsatisfactory symptom control. Doses > 500 mg/day were not tolerated due to gastric symptoms.

Table 1

Results of initial laboratory tests

	Results	Reference values
C4	29 mg/dL	10-40 mg/dL
C1-INH	28 mg/dL	21-29 mg/dL

At 30 weeks of gestation, the patient had an attack of oropharyngeal AE (Figure 1) with no other associated symptoms. Due to the risk of progression and potential obstruction of the upper airways, as well as the unavailability of pdC1-INH, the first-line treatment during pregnancy, it was decided to use subcutaneous icatibant 30 mg, to which the patient consented after the risks and benefits were explained. Icatibant was selected because it had been available since diagnosis prior to the pregnancy. The drug was administered approximately 4 hours after attack onset. Improvement was reported after 2 hours, and complete resolution occurred after 10 hours. There were no immediate or late adverse events, either local or systemic. Delivery occurred after 35 weeks and 2 days of gestation due to bleeding secondary to placenta previa, which was diagnosed at the beginning of pregnancy. The delivery and postpartum period were uneventful for both the mother and the newborn.

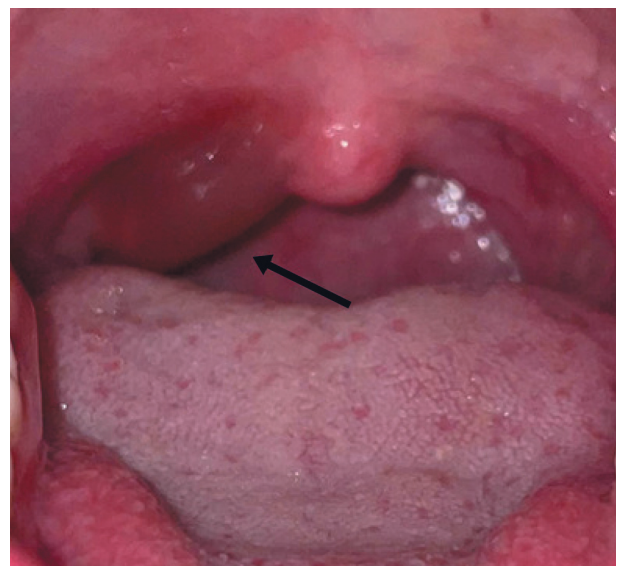
Discussion

Pregnant women with HAE may experience a significant worsening in disease frequency and severity. Exposure to estrogen, whether endogenous or exogenous, influences patients with HAE-C1INH types I and II, as well as carriers of HAE-FXII, but this relationship is not yet fully understood. HAE-FXII was once considered estrogen-dependent, since some

patients with pathogenic variants in F12 only begin to have clinical manifestations when exposed to this hormone, such as during pregnancy or when using estrogen-containing contraceptives. This hormone can act during several stages of the activation cascades of the contact and kallikrein-kinin systems, both at the genomic level and through several endothelial membrane receptors. Its effects include stimulating the release of certain cytokines and the heat shock protein Hsp90, which can act on endothelial cells, leading to the conversion of prekallikrein into kallikrein, with subsequent cleavage of HMWK and BK release. Kallikrein also activates FXII, both directly and by inducing the degradation of plasminogen into plasmin and consequent activation by the latter. Estrogen can increase the expression of the BK receptor B2, in addition to intervening in the activity of the angiotensin-converting enzyme, reducing the degradation of BK.^{1,16}

Although the therapy of choice for AE attacks during pregnancy is pdC1-INH,⁷ we decided to use icatibant in this patient due to the severity of the crisis and the location of the AE in the oropharynx, including potential progression and upper airway obstruction. The first-line medication was also unavailable at the time.

Icatibant is classified as category C due to adverse events in animal studies,¹³ including premature birth, abortion, fetal death, and pre-implantation loss, with

**Figure 1**

Oropharyngeal hereditary angioedema during pregnancy, which was treated with icatibant

no evidence of teratogenicity. Observational studies in humans have reported preterm births in pregnant women who received icatibant during HAE attacks, with no other adverse events reported. However, the dataset is too small to draw conclusions about the relationship between icatibant and increased incidence of prematurity.¹⁴ One concern related to icatibant use during pregnancy is the fact that human decidual cells express BDKRB2 receptors and the effects of inhibition of these receptors, even during transient periods, are still unknown.¹⁵ Although some observational studies have reported preterm births among women using icatibant, in the present case the preterm birth could not be attributed to medication, since this outcome was secondary to complications of placenta previa, which was diagnosed during the first trimester of pregnancy.

No drugs have been approved for HAE-FXII due to a lack of solid clinical trial data. Treatment for these patients is based on well-established clinical experience with HAE-C1INH. Discontinuing exogenous estrogen is the first step for women with suspected HAE-FXII, prior to any other therapies. Because the drugs used for crisis or prophylaxis in HAE-C1INH, such as icatibant, pdC1-INH (intravenous and subcutaneous), tranexamic acid, injectable lanadelumab and, more recently, oral berotralstat, directly or indirectly modulate bradykinin metabolism, they may be useful in patients with HAE-FXII. Of note, tranexamic acid is more effective for prophylaxis in HAE-FXII than HAE-C1INH.¹⁷

All forms of HAE significantly affect the quality of life, education, and professional performance of patients. Difficulty in early diagnosis is often associated with multiple emergency room visits, misdiagnosis, unnecessary surgical interventions, and increased anxiety and depression, resulting in greater mortality risk.^{3,17} Some studies have estimated that the delay in diagnosing HAE varies between 14-18 years in Brazil. Both a lack of knowledge by physicians and difficulty accessing screening and diagnostic tests contribute to this delay. Coordinated effort to increase awareness of HAE is urgently needed among health professionals (whether specialists or non-specialists) and the general public.^{7,18}

Conclusions

No targeted treatment for HAE-FXII has been developed. Current therapies are based on treatment for HAE-C1INH. Despite the unavailability of controlled

studies on icatibant during pregnancy, this drug has been described as effective and safe in these patients. In the various reports to date, there has been no evidence of adverse effects to the patient or fetus. Therefore, this drug may be considered when the first-line option is unavailable, after the risks and benefits have been discussed with the patient.

References

1. Campos RA, Serpa FS, Mansour E, Alonso MLO, Arruda LK, Aun MV, et al. Diretrizes brasileiras do angioedema hereditário 2022 - Parte 1: definição, classificação e diagnóstico. *Arq Asma Alerg Imunol.* 2022;6(2):151-69.
2. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema - The 2021 revision and update. *Allergy.* 2022. doi:10.1111/all.15214.
3. Gutierrez M, Veronez CL, Rodrigues Valle SO, Gonçalves RF, Ferriani MPL, Moreno AS, et al. Unnecessary Abdominal Surgeries in Attacks of Hereditary Angioedema with Normal C1 Inhibitor. *Clin Rev Allergy Immunol.* 2021;61:60-5.
4. Dias MM, Moreno AS, Maia LSM, Nunes FL, Campos WN, Ferriani MPL, et al. A cost-effective algorithm for diagnosis of hereditary angioedema with normal C1 inhibitor: Applying molecular approach to clinical practice. *The Journal of Allergy and Clinical Immunology: In Practice.* 2020;8:419-421.e4.
5. Arruda LK, Ferriani MPL. Treatment of hereditary angioedema: When the goal is having a normal life. *J Allergy Clin Immunol.* 2021;148:80-2.
6. Cohn DM, Arruda LK. Preventing Deaths from Angioedema: It's Time to Look Ahead. *J Allergy Clin Immunol Pract.* 2020;8:1775-6.
7. Campos RA, Serpa FS, Mansour E, Alonso MLO, Arruda LK, Aun MV, et al. Diretrizes brasileiras de angioedema hereditário 2022 - Parte 2: terapêutica. *Arq Asma Alerg Imunol.* 2022;6(2):170-96.
8. Garcia JFB, Takejima P, Veronez CL, Aun MV, Motta AA, Kalil J, et al. Use of pdC1-INH concentrate for long-term prophylaxis during pregnancy in hereditary angioedema with normal C1-INH. *J Allergy Clin Immunol Pract.* 2018;6:1406-8.
9. Bork K, Machnig T, Wulff K, Witzke G, Prusty S, Hardt J. Clinical features of genetically characterized types of hereditary angioedema with normal C1 inhibitor: a systematic review of qualitative evidence. *Orphanet J Rare Dis.* 2020;15:289.
10. Veronez CL, Moreno AS, Constantino-Silva RN, Maia LSM, Ferriani MPL, Castro FFM, et al. Hereditary Angioedema with Normal C1 Inhibitor and F12 Mutations in 42 Brazilian Families. *The Journal of Allergy and Clinical Immunology: In Practice.* 2018;6:1209-16.e8.
11. Loli-Ausejo D, Hernández-Martín I, Cabañas R, Entrala A, Gutiérrez-Alvarino M, Martínez-Sánchez N, et al. Tranexamic Acid Plus Bemiparin Sodium as Long- Term Prophylaxis in a Patient With FXII-HAE During Pregnancy: A Case Report. *J Investig Allergol Clin Immunol.* 2020;30:464-5.
12. Gabriel N, Marcelino F, Ferriani MPL, Arruda LK, Campos RA, Gonçalves RF, et al. Pregnancy in Patients With Hereditary Angioedema and Normal C1 Inhibitor. *Front Allergy.* 2022;3:846968.
13. Šimac DV, Štimac T, Novak S. Is Icatibant Safe for the Treatment of Hereditary Angioedema During Pregnancy? *Curr Allergy Asthma Rep.* 2022;22:135-40.
14. Riedl MA. Hereditary Angioedema During Pregnancy: Considerations in Management. *Immunol Allergy Clin North Am.* 2023;43(1):145-57.
15. Kaminsky LW, Kelbel T, Ansary F, Craig T. Multiple doses of icatibant used during pregnancy. *Allergy Rhinol (Providence).* 2017;8:178-81.

16. Gompel A, Fain O, Boccon-Gibod I, Gobert D, Bouillet L. Exogenous hormones and hereditary angioedema. *Int Immunopharmacol*. 2020;78:106080.
17. Jones D, Zafra H, Anderson J. Managing Diagnosis, Treatment, and Burden of Disease in Hereditary Angioedema Patients with Normal C1-Esterase Inhibitor. *JAA*. 2023;16:447-60.
18. Chong-Neto HJ, Aroni BP, Mansour E, Toledo E, Serpa FS, Arruda LK, et al. Are pediatricians familiar with hereditary angioedema? *World Allergy Organ J*. 2023 Jun 10;16(6):100783.

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Severe mixed-endotype asthma responsive to tezepelumab: a case report of an adolescent

Asma grave de endótipo misto com resposta a tezepelumabe: relato de caso de um adolescente

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ABSTRACT

Most children and adolescents with severe asthma have an eosinophilic inflammatory phenotype and are at risk of exacerbations, systemic corticosteroid use, and reduced quality of life. Children with type 2 inflammation respond well to conventional treatment; however, there is a small group that is unresponsive to conventional therapy and requires additional medication for disease control, such as immunobiologic agents. Knowledge of the pathophysiology of bronchial inflammation and biomarker assessment are essential for the appropriate choice of an immunobiologic agent. We report the case of a 13-year-old patient with severe type 2 allergic asthma, with no indication for omalizumab, who did not respond to mepolizumab after 12 months of treatment. The sputum cytology identified a mixed inflammatory endotype that led to replacement with another immunobiologic agent, tezepelumab, achieving control of exacerbations by probable reduction in bronchial hyperresponsiveness. Assessment of asthma endotype with the available biomarkers allowed precise and personalized treatment for this patient.

Keywords: Severe asthma, bronchial hyperresponsiveness, type 2 inflammation, thymic stromal lymphopoietin.

RESUMO

A maioria das crianças e adolescentes com asma grave apresenta fenótipo de inflamação eosinofílica, com risco de exacerbações, uso de corticosteroides sistêmicos e redução na qualidade de vida. Crianças com inflamação tipo 2 respondem bem aos tratamentos convencionais, no entanto, há um grupo pequeno que falha na resposta terapêutica habitual e necessita medicamentos adicionais, como imunobiológicos, para o controle da doença. O conhecimento da fisiopatologia da inflamação brônquica e a avaliação de seus biomarcadores é fundamental para escolha adequada do imunobiológico. Relatamos o caso de um paciente de 13 anos, com asma grave do tipo 2 alérgico, sem indicação de omalizumabe, e que em uso de mepolizumabe não apresentou controle da doença depois de 12 meses de tratamento. A avaliação do endótipo com citologia de escarro identificou fenótipo inflamatório misto, direcionando a substituição por outro imunobiológico, o tezepelumabe, atingindo o controle das exacerbações, por provável redução da hiper-responsividade brônquica. A avaliação do endótipo da asma com os biomarcadores disponíveis permitiu um tratamento preciso e individualizado para o paciente.

Descritores: Asma grave, hiper-responsividade brônquica, Inflamação tipo 2, linfopoietina do estroma tímico.

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Introduction

Severe asthma requires treatment with high doses of an inhaled corticosteroid plus a second controller medication (and/or systemic corticosteroid) to prevent it from becoming "uncontrolled" or remaining "uncontrolled" despite treatment.¹ Although most children with asthma achieve symptom control with low or medium doses of inhaled corticosteroids, there is a small but significant group with severe asthma who either require higher doses of inhaled corticosteroids plus controller medication to control their symptoms or who remain uncontrolled despite such therapy.²

According to the International Study of Asthma and Allergies in Childhood, the global prevalence of severe asthma among adolescents is 6.9%, ranging from 3.8% in the Asia Pacific region and in Northern and Eastern Europe to 11.3% in North America.³

Children with severe asthma are at increased risk of adverse outcomes, including medication-related side effects, life-threatening exacerbations, and impaired quality of life.⁴ The economic impact of severe asthma in the United States is significant, costing \$56 billion in 2007, with 50% of these costs being indirect, such as doctor visits, hospitalizations, medications, and missed days of school and work.⁵ Among children aged 5 to 17 years, asthma is one of the most common causes of school absence, impaired academic performance, and low participation in school-related activities.⁶

In the last decade, as knowledge of the pathophysiology of asthma has increased, biomarkers have been used to determine the endotype of asthma according to the inflammation profile. Elevated total serum immunoglobulin E (IgE), specific serum IgE, immediate skin-test reactivity, elevated exhaled nitric oxide (FeNO), eosinophilia in peripheral blood, and sputum are biomarkers of type 2 inflammation, the phenotype of most children with asthma. These biomarkers are increased in type 2 inflammation, since it is dependent on inflammatory cytokines such as IL-4, IL-5, and IL-13, which are produced by innate immune cells, as well as type 2 lymphoid cells and adaptive immune cells, such as Th2 lymphocytes, which are activated shortly after the release of alarmins such as thymic stromal lymphopoietin (TSLP).^{1,7} However, non-type 2 inflammation with a mixed granulocytic profile can also occur, involving Th1, Th17 lymphocytes, and neutrophils, in addition to eosinophils.⁷

A randomized, double-blind, placebo-controlled study of adolescents and adults found that 52 weeks of tezepelumab reduced the annual rate of exacerbations by 39% in patients with non-type 2 inflammation with < 150 eosinophils/ μ L.⁸

Case report

The patient was a 13-year-old boy born and raised in Curitiba, Brazil. Episodes of wheezing began at six months of age and he was diagnosed with persistent severe allergic asthma at 8 years of age, having 2 to 3 exacerbations per year that required emergency room visits and oral corticosteroids. He was admitted to the intensive care unit for asthma at 10, 11, and 12 years of age, requiring orotracheal intubation. He had been taking budesonide 800 μ g + formoterol 24 μ g since 8 years of age, without improvement. He was given montelukast 5 mg daily at 9 years of age and tiotropium 5 μ g daily at 10 years of age, with continued exacerbations requiring emergency room visits, oral corticosteroids, and hospitalization. He was also diagnosed with allergic rhinitis, for which he was treated with budesonide 32 μ g twice daily. He had no history of smoking, no pets, and a positive family history of asthma (mother).

Differential diagnosis was based on sweat chloride, serum immunoglobulin, and chest tomography, which were normal. Spirometry showed mild obstructive lung disease, and the bronchodilator test was positive. The patient's forced vital capacity (FVC) = 2.54 L (91%), forced expiratory volume in 1 second (FEV₁) = 1.64 L (65%), FEV₁/FVC ratio = 0.65, and mean forced expiratory flow 25-75 = 0.78 L (39%). Other tests showed an allergic phenotype: total IgE = 1726 kU/L, eosinophils 663 cells/ μ L, *Dermatophagoides pteronyssinus* skin test = 7x5 mm in diameter.

At 12 years of age, mepolizumab 100 mg was administered every 4 weeks, but poor disease control persisted: Asthma Control Test = 13 points, 2 exacerbations with systemic corticosteroids administered at home, and 1 ICU admission with noninvasive ventilation within 1 year. After 12 months of treatment with mepolizumab, the disease persisted uncontrolled: FeNO = 46 ppb and sputum cytology analysis showed a mixed pattern (neutrophils = 58%; eosinophils = 3%) (Figure 1).

At the age of 13, anti-TSLP (tezepelumab) 210 mg was administered subcutaneously every 4 weeks, with

a good response, no new exacerbations, and no need for oral corticosteroids. In follow-up consultations, after 2 months of medication use, the disease was under control (Asthma Control Test = 25 points), and spirometry revealed improved lung function: FVC = 2.80 L (100%); FEV₁ = 1.88 L (75%); FEV₁/FVC ratio = 0.68; FEF 25%-75% = 0.94 L (47%), and FeNO = 116 ppb.

After 3 months of tezepelumab use, the disease remained under control and lung function was stable. A new analysis of biomarkers indicated increased peripheral and sputum eosinophils, reduced FeNO, and total serum IgE stability.

In the 6-month evaluation after starting tezepelumab, a mild exacerbation occurred between

consultations, which was resolved with salbutamol and no oral corticosteroids. Approximately 2 weeks later, the patient was infected with influenza, which was resolved through symptomatic medications, with no new exacerbations. The markers showed increased FeNO, continued high levels of total IgE and eosinophils in peripheral blood. A new spirometry test was performed, showing stable pulmonary function (Table 1).

Discussion

Ten percent of asthma cases are severe, significantly impacting the lives of children/adolescents and their families and resulting in increased morbidity.¹ This adolescent, who had suffered asthma symptoms

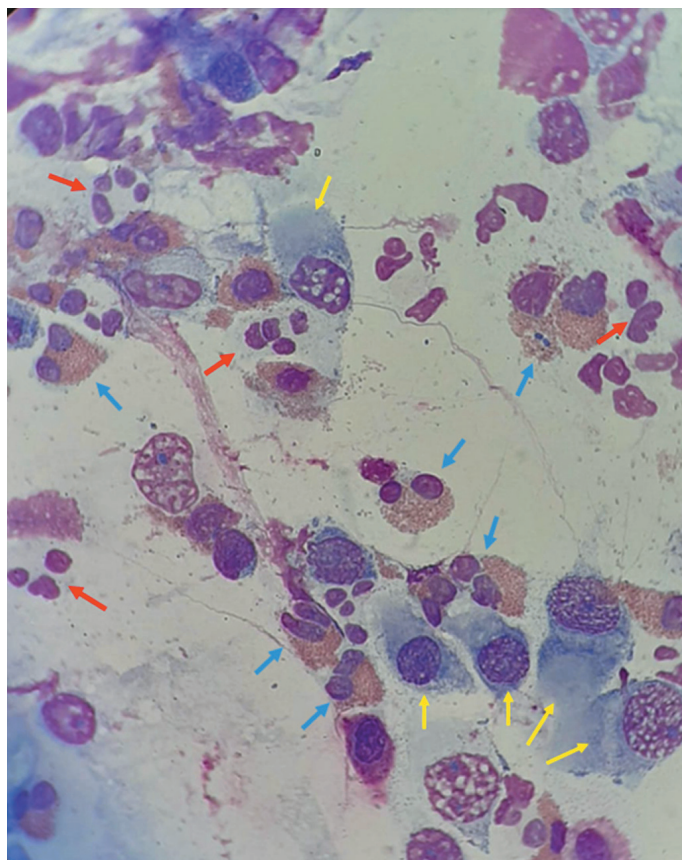


Figure 1

Sputum cytology with mixed inflammatory pattern (May-Grunwald-Giemsa staining). Blue arrows: eosinophils; red arrows: neutrophils; yellow arrows: macrophages

Table 1

Clinical, functional, and biomarker response to treatment with mepolizumab and tezepelumab

	Before mepolizumab	12 months after mepolizumab	2 months after tezepelumab	3 months after tezepelumab	6 months after tezepelumab
Clinical control					
ACT score	13 points	13 points	25 points	25 points	25 points
Number of exacerbations	3	2	0	0	1
Biomarker					
Peripheral blood eosinophil count (cells/ μ L)	663	32	–	744	520
Fraction of exhaled nitric oxide (ppb)	–	46	116	38	102
Sputum cytology (% cells)	–	Neutrophils = 58 Eosinophils = 3	–	Neutrophils = 4 Eosinophils = 80	Neutrophils = 44 Eosinophils = 48
Total IgE (kU/L)	1946	–	–	1781	1469
Lung function					
FEV ₁ (%)	–	65%	75%	73%	76%
FVC (%)	–	91%	100%	99%	105%
FEV ₁ /FVC	–	0.65	0.68	0.67	0.65
FEF 25-75 (%)	–	39%	47%	48%	39%

ACT: Asthma Control Test; FEF: forced expiratory flow; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity.

since early childhood, had been using high doses of inhaled corticosteroids associated with two other controller medications (a LABA and a LAMA), but without success. Given his type 2 inflammation profile and lack of response to treatment in step 4 of the Global Initiative on Asthma guidelines, it was decided to associate a biological agent.²

Due to the patient's type 2 allergic inflammatory profile, the recommended biological agent was omalizumab, but his serum IgE levels were too high for it² and mepolizumab was used instead, which failed to control the disease. Exacerbations ensued, requiring oral corticosteroids and ICU admission.

After 12 months of mepolizumab treatment, the eosinophil count in peripheral blood dropped significantly, which suggested anti-IL5 action, although it was not correlated with clinical manifestations due to continued exacerbations and poorly controlled disease.

In further evaluation of the patient's endotype, a mixed inflammatory pattern was identified in sputum cytology when mepolizumab was replaced with tezepelumab. This indicated a favorable response to treatment, with a high and low type-2 endotype,⁸ and the patient showed clinical improvement, despite the short observation time. Only a mild exacerbation

occurred, but there were no emergency room visits or need for oral corticosteroids.

Tezepelumab is an antibody that blocks TSLP, an alarmin derived from epithelial cells that is involved in airway inflammation. TSLP is released after epithelial injury, promoting activation of type 2 inflammatory cells and cytokines (dendritic cells, group 2 innate lymphoid cells, Th2 lymphocytes, mast cells, IL-4, IL-5, and IL-13), in addition to affecting the regulation of factors related to neutrophilic inflammation, which results from the activation of Th1 and/or Th17 cells and the release of their cytokines, such as IFN γ and IL-17. It also exerts a direct action on smooth muscle, contributing to airway remodeling by increasing collagen production through fibroblast and myocyte proliferation.⁹

In phase 2 and 3 studies of patients with severe uncontrolled asthma, tezepelumab significantly reduced exacerbations compared to placebo, regardless of type 2 inflammation biomarkers. In the present case, after 6 months of medication use and clinical improvement, type-2 inflammation biomarkers had not reduced, but blood eosinophils increased and the mixed sputum pattern changed to an eosinophilic pattern. The FeNO results were variable, increasing in the first assessment (after 2 months of tezepelumab), decreasing at 3 months of treatment, and increasing again at 6 months of treatment. Lung function improved significantly after 2 months and remained stable at 3 and 6 months of treatment.

The small effect on type-2 inflammation biomarkers associated with improved clinical and pulmonary function suggests that the most important inflammatory profile in this patient was neutrophilic, although this does not explain the inefficiency of anti-TSLP for eosinophilic inflammation, as observed in pivotal studies.⁸ TSLP can act on other cells, such as bronchial smooth muscle, mast cells, etc., which may be related to bronchial hyperresponsiveness (BHR).¹⁰

BHR, a pathophysiological process of asthma, is defined as airway predisposition to narrowing (bronchoconstriction) in response to stimuli that have little or no effect on healthy individuals.¹¹ It is a marker of symptomatic asthma, independent of the eosinophilic pattern, leading to exacerbations and reduced disease control.¹⁰

The clinical improvement confirms that tezepelumab reduces exacerbations independently of type-2 inflammation biomarkers and reduces BHR.^{8,9}

Andreasson et al. described the effects of TSLP on BHR, investigating the association between BHR (by bronchoprovocation with mannitol) and TSLP levels in serum, sputum, and bronchoalveolar lavage in patients with asthma with and without type 2 inflammation. They found that sputum TSLP levels were associated with the degree of BHR in patients with eosinophilic and non-eosinophilic asthma, corroborating the role of TSLP and BHR beyond type 2 inflammation.¹²

Similarly, a phase 2 study by Diver et al. found significantly lower BHR in the tezepelumab group than the placebo group in the mannitol test ($p = 0.03$). At the end of treatment, more patients who used tezepelumab had a negative bronchoprovocation test than the placebo group (43% vs. 25%). These results were independent of the peripheral eosinophil count or type 2 inflammation markers.⁹

The exact mechanism by which tezepelumab reduces exacerbations in patients with non-type-2 inflammation is not yet fully understood. Studies have shown that a wide range of cells express TSLP receptors, such as ILC-3 and IL-17, which are involved in the non-type 2 inflammation pathway, in addition to having a direct effect on mast cell activation and mediation between structural muscle cells and immune cells, which are directly involved in BHR.^{13,14} Mast cell activation by TSLP leads to bronchoconstriction, mucus secretion, and collagen release by fibroblasts, factors that may be related to structural changes in the disease and lung function decline.^{11,15}

Unfortunately, bronchoprovocation was not performed in this case but, due to the relationship between BHR and TSLP, it is likely that a reduction in our patient's BHR was the main factor in controlling the disease, regardless of type 2 inflammatory marker reduction.

Conclusion

Tezepelumab, a human monoclonal antibody that specifically binds to TSLP, may be the first-choice biological agent for patients with severe asthma who are at least 12 years of age. The response is greater in patients with a type 2 inflammation profile and it is the only agent that can also improve asthma in patients with non-type 2 inflammation. Although type-2 inflammation biomarkers were not reduced, our patient achieved disease control. In this case, the role of non-type-2 inflammation was predominant,

and the action of anti-TSLP on inflammatory cells other than eosinophils was predominant, probably reducing BHR.

References

- Chong-Neto HJ, Wandalsen GF, Pastorino AC, Dela Bianca C, Chong-Silva DC, Riedi CA, et al. Guia prático de abordagem da criança e do adolescente com asma grave: documento conjunto da Associação Brasileira de Alergia e Imunologia e Sociedade Brasileira de Pediatria. *Arq Asma Alerg Imunol.* 2020;4(1):3-34.
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2022 – up date [Internet]. Available from: <https://ginasthma.org/wp-content/uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf>. Accessed feb 2024.
- Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax.* 2009;64(4):476-83.
- Fleming L, Wilson N, Bush A. Difficult to control asthma in children. *Curr Opin Allergy Clin Immunol.* 2007;7(2):190-5.
- Centers for Disease Control and Prevention. Asthma in the US. [Internet]. Available from: <<https://www.cdc.gov/vitalsigns/pdf/2011-05-vitalsigns.pdf>>. Acessado em fevereiro/2024.
- Moonie SA, Sterling DA, Figgs L, Castro M. Asthma status and severity affects missed school days. *J Sch Health.* 2006;76(1):18-24.
- Busse WW. Biological treatments for severe asthma: A major advance in asthma care. *Allergol Int.* 2019;68(2):158-66.
- Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME, et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. *N Engl J Med.* 2021;384(19):1800-9.
- Diver S, Khalfaoui L, Emson C, Wenzel SE, Menzies-Gow A, Wechsler ME, et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med.* 2021;9(11):1299-312.
- Sverrild A, Andreassen AH, Westergaard CG, von Bulow A, Udesen PB, Thomsen SF, et al. Hyperresponsiveness to inhaled mannitol identifies a cluster of noneosinophilic asthma patients with high symptom burden. *J Allergy Clin Immunol Pract.* 2021;9:4029-36.
- Bradding P, Porsbjerg C, Côté A, Dahlén SE, Hallstrand TS, Brightling CE. Airway hyperresponsiveness in asthma: The role of the epithelium. *J Allergy Clin Immunol.* 2024;153(5):1181-93.
- Andreasson LM, Dyhre-Petersen N, Hvidtfeldt M, Jørgensen GØ, Von Bülow A, Klein DK, et al. Airway hyperresponsiveness correlates with airway TSLP in asthma independent of eosinophilic inflammation. *J Allergy Clin Immunol.* 2024 Apr;153(4):988-97.
- Gauvreau GM, Sehmi R, Ambrose CS, Griffiths JM. Thymic stromal lymphopoietin: its role and potential as a therapeutic target in asthma. *Expert Opin Ther Targets.* 2020;24(8):777-92.
- Panettieri R Jr, Lugogo N, Corren J, Ambrose CS. Tezepelumab for Severe Asthma: One Drug Targeting Multiple Disease Pathways and Patient Types. *J Asthma Allergy.* 2024;17:219-36.
- Caminati M, Buhl R, Corren J, Hanania NA, Kim H, Korn S, et al. Tezepelumab in patients with allergic and eosinophilic asthma. *Allergy.* 2024;79(5):1134-45.

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Sublingual immunotherapy in the management of local allergic rhinitis in childhood: a case report

Imunoterapia sublingual no tratamento da rinite alérgica local na infância: relato de caso

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ABSTRACT

Local allergic rhinitis (LAR) is a recently defined rhinitis phenotype, and its diagnosis represents a major challenge for both physicians and patients. LAR shows no evidence of systemic sensitization and is therefore often inappropriately classified as non-allergic rhinitis. This rhinitis phenotype shows a nasal T2 allergic inflammatory response and local IgE synthesis, and nasal allergen challenge is considered the gold standard method for its diagnosis. LAR has clinical features similar to those of other rhinitis phenotypes, and due to diagnostic difficulties, it is underdiagnosed in all age groups. The correct phenotypic diagnosis of LAR offers potential benefits for patients not only by enabling the implementation of care to reduce environmental exposure to identified allergens, but mainly by allowing allergen-specific immunotherapy.

Keywords: Allergic rhinitis, dust mite allergy, child, sublingual immunotherapy.

RESUMO

A rinite alérgica local (RAL) é um fenótipo de rinite definido recentemente e seu diagnóstico configura um grande desafio tanto para médicos, como para os seus pacientes. A RAL não apresenta evidências de sensibilização sistêmica e, por essa razão, é frequentemente classificada de forma inadequada como uma rinite não alérgica. Este fenótipo de rinite apresenta resposta inflamatória alérgica T2 nasal e síntese local de IgE específica, sendo que o teste de provocação nasal específico é considerado o método padrão ouro para realizar o seu diagnóstico. A RAL possui características clínicas semelhantes aos outros fenótipos de rinite, e pela dificuldade diagnóstica é subdiagnosticada em todas as faixas etárias. O diagnóstico fenotípico correto da rinite tem potenciais benefícios para os pacientes, não apenas por possibilitar a implementação de cuidados para a redução da exposição ambiental aos alérgenos identificados, mas principalmente por permitir a realização de imunoterapia alérgeno específica.

Descritores: Rinite alérgica, alergia a ácaros, criança, imunoterapia sublingual.

Introduction

Local allergic rhinitis (LAR) is a recently defined rhinitis phenotype whose diagnosis poses a major challenge for both physicians and patients. Because there is no evidence of systemic sensitization in LAR, it is often misclassified as non-allergic rhinitis. It presents with a nasal type 2 allergic inflammatory response and local synthesis of specific IgE.¹ A specific nasal

allergen challenge is considered the gold standard diagnostic method.^{2,3} The clinical characteristics of LAR are similar to other rhinitis phenotypes¹ and, due to diagnostic difficulty, it is underdiagnosed in all age groups. In adults, it is estimated that up to 50% of rhinitis patients without systemic sensitization could be diagnosed with LAR.⁴ In children, a recent systematic

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review⁵ found great variability in the prevalence of LAR, being higher in Western countries (22.3% to 83.3%) than Eastern countries (3.7% to 16.6%). In Brazil, the incidence of LAR among children and adolescents has been estimated at 40% in a tertiary allergy and immunology service among patients with rhinitis and without systemic sensitization.⁶

The correct phenotypic diagnosis of rhinitis can benefit patients, not only by enabling care implementation through reducing environmental exposure to identified allergens, but by allowing allergen-specific immunotherapy.

Case description

This case report describes a 14-year-old female patient with sporadic rhinitis symptoms that began at approximately 2 years of age and were associated with weather changes. At 8 years of age, the symptoms became more frequent, and treatment with a topical nasal corticosteroid (budesonide) and oral antihistamines was initiated.

At 11 years of age, due to persistent symptoms, the patient was referred to a tertiary allergy and immunology service. During the etiological investigation, she showed no positive response to systemic sensitization tests (ie, an immediate hypersensitivity skin test and specific serum IgE measurement) for the following allergens: *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, *Blattella germanica*, *Periplaneta americana*, dog epithelium, cat epithelium, and a mix of fungi. An endoscopic evaluation of the upper airway (nasofibroscope) ruled out other local diseases that could explain or contribute to the lack of therapeutic response.

During the first months of follow-up, despite treatment with a combination of leukotriene receptor antagonists and corticosteroids + nasal antihistamine (fluticasone + nasal azelastine), the symptoms and frequent need for oral antihistamines persisted, including a nasal symptom score of 6 (on a scale of 0 to 12), which indicated uncontrolled severe rhinitis.

Thus, the etiological investigation was continued by performing a multiple specific nasal allergen challenge with *Dermatophagoides pteronyssinus* and *Blomia tropicalis* (FDA ALLERGENIC Brazil, 5000 UBE/ml) according to a previously validated protocol for children and adolescents.⁶ This test consists of sequentially increasing concentrations of the allergens (bilateral nasal spray) in 15-minute intervals during the

same visit. The results were monitored subjectively by a symptom questionnaire and objectively by acoustic rhinometry (Figure 1).

The nasal allergen challenge results were negative for *Dermatophagoides pteronyssinus* and positive for *Blomia tropicalis* at a concentration of 1:100, which was documented through acoustic rhinometry by a 32% volume reduction in the first 5 cm of the nasal cavity (V5)(Figure 2A).

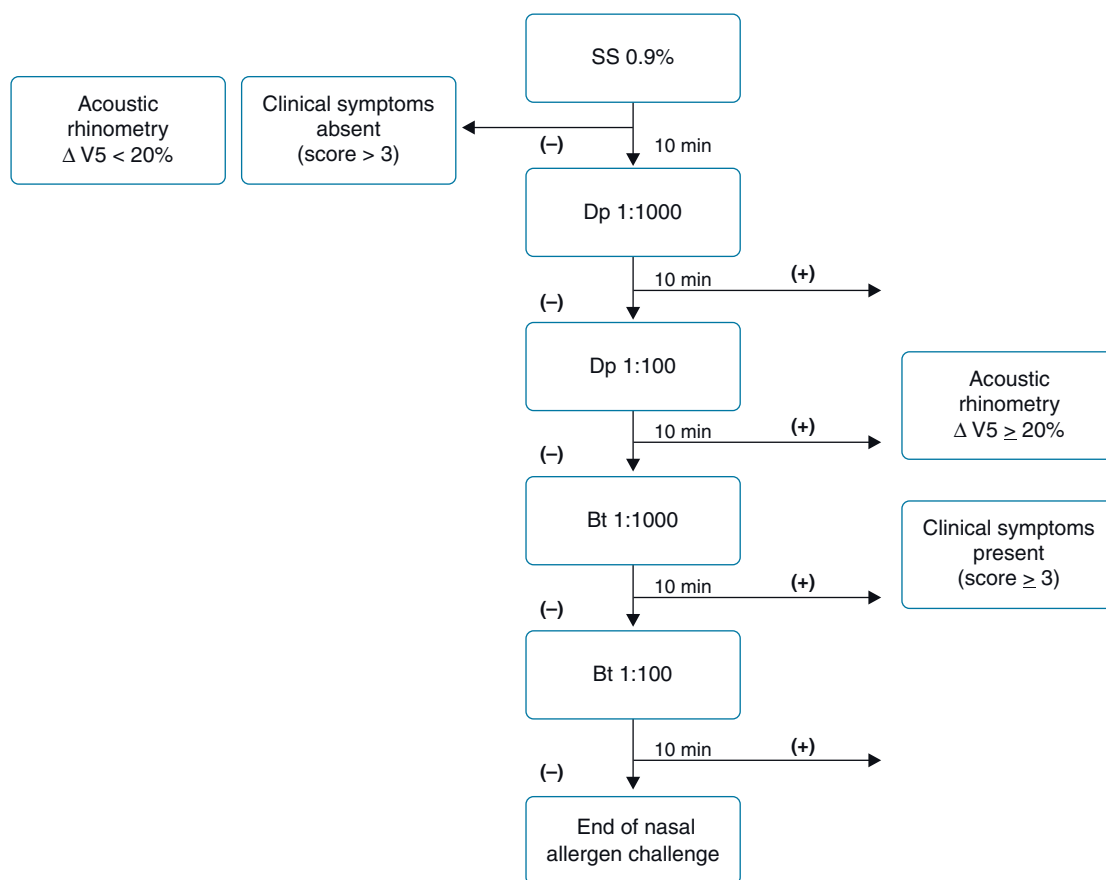
After LAR was confirmed, sublingual immunotherapy for *Blomia tropicalis* (IPI ASAC Pharma, Brazil) was initiated. Nasal symptoms were partially reduced after the fourth month of treatment (nasal symptom score = 4) and progressed to adequate control beginning in the ninth month of sublingual immunotherapy (nasal symptom score = 3), allowing a gradual reduction in medication, including topical nasal corticosteroids; oral antihistamines were used only as needed.

After 18 months of sublingual immunotherapy, the patient remained in the maintenance phase with controlled nasal symptoms (nasal symptom score = 3), only occasionally using oral antihistamine. At this point, new multiple nasal allergen challenges were performed with *Dermatophagoides pteronyssinus* and *Blomia tropicalis*, both of which were negative (Figure 2B).

Discussion

The present case highlights not only the difficulties in diagnosing LAR, but also the potential benefits of doing so. It also illustrates that LAR severity does not differ from other rhinitis phenotypes, as has been demonstrated by other authors.⁷ Correct diagnosis of this phenotype is important, since without proper diagnosis, specific allergen immunotherapy cannot be administered, limiting the therapeutic arsenal for individualized treatment.

Sublingual immunotherapy containing *Blomia tropicalis* is an important tool for children and adolescents with LAR. In adults with LAR, subcutaneous allergen immunotherapy has shown good results.^{8,9} Two recent meta-analyses^{8,9} have investigated the efficacy and safety of subcutaneous allergen immunotherapy for adults with LAR. Both suggested that immunotherapy has a significant effect on symptom improvement, reduces medication consumption, increases serum-specific IgG4 after 2 years of treatment, and results in increased

**Figure 1**

Flowchart for multiple specific nasal allergen challenge with *Dermatophagoides pteronyssinus* (5000 UBE/mL) and *Blomia tropicalis* (5000 UBE/mL) in children and adolescents⁶

SS: saline solution; V5: volume reduction in the first 5 cm of the nasal cavity.

tolerance to the allergen after subcutaneous allergen immunotherapy.⁹ Another meta-analysis⁸ found a trend towards greater benefit in patients with seasonal LAR compared to those with perennial symptoms. No study in these meta-analyses determined long-term response after treatment. It is noteworthy that in these meta-analyses, the efficacy of sublingual immunotherapy for LAR could not be determined due to a lack of data.

In the exclusively pediatric range, few studies are available on LAR, and there are no reports in the literature on therapeutic response to subcutaneous allergen immunotherapy or sublingual immunotherapy.

In this case, sublingual immunotherapy with *Blomia tropicalis* not only had a good clinical response, as demonstrated by decreased symptom scores and medication consumption, but also resulted in greater tolerance to the allergen during treatment, as shown by the negative multiple nasal allergen challenge results after 18 months of treatment.

New studies in adults and children should be conducted on the short-term benefits of sublingual immunotherapy and subcutaneous allergen immunotherapy, as well as their long-term benefits after 3 years of immunotherapy to determine persistent response and definitive impact on quality of life.

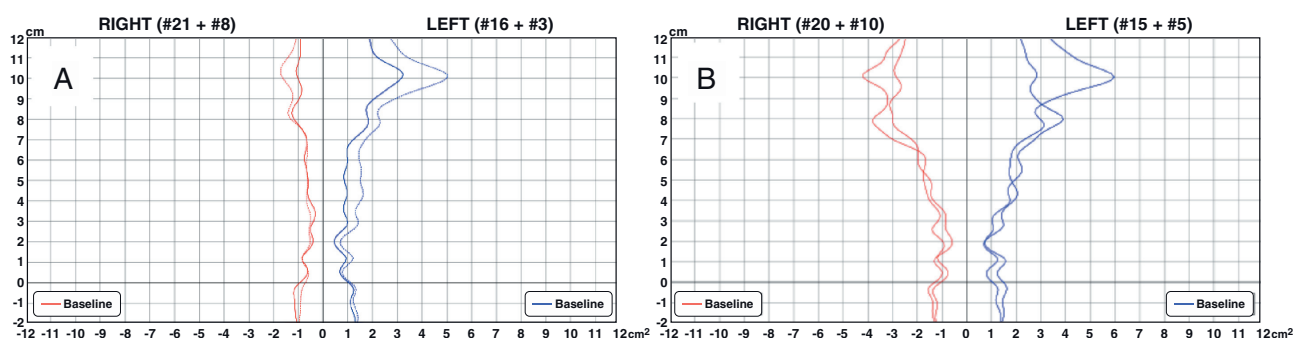


Figure 2

(A) Multiple specific nasal allergen challenge with *Dermatophagoides pteronyssinus* and *Blomia tropicalis*, demonstrating a 32% decrease in volume reduction in the first 5 cm of the nasal cavity (V5) at a *Blomia tropicalis* concentration of 1:100; **(B)** Multiple specific nasal allergen challenge with *Dermatophagoides pteronyssinus* and *Blomia tropicalis* after 18 months of sublingual immunotherapy, demonstrating a 6% decrease in V5 at the end of the test

References

- Rondón C, Fernandez J, Canto G, Blanca M. Local allergic rhinitis: Concept, clinical manifestations, and diagnostic approach. *J Invest Allergol Clin Immunol*. 2010;20(5):364-71.
- Cho SH, Nanda A, Keswani A, Adinoff A, Baroody FM, Bernstein JA, et al. Nasal allergen challenge (NAC): Practical aspects and applications from an EU/US perspective-a Work Group Report of the AAAAI Rhinitis, Rhinosinusitis and Ocular Allergy Committee. *J Allergy Clin Immunol*. 2023 May 1;151(5):1215-1222.e4.
- Augé J, Vent J, Agache I, Airaksinen L, Campo Mozo P, Chaker A, et al. EAACI Position paper on the standardization of nasal allergen challenges. *Allergy: European Journal of Allergy and Clinical Immunology*. 2018;73(8):1597-608.
- Rondón C, Campo P, Zambonino MA, Blanca-Lopez N, Torres MJ, Melendez L, et al. Follow-up study in local allergic rhinitis shows a consistent entity not evolving to systemic allergic rhinitis. *Journal of Allergy and Clinical Immunology*. 2014;133(4):1026-31.
- Matsumoto FY, Tranquillini Gonçalves TR, Solé D, Wandalsen GF. Local allergic rhinitis in children: A systematic review. *Allergol Immunopathol (Madr)*. 2022 Mar 1;50(2):40-7.
- Matsumoto FY, Tranquillini Gonçalves TR, Solé D, Wandalsen GF. Local allergic rhinitis in children: identification and characterization in a specialty outpatient clinic. *Eur Ann Allergy Clin Immunol*. 2024 Jan 23. doi: 10.23822/EurAnnACI.1764-1489.327.
- Rondon C, Campo P, Eguiluz-Gracia I, Plaza C, Bogas G, Galindo P, et al. Local allergic rhinitis is an independent rhinitis phenotype: The results of a 10-year follow-up study. *Allergy: European Journal of Allergy and Clinical Immunology*. 2018;73(2):470-8.
- Hoang MP, Samuthpongton J, Chitsuthipakorn W, Seresirikachorn K, Snidvongs K. Allergen-specific immunotherapy for local allergic rhinitis: a systematic review and meta-analysis. *Rhinology*. 2022 Feb 1;60(1):11-9.
- Zhu W, Gao P, Zhang Q, Chen J. Efficacy and Safety of Subcutaneous Immunotherapy for Local Allergic Rhinitis: A Meta-Analysis of Randomized Controlled Trials. *Am J Rhinol Allergy*. 2022 Mar 19;36(2):245-52.

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Adult IgE-mediated cow's milk allergy – a rare phenotype

Alergia IgE mediada ao leite de vaca no adulto – fenótipo raro

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ABSTRACT

Cow's milk protein allergy is the most common food allergy in children, but it is rare in adults, with an estimated prevalence of 0.49%-0.60%. Previous studies have shown that spontaneous tolerance rarely occurs in adults and that, during follow-up, the double-blind, placebo-controlled oral food challenge should be used to assess tolerance acquisition. We report the case of an adult patient with cow's milk protein allergy, sensitized to casein.

Keywords: Milk hypersensitivity, cow's milk allergy, IgE, casein, adult.

RESUMO

A alergia às proteínas do leite de vaca é a alergia alimentar mais frequente em crianças, mas, na idade adulta, é rara, com uma prevalência estimada de 0,49-0,6%. Estudos prévios demonstraram que a tolerância espontânea na idade adulta raramente ocorre e que, durante o seguimento, a prova de provocação oral duplamente cega controlada com placebo deve ser usada para avaliação de aquisição da tolerância. Os autores apresentam um caso clínico de uma doente adulta com alergia às proteínas do leite de vaca, sensibilizada à caseína.

Descritores: Hipersensibilidade ao leite, alergia ao leite de vaca, IgE, caseína, adulto.

Introduction

Food allergy is a major public health problem, affecting individuals at any age.¹ It is characterized by a specific immune response that occurs reproducibly on exposure to a given food.²

Cow's milk protein allergy (CMPA) is the most common food allergy in children under 3 years of age, but it is rare in adults, with an estimated prevalence of 0.49%-0.60%. The mechanisms underlying sensitization after the first years of life are unknown,

with only a few cases reported in the literature.^{2,3} CMPA is likely to be more severe and persistent in adults.⁴⁻⁶

Cow's milk contains 20 potentially sensitizing proteins, with structural homology and consequently cross-reactivity >90% with allergens from other mammals' milk (eg, sheep, goat, and camel milk).⁷ Casein (Bos d8-12) and beta-lactoglobulin (Bos d5) are most frequently responsible for the occurrence of

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CMPA, with casein being highly heat stable.^{8,9} Studies also suggest that sensitization to casein is common in cases of persistent allergy and in patients with atopic comorbidities.¹⁰

Food allergy should be diagnosed based on the patient's medical history, skin tests, specific IgE assays, and double-blind placebo-controlled food challenge (DBPCFC). Previous studies have shown that spontaneous tolerance in CMPA rarely occurs in adults and that, during follow-up, DBPCFC should be used to assess tolerance acquisition. Desensitization in these patients is a solution. However, anaphylactic reactions occur in 25% of these phenotypes, and it is important to note that there is no allergen-specific immunotherapy for CMPA.^{11,12}

Case report

A 59-year-old woman was referred to the immunoallergy department due to an episode of anaphylaxis after having caramel ice cream, with no previous history of CMPA. A few minutes after having the ice cream, she developed oropharyngeal itching, lip swelling, a sensation of dyspnea and tightness in the oropharynx, dysarthria, and diffuse macular rash. She went to the emergency department and received intravenous medication (which she was unable to describe), with resolution of the condition in less than 4 hours. She did not have ice cream again. Until her first appointment, she used to consume butter and caffè latte, showing associated oropharyngeal pruritus. She did not drink raw milk or yogurt because she did not like the taste. She consumes beef without any symptoms.

Investigation included skin prick tests using commercial extracts from LETI Pharma® for milk and proteins, wheat, egg, shrimp, fish mix, meat mix, peanut, and hazelnut, and the mean papule diameters were: histamine 5 mm, milk 7 mm, and casein 7 mm.

Total IgE assay: 1098 KU/L; and assay for specific IgE using the ImmunoCAP FEIA system® (Thermo Fisher Scientific, Uppsala, Sweden): milk 8.41 kUA/L, casein 13.30 kUA/L, alpha-lactalbumin 0.01 kUA/L, and beta-lactoglobulin 0.02 kUA/L.

The patient refused to undergo both oral food challenge testing and milk desensitization.

She is currently avoiding cow, sheep, and goat milk proteins in all forms, with no new episodes of anaphylaxis or oropharyngeal pruritus. She was

warned about the importance of reading labels. She carries an epinephrine autoinjector and has a treatment plan with oral corticosteroids and antihistamines for use in case of accidental ingestion, according to the symptoms.

Discussion

We reported the case of an adult patient with CMPA and draw attention to the rarity of the development of this entity after the first years of life. We warned the patient about the persistence of the allergy and the possibility of severe reactions occurring after the consumption of raw, boiled, or processed cow's milk, since she became sensitized to casein. The patient's refusal to undergo oral food challenge testing and desensitization hinders the assessment of tolerance acquisition. CMPA in adults is still poorly characterized in the available literature, and is probably underdiagnosed. Further studies with larger cohorts are needed to better understand its risk factors, different phenotypes, and prognosis.

References

1. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID sponsored expert panel. *J Allergy Clin Immunol*. 2010;126:S1-58.
2. Sousa MJCS, Reis Ferreira AL, Moreira da Silva JP. Bodybuilding protein supplements and cow's milk allergy in adult. *Eur Ann Allergy Clin Immunol*. 2018;50(1):42-4.
3. Luyt D, Ball H, Makwana N, Green MR, Bravin K, Nasser SM, Clark AT. BSACI guideline for the diagnosis and management of cow's milk allergy. *Clin Exp Allergy*. 2014;44(5):642-72.
4. Stoger P, Wuthrich B. Type I allergy to cow milk proteins in adults. A retrospective study of 34 adult milk- and cheese-allergic patients. *Int Arch Allergy Immunol*. 1993;102(Suppl4):399-407.
5. Fiocchi A, Dahdah L, Albarini M, Martelli A. Cow's milk allergy in children and adults. *Chem Immunol Allergy*. 2015;101:114-23. doi: 10.1159/000375415.
6. Lam HY, van Hoffen E, Michelsen A, Guikers K, van der Tas CHW, Bruijnzeel-Koomen CAFM, et al. Cow's milk allergy in adults is rare but severe: both casein and whey proteins are involved. *Clin Exp Allergy*. 2008;38(6):995-1002.
7. Fiocchi A, Brozek J, Schünemann H, Bahna SL, von Berg A, Beyer K, et al. World Allergy Organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. *WAO J*. 2010;3:57-161.
8. Wal JM. Cow's milk allergens. *Allergy*. 1998;53:1013-22.
9. Businco L, Marchetti F, Pellegrini G, Perlini R. Predictive value of cord blood IgE levels in "at-risk" newborn babies and influence of type of feeding. *Clin Allergy*. 1983;13:503-8.

10. Garcia-Ara MC, Boyano-Martinez MT, Diaz-Pena JM, Martin-Munoz MF, Martin-Esteban M. Cow's milk-specific immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy infants. *Clin Exp Allergy*. 2004;34:866-70.
11. Regula P, Agress A, Rosenstreich D, Rubinstein A, Ramesh M. Adult-onset IgE-mediated cow's milk allergy-a rare phenotype. *J Allergy Clin Immunol Glob*. 2023;2(4):100142.
12. Klein B, Simon JC, Treudler R. Treatment of severe cow's milk allergy with omalizumab in an adult. *Allergol Select*. 2023;7:20-4.

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Contact dermatitis to cinchocaine: is cross-reactivity between local anesthetics a problem?

*Dermatite de contato à cinchocaína:
a reatividade cruzada dos anestésicos locais é um problema?*

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ABSTRACT

Contact dermatitis caused by local anesthetics from the ester group is more common than with the amide group. While cross-reactivity is well-documented within the ester group, it is less understood within the amide group and does not appear to occur between the ester and amide groups. We report a case of allergic contact dermatitis to cinchocaine, an amide anesthetic, with no reactivity to lidocaine. Differences in the chemical structure of amide anesthetics, such as cinchocaine's unique aromatic double-ring, might explain the lack of cross-reactivity. This case highlights the importance of accurate diagnosis and thorough allergological evaluation. Testing as many amide-type anesthetics as possible is recommended in cases of delayed allergy to any member of this family.

Keywords: Local anesthetics, drug hypersensitivity, contact dermatitis.

RESUMO

A dermatite de contato causada por anestésicos locais é mais comum no grupo dos ésteres do que no grupo das amidas. Embora a reatividade cruzada esteja bem documentada no grupo dos ésteres, é menos conhecida no grupo das amidas e não parece ocorrer entre os grupos dos ésteres e das amidas. Este caso de dermatite de contato alérgica à cinchocaína, um anestésico amida, sem reatividade à lidocaína, realça a importância de um diagnóstico preciso e de uma avaliação alergológica completa. Sugere que as diferenças na estrutura química dos anestésicos amida, como o duplo anel aromático único da cinchocaína, podem explicar a falta de reatividade cruzada. Testar o maior número possível de anestésicos do tipo amida é recomendado em casos de alergia tardia a qualquer membro desta família.

Descritores: Anestésicos locais, hipersensibilidade a drogas, dermatite de contato.

Introduction

Local anesthetics from the ester group are relatively common causes of contact sensitization. In contrast, sensitization to anesthetics from the amide group is considered rare. Cross-reactivity within the ester group is common and well recognized, whereas cross-reactivity between the amide and ester groups is not observed, and cross-reactivity within the amide group is poorly understood.¹⁻⁴

Case report

A 42-year-old woman reported the development of pruritic, erythematous, and exudative skin lesions in the perianal region, extending to the upper posterior region of the lower limbs (Figure 1), on day 6 (D6) of using Scheriproct[®] rectal ointment (prednisolone caproate + cinchocaine hydrochloride) and Vessel[®] capsules (sulodexide). Her treatment was switched to Faktu[®] rectal ointment (policresulen + cinchocaine

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**Figure 1**

Clinical presentation of pruritic erythema in the perianal region

hydrochloride) and Daflon® tablets (bioflavonoids). However, her condition continued to worsen, leading to the appearance of a fungal infection in the same region. Her therapy was changed to Pevisone® ointment (econazole + triamcinolone acetonide), with no improvement, and then to Baycuten® (clotrimazole + dexamethasone acetate) and Salofalk® suppositories (mesalazine), with clinical resolution.

The patient was referred to the Allergy and Clinical Immunology department, where epicutaneous testing was conducted using corticosteroid and caine series, along with the medications previously used by the patient (to rule out reaction to inactive ingredients if all corticosteroids and local anesthetics were negative). The results showed strong positive reactions at D2 to cinchocaine hydrochloride (dibucaine, percaine) 5% (+++), quinoline mix 6% (+++ with cutaneous detachment), Faktu® (++) and Scheriproct® (++) (Figure 2). The other tests were negative, with readings on D2, D3, and D7 (Table 1).

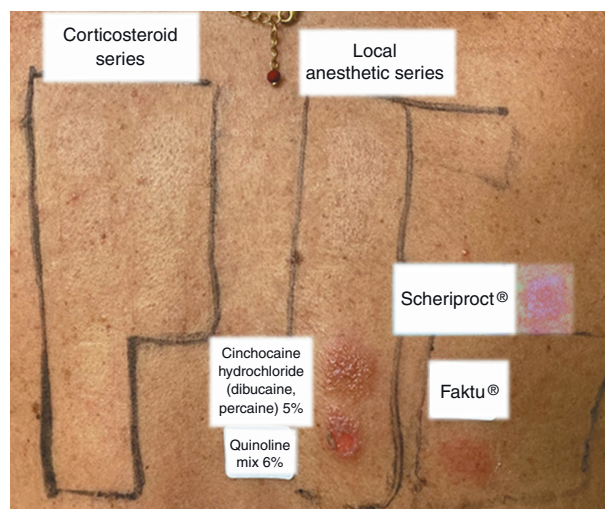
Given the negative epicutaneous results for lidocaine hydrochloride and the patient's own ointment – Ultraproct® (fluocortolone pivalate + lidocaine hydrochloride, tested as a safe alternative) –, a drug challenge test with Ultraproct® cream was performed, with no skin reaction or local pruritus. Additionally, a subcutaneous challenge test with lidocaine produced no immediate or delayed reaction.

Discussion

The patient in this report presented allergic contact dermatitis to cinchocaine with tolerance to lidocaine hydrochloride, both of which belong to the amide group. The lack of cross-reactivity between these drugs underscores the importance of accurate diagnosis and thorough allergological examination, allowing the identification of the causative drug and the exploration of safe alternatives. Moreover, this case highlights the complexity of classifying and understanding cross-reactivity between local anesthetic agents, particularly within the amide group.

There are 3 potential sensitization groups among amide-type local anesthetics: benzene ring, thiophene ring, and quinoline derivatives. Notably, cinchocaine is a quinoline derivative that has a distinctive aromatic double-ring structure in its lipophilic aromatic ring.² This structural difference from other local amide anesthetics could explain the lack of cross-reactivity.

In the absence of definitive guidelines on cross-reactivity between different amide-type local anesthetics, it is recommended to test as many of them as possible in cases of delayed allergy to any member of this family. Although reports of concomitant contact allergies within the amide group are rare, it remains uncertain whether these cases represent true cross-reactivity or only concomitant contact allergies.

**Figure 2**

Patch testing with corticosteroids, local anesthetics, and ointments and medications used by the patient

Existing evidence on cross-reactivity between the ester and amide groups is limited to isolated case reports and a single series of 29 cases of allergic contact dermatitis from lignocaine, with

inconsistent findings.⁵ A comprehensive study involving simultaneous testing of multiple local anesthetics across all classes could be helpful in further clarifying these cross-reactivities.

Table 1

Patch testing results

	Patch results on D2 and D3	Patch results on D7
Corticosteroid series (in petrolatum)		
Hydrocortisone 0.1	Negative	Negative
Prednisolone 50 mg/mL	Negative	Negative
Betamethasone 1%	Negative	Negative
Betamethasone dipropionate 0.5%	Negative	Negative
Dexamethasone 1%	Negative	Negative
Hydrocortisone 17-butyrate 0.1%	Negative	Negative
Triamcinolone acetonide	Negative	Negative
Local anesthetic series (in petrolatum)		
Benzocaine (Anesthesin) 5%	Negative	Negative
Lidocaine (lignocaine, xylocaine) 5%	Negative	Negative
Procaine hydrochloride (novocaine chloride) 1%	Negative	Negative
Lidocaine hydrochloride 1%	Negative	Negative
Caine mix 10%	Negative	Negative
Cinchocaine hydrochloride (dibucaine, percaine) 5%	+++	+++
Quinoline mix 6%	+++	+++
Previously used medications (“as is”)		
Daflon®	Negative	Negative
Vessel®	Negative	Negative
Pevisone®	Negative	Negative
Faktu®	++	+
Scheriproct®	++	++
Baycuten®	Negative	Negative
Ultraproct®	Negative	Negative

It is acknowledged that patients with contact allergy to one local anesthetic do not necessarily need to avoid all other local anesthetics within the same group. However, whether all patients with allergic contact dermatitis to a specific anesthetic should be evaluated for potential cross-reactivity and alternative therapeutic options is a topic that warrants further discussion. The possibility of providing a therapeutic alternative without allergological examination remains uncertain.

References

1. Kearney CR, Fewings J. Allergic contact dermatitis to cinchocaine. *Australas J Dermatol*. 2001;42(2):118-9.
2. Gonzalez Mahave I, Lobera T, Blasco A, Del Pozo MD. Allergic contact dermatitis caused by cinchocaine. *Contact Dermatitis*. 2008;58(1):55-8.
3. Ramirez P, Sendagorta E, Floristan U, Feltes RA, Vidaurrazaga C. Allergic contact dermatitis from antihemorrhoidal ointments: concomitant sensitization to both amide and ester local anesthetics. *Dermatitis*. 2010;21(3):176-7.
4. Lee AY. Allergic contact dermatitis from dibucaine in Proctosedyl ointment without cross-sensitivity. *Contact Dermatitis*. 1998;39(5):261.
5. Curley RK, Macfarlane AW, King CM. Contact sensitivity to the amide anesthetics lidocaine, prilocaine, and mepivacaine. Case report and review of the literature. *Arch Dermatol*. 1986;122(8):924-6.

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Ataxia-telangiectasia: an important cause of progressive ataxia and primary immunodeficiency in childhood

*Ataxia-telangiectasia: uma causa importante
de ataxia progressiva e imunodeficiência primária na infância*

Gleyson da Cruz Pinto¹, Mara Morelo Rocha Felix², Suely Rodrigues dos Santos³

ABSTRACT

Ataxia-telangiectasia (AT) is a rare autosomal recessive disorder caused by homozygous or compound heterozygous pathogenic variants in the ataxia telangiectasia mutated (*ATM*) gene, located at the 11q22-23 locus. This gene encodes a serine/threonine kinase involved in DNA double-strand break repair, genomic stability, cell cycle control, and apoptosis. The clinical manifestations of AT include cerebellar ataxia, oculocutaneous telangiectasia, primary immunodeficiency, and an increased risk of malignancies. The global incidence of AT ranges from 1:40,000 to 1:300,000 live births. In this report, we describe the case of a 6-year-old girl referred to the Medical Genetics Service for investigation of ataxia and primary immunodeficiency. She was the only child of a young, healthy, nonconsanguineous couple, with no family history of similar cases, malformations, or genetic diseases. The proband presented with the typical AT phenotype, including progressive gait ataxia in childhood, oculocutaneous telangiectasia, and primary immunodeficiency. The diagnosis of AT was confirmed through next-generation sequencing of the *ATM* gene with copy number variation analysis that identified 2 compound heterozygous pathogenic variants.

Keywords: Ataxia-telangiectasia, primary immunodeficiency diseases, DNA breaks, double-stranded, neoplasms.

RESUMO

A ataxia-telangiectasia (AT) é uma doença rara de herança autossômica recessiva causada pela presença de variantes patogênicas em homozigose ou heterozigose composta no gene *ATM*. Este gene, localizado na região cromossômica 11q22-23, codifica uma serina/treonina quinase, cujas funções estão relacionadas ao reparo de quebras de fita dupla do DNA, estabilidade genômica, controle do ciclo celular e apoptose. As manifestações clínicas são caracterizadas por ataxia cerebelar, telangiectasia oculocutânea, imunodeficiência primária e risco aumentado de malignidades. A incidência global de AT é de 1:40.000 a 1:300.000 nascimentos. Probanda, do sexo feminino, 6 anos, encaminhada ao serviço de Genética Médica para investigação de ataxia e imunodeficiência primária. Filha única de casal jovem, saudável, não consanguíneo, sem histórico familiar de outros casos semelhantes, malformações ou doenças genéticas. A probanda apresenta o fenótipo típico de AT com ataxia de marcha progressiva de início na infância, telangiectasia oculocutânea e imunodeficiência primária. O diagnóstico de AT foi confirmado através do sequenciamento por NGS (*Next-Generation Sequencing*) do gene *ATM* com análise de CNV (*Copy Number Variation*) que identificou duas variantes patogênicas em heterozigose composta.

Descritores: Ataxia telangiectasia, doenças da imunodeficiência primária, quebras de DNA de cadeia dupla, neoplasias.

Introduction

Ataxia-telangiectasia (AT) (OMIM #208900) was first described by Madame Louis-Bar in 1941 as a syndrome characterized by progressive cerebellar

ataxia and oculocutaneous telangiectasia.¹ In 1957, Boder and Sedgwick documented 7 patients from the same family who exhibited increased susceptibility

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to recurrent pulmonary infections in association with the symptoms described above.² That same year, Wells and Shy reported cases of progressive familial choreoathetosis associated with cutaneous telangiectasia.³

AT is a rare autosomal recessive disorder caused by homozygous or compound heterozygous pathogenic variants in the ataxia telangiectasia mutated (*ATM*) gene, located at the 11q22–23 locus.⁴ The ATM protein, a serine/threonine kinase, is involved in several molecular processes, being particularly important in DNA double-strand break repair, genomic stability, cell cycle control, and apoptosis.^{5,6}

The clinical manifestations of AT are multisystemic and generally include progressive cerebellar ataxia in childhood, oculocutaneous telangiectasia, primary immunodeficiency, oculomotor apraxia, and sensitivity to ionizing radiation.⁷ In addition, there is an increased lifetime risk of various neoplasms (such as leukemia and lymphomas), particularly in childhood, and cancers, including breast (in women and men), ovarian, pancreatic, gastric, colorectal, prostatic, and melanoma (Table 1).⁸ Other findings that have also been described in patients with AT include pulmonary disease, recurrent sinopulmonary infections, diabetes mellitus, growth failure, delayed puberty, and gonadal dysfunction.^{9–11} The incidence of AT ranges from 1:40,000 to 1:300,000 live births.¹² In Brazil, as in other South American countries, the incidence remains unknown due to underreporting.¹³ Here,

we report the case of a patient diagnosed with AT in childhood.

Case report

A 6-year-old girl was referred to the Medical Genetics Service by the Immunology Department for investigation of ataxia and primary immunodeficiency. At age 1, she experienced an episode of bronchiolitis that required hospitalization. At age 2, she began to show progressive cerebellar ataxia and recurrent skin infections secondary to insect bites. Between the ages of 4 and 5, she had recurrent episodes of pneumonia and upper respiratory tract infections, which were treated on an outpatient basis.

The patient was the only child of a healthy, nonconsanguineous couple, with no family history of similar cases, malformations, or genetic diseases. Pregnancy was uneventful, and the patient was delivered vaginally at 39 weeks of gestation, with no signs of perinatal asphyxia (Apgar scores of 9 and 9 at 1 and 5 minutes, respectively). Her birth weight was 2.78 kg (10th–25th percentile), length 47 cm (10th–25th percentile), and head circumference 33 cm (25th–50th percentile), all within normal ranges for the gestational age. There were no perinatal complications, and the patient was discharged from the maternity ward at 2 days old. Neuropsychomotor development milestones during the first year of life were also within the expected range for her age.

Clinical and morphological examination showed normal height, normocephaly, and Tanner stages M1/P1. However, the patient also exhibited gait ataxia, head tilting, oculomotor apraxia, oculocutaneous telangiectasia (Figure 1), slurred speech, hypoplastic nasal alae, and left clubfoot.

Genetic analysis identified a karyotype of 46,XX [10]. Sequence analysis of the *ATM*, including copy number variation (CNV) analysis, identified two heterozygous pathogenic variants: c.3894dup (p.Ala1299Cysfs*3) and c.3802del (p.Val1268*). Additional examinations of the proband are described in Table 2.

Following initiation of human immunoglobulin (Ig) therapy for immunodeficiency, there was a significant reduction in the frequency of infectious episodes. Despite this, the levels of IgA, IgE, and IgG (including the IgG1, IgG2, and IgG3 subclasses) remained low, whereas α -fetoprotein levels were significantly elevated. Gait ataxia worsened, leading to significant fatigue during ambulation, with a wheelchair being

Table 1

Neoplasms with increased risk in patients with AT

Type of cancer	Probability
Female breast – invasive ductal carcinoma	2.03
Female breast – ductal carcinoma <i>in situ</i>	1.80
Male breast	1.72
Ovarian	1.57
Pancreatic	4.21
Gastric	2.97
Colorectal	1.49
Prostatic	2.58
Melanoma	1.46



Figure 1
Ocular telangiectasia in the proband

required for distances > 100 m. Additional symptoms included dysphagia for liquids (with frequent choking), sialorrhea, and difficulties with speech, writing, and drawing. Bilateral tympanoplasty was performed to treat recurrent otitis media, yielding good results.

The patient is currently undergoing integrated rehabilitation therapy with a multidisciplinary team, including motor and respiratory physical therapy and nutritional support, as well as interdisciplinary follow-up involving pediatrics, pulmonology, immunology, genetics, and neurology.

Discussion

The rarity of AT makes its diagnosis challenging. Clinical suspicion should be considered in children who present with early-onset progressive gait ataxia, oculocutaneous telangiectasia, and recurrent sinopulmonary infections. However, AT exhibits phenotypic variability, with some patients manifesting milder symptoms only in adulthood. These cases, referred to as “atypical AT,” are generally associated with a longer life expectancy.¹⁴ The diagnosis of AT is primarily based on clinical features and then confirmed through molecular techniques that detect homozygous or compound heterozygous pathogenic variants of the *ATM* gene.¹⁵ In few cases, AT may involve chromosomal alterations, such as translocation between chromosomes 7p and 14q, which can

be visualized by karyotyping. It may also involve submicroscopic alterations, such as microdeletions or microduplications in the DNA segment, which can be identified using techniques such as multiplex ligation-dependent probe amplification or array comparative genomic hybridization.^{16,17} Furthermore, reports have demonstrated that during karyotyping, the presence of breakage sites in bands 2p11, 2p12, 7p14, 7q35, 14qter, and 22q11-q12 have been implicated in AT, within the detection limits of standard light microscopy.^{18,19}

Table 2
Additional examinations of the proband

Test	Results	Reference ranges
α -Fetoprotein	509.5 μ g/L	< 7.5 μ g/L
Glucose	77 mg/dL	70-99 mg/dL
Hb1Ac	5.7%	< 5.7%
TSH	3.95 mUI/L	0.9-6.5 m IU/L
Free T4	1.37 ng/dL	0.7-1.8 ng/dL
AST	35 U/L	5-40 U/L
ALT	22 U/L	7-56 U/L
IgA	7 mg/dL	15-250 mg/dL
IgM	45.2 mg/dL	45-300 mg/dL
IgE	< 1 UI/mL	$\leq$ 52 IU/mL
IgG	51 mg/dL	340-1,600 mg/dL
IgG1	47 mg/dL	288-918 mg/dL
IgG2	< 2 mg/dL	44-375 mg/dL
IgG3	6.8 mg/dL	15-85.3 mg/dL
IgG4	0.7 mg/DI	0.4-99.2 mg/dL
Absolute CD19	27/ μ L	236-646/ μ L
CD19%	4.2%	9.7-20.7%
Absolute CD3	399/ μ L	1,260-2,610/ μ L
CD3%	61.4%	61.1-77.4%
CH50, Complement	79.61 U/mL	41.68-95.06 U/mL
C3, Complement	139 mg/dL	90-180 mg/dL
C4, Complement	25.2 mg/dL	10-40 mg/dL
Vitamin B12	999 pg/mL	197-771 pg/mL
Anti-HIV antibody	Nonreactive	Nonreactive

The AT phenotype observed in our patient corresponded to that described in the literature, including early-onset progressive gait ataxia, oculocutaneous telangiectasia, oculomotor apraxia, slurred speech, primary immunodeficiency, and recurrent sinopulmonary infections. These findings supported the suspicion and clinical diagnosis of AT. The patient's karyotype was normal, consistent with the lack of consanguinity between the parents and the absence of other cases in the family. However, because this test does not detect microdeletions, microduplications, or submicroscopic rearrangements, the diagnostic investigation was expanded to include sequence analysis of the *ATM* gene and CNV analysis. This approach identified 2 compound heterozygous pathogenic variants, thereby confirming the diagnosis of AT.

There is currently no treatment for AT, although therapeutic trials are underway.²⁰ Because AT may present a wide variety of clinical manifestations, patients should receive counseling from a multidisciplinary team involving a pediatrician, neurologist, geneticist, immunologist, pulmonologist, endocrinologist, hematologist, oncologist, and nutritionist.²¹ Addressing specific AT-related symptoms is crucial. Patients and parents should be advised to avoid exposure to harmful factors, such as ionizing radiation (unnecessary exposure to sunlight, radiography, and computed tomography), and to monitor for signs or symptoms suggestive of malignancy. Immunizations with inactivated vaccines are safe for all individuals with AT and should be performed to prevent infections. However, rubella vaccination should be avoided in those with severe immunodeficiency due to the increased risk of granuloma formation.²² These measures can improve quality of life, prolong survival, and minimize potentially fatal complications.

Genetic counseling and risk estimation for familial recurrence was not possible because the parents were divorced, precluding the sequencing of the *ATM* gene in both parents to determine whether the proband's pathogenic variants were inherited or the result of a *de novo* mutation. Given that the genetic alterations found in the proband were compound heterozygous, the possibility of new variants cannot be excluded, underscoring the need for parental sequencing. Since AT has an autosomal recessive pattern of inheritance, the couple theoretically has a 25% risk of recurrence with each pregnancy.

References

1. Louis-Bar D. Sur un syndrome progressif comprenant des télangiectasies capillaires cutanées et conjonctivales symétriques, à disposition naevoïde et des troubles cérébelleux. *Confin Neurol*. 1941;4:32-42.
2. Boder E, Sedgwick RP. Ataxia-telangiectasia: familial syndrome of progressive cerebellar ataxia, oculocutaneous telangiectasia and frequent pulmonary infection. *Univ Southern Calif Med Bull*. 1957;9:15-27.
3. Wells CE, Shy GM. Progressive familial choreoathetosis with cutaneous telangiectasia. *J Neurol Neurosurg Psychiatr*. 1957;20:98-104.
4. Gatti RA, Berkel I, Boder E, Braedt G, Charmley P, Concannon P, et al. Localization of an ataxia-telangiectasia gene to chromosome 11q22-23. *Nature*. 1988;336(6199):577-80.
5. Lee JH, Paull TT. Cellular functions of the protein kinase ATM and their relevance to human disease. *Nat Rev Mol Cell Biol*. 2021;796-814.
6. Blackford AN, Jackson SP. ATM, ATR, and DNA-PK: The Trinity at the Heart of the DNA Damage Response. *Mol Cell*. 2017;66(6):801-17.
7. Amirifar P, Ranjouri MR, Yazdani R, Abolhassani H, Aghamohammadi A. Ataxia-telangiectasia: A review of clinical features and molecular pathology. *Pediatr Allergy Immunol*. 2019 May;30(3):277-88.
8. Hall MJ, Bernhisel R, Hughes E, Larson K, Rosenthal ET, Singh NA, et al. Germline Pathogenic Variants in the Ataxia Telangiectasia Mutated (ATM) Gene are Associated with High and Moderate Risks for Multiple Cancers. *Cancer Prev Res (Phila)*. 2021 Apr;14(4):433-40.
9. McGrath-Morrow SA, Rothblum-Oviatt CC, Wright J, Schlechter H, Lefton-Greif MA, Natale VA, et al. Multidisciplinary Management of Ataxia Telangiectasia: Current Perspectives. *J Multidiscip Healthc*. 2021 Jun 28;14:1637-44.
10. Donath H, Hess U, Kieslich M, Theis M, Ohlenschläger U, Schubert R, et al. Diabetes in Patients With Ataxia Telangiectasia: A National Cohort Study. *Front Pediatr*. 2020;8:317.
11. Nissenkorn A, Levy-Shraga Y, Banet-Levi Y, Lahad A, Sarouk I, Modan-Moses D. Endocrine abnormalities in ataxia telangiectasia: findings from a national cohort. *Pediatr Res*. 2016;79(6):889-94.
12. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: a review. *Orphanet J Rare Dis*. 2016;11(1):159.
13. Petley E, Yule A, Alexander S, Ojha S, Whitehouse WP. The natural history of ataxia-telangiectasia (A-T): A systematic review. *PLoS One*. 2022 Mar 15;17(3):e0264177.
14. Lee HY, Jang DH, Kim JW, Lee DW, Jang JH, Joo J. Compound heterozygous variants including a novel copy number variation in a child with atypical ataxia-telangiectasia: a case report. *BMC Med Genomics*. 2021;14(1):204.
15. Shamriz O. Novel Approach for Screening and Early Diagnosis of Ataxia-Telangiectasia. *J Allergy Clin Immunol Pract*. 2021;9(2):733-4.
16. Cavalieri S, Funaro A, Pappi P, Migone N, Gatti RA, Brusco A. Large genomic mutations within the ATM gene detected by MLPA, including a duplication of 41 kb from exon 4 to 20. *Ann Hum Genet*. 2008 Jan;72(Pt 1):10-8.
17. Moeini Shad T, Yazdani R, Amirifar P, Delavari S, Heidarzadeh Arani M, Mahdavian SA, et al. Atypical Ataxia Presentation in Variant Ataxia Telangiectasia: Iranian Case-Series and Review of the Literature. *Front Immunol*. 2022 Jan 14;12:779502.
18. Gatti RA, Aurias A, Griscelli C, et al. Translocations involving chromosomes 2p and 22q in ataxia-telangiectasia. *Dis Markers*. 1985;3:169-95.
19. Aurias A, Dutrillaux B. A possible new type of chromosome rearrangement: telomere-centromere translocation (tct) followed by double duplication. *Hum Genet*. 1986;72:25-6.

20. Veenhuis SJG, van Os NJH, Janssen AJWM, van Gerven MHJC, Coene KLM, Engelke UFH, et al. Nicotinamide Riboside Improves Ataxia Scores and Immunoglobulin Levels in Ataxia Telangiectasia. *Mov Disord*. 2021 Dec;36(12):2951-7.
21. van Os NJH, Haaxma CA, van der Flier M, Merkus PJFM, van Deuren M, de Groot IJM, et al.; A-T Study Group. Ataxia-telangiectasia: recommendations for multidisciplinary treatment. *Dev Med Child Neurol*. 2017 Jul;59(7):680-9.
22. Buchbinder D, Hauck F, Albert MH, Rack A, Bakhtiar S, Shcherbina A, et al. Rubella Virus-Associated Cutaneous Granulomatous Disease: a Unique Complication in Immune-Deficient Patients, Not Limited to DNA Repair Disorders. *J Clin Immunol*. 2019 Jan;39(1):81-9.

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Provocation tests in cholinergic urticaria: unmet needs

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Dear Editor,

Urticaria is a skin disease defined by the development of hives, angioedema, or both. Hives are erythematous, edematous lesions of variable size, characterized by intense itching, which occur in reaction to vasodilation and increased vascular permeability in the superficial dermis. They are fleeting, with the skin returning to normal appearance within 30 minutes to 24 hours, without leaving any residual lesions. Angioedema presents as sudden, marked edema of the deep dermis, subcutaneous tissue, or mucous membranes, characterized by pain and a burning sensation rather than itching, and resolving gradually within 72 hours.

Depending on the duration of its clinical manifestations, urticaria is classified as acute (less than 6 weeks) or chronic (greater than or equal to 6 weeks). Chronic urticaria can occur spontaneously or be induced by specific stimuli, which are diagnosed through provocation tests with external triggers.

Chronic inducible urticarias (CIndUs) can be subdivided according to the triggering external stimulus as physical (dermographism, delayed pressure urticaria, cold-, heat-, solar and vibratory urticaria) or non-physical (adrenergic, contact, aquagenic, and cholinergic urticaria). Cholinergic urticaria (CholU) is triggered by a systemic increase in body temperature with consequent sweating—unlike some of its differential diagnoses, such as heat urticaria (HU), which has localized external heat as its primary trigger, or solar urticaria (SU), which is due to exposure to UVA, UVB, or visible light.

CholU was first described by Duke in 1924 and is characterized by the onset of highly pruritic or painful

micropapular lesions with surrounding erythema in the context of increased core body temperature as a result of physical exercise, hot baths, emotional stress, or intake of spicy foods or hot beverages. The lesions of CholU are approximately 1 to 3 mm in size and can occur anywhere on the body, except the palmoplantar and axillary regions. Nevertheless, they mainly affect the trunk and upper limbs. These small papules may coalesce to form large wheals. Symptoms are usually rapidly evanescent, lasting no more than 1 hour. They may worsen with higher ambient temperatures, although some patients report the onset of lesions even in low-temperature environments, especially during physical activity.

CholU is incident and prevalent predominantly between the second and third decades of life. There is no difference in prevalence between males and females. Some studies suggest an estimated overall prevalence of 4.1–11.2% in the general population.

A study with 111 participants sought to characterize the unmet medical needs of patients regarding assessment and follow-up of CholU in German-speaking countries. The authors conducted an online survey on symptoms, delay in diagnosis, impact on activities of daily living, quality of life, and experience of medical care. Although virtually all patients reported typical signs and symptoms of CholU, they reported a significant diagnostic delay of 30.2 months (range 0 to 279 months). Only 16% underwent provocation testing, demonstrating the lack of practical diagnostic tests. Ninety percent of patients reported having uncontrolled disease, resulting in severe impact on their everyday activities, sleep, and quality of life. This study reveals a pressing need for improvements in the diagnostic workup and care of patients with this condition, as well as better treatment options.¹

The etiology of each CholU subtype is gradually being investigated and elucidated, but its overall pathophysiology is still not fully understood. It is believed to involve acetylcholine, pore occlusion, the M3 cholinergic receptor (CHRM3), allergy to sweat components, serum inflammatory factors, and dyshidrosis, and each CholU subtype has been suggested to involve different or mixed causes. Despite numerous gaps in the proposed pathophysiology of CholU, four subtypes have been proposed: type I, CholU with sweat allergy; type II, follicular-

type CholU; type III, CholU with palpebral angioedema (CholU-PA); and type IV, CholU with acquired anhidrosis and/or hypohidrosis.² Histamine is a mediator involved in a similar manner in all reported CholU subtypes.

Unlike in other types of urticaria, many patients with CholU complain of paresthesias, which have a major impact on quality of life. CholU is a disease that drastically alters the individual's concept of biopsychosocial well-being, as it markedly reduces quality of life, favors indiscriminate self-medication, and predisposes to absenteeism. CholU is incident and prevalent predominantly between the second and third decades of life. Lesions tend to last 15 to 60 minutes and may be associated with local angioedema. When CholU is suspected, it is essential to distinguish it from exercise-induced anaphylaxis, aquagenic urticaria, cold-induced CholU, HU, and SU.¹⁻²

Provocation testing to confirm CholU also aims to rule out the diagnosis of exercise-induced anaphylaxis. Caution should be exercised when performing this test on individuals with heart disease and in patients with presentations other than the classical skin lesions. It is generally agreed that an increase in body temperature above 1 °C from baseline, as indicated by a passive warming test (sitting for ≤ 15 min in a 42 °C water bath), confirms the diagnosis of CholU.²

A standardized protocol has been proposed to diagnose and measure CholU thresholds, using a cycle ergometer with heart rate and temperature monitoring. The test is performed by ergometry with heart rate control. The patient mounts the cycle ergometer and starts pedaling, after being instructed that the pulse should rise by 15 bpm every 5 minutes, reaching 90 bpm above baseline within 30 minutes. Body temperature is also measured throughout the test. The time to onset of urticaria is inversely proportional to disease severity, i.e., the sooner lesions appear, the more severe the patient's CholU.³

CholU is extremely detrimental to the biopsychosocial well-being of affected individuals, and provocation tests and other diagnostic tools that can be easily reproduced in settings outside specialist referral centers are still lacking. There is a pressing need for novel low-cost, low-tech, safe techniques with good reproducibility that can supplement diagnosis by specialist physicians in private outpatient clinics or in primary health care, especially in the context of the Unified Health System and in other developing countries.

References

1. Mellerowicz E, Weller K, Zuberbier T, Maurer M, Altrichter S. Real-life treatment of patients with cholinergic urticaria in German-speaking countries. *J Dtsch Dermatol Ges.* 2019 Nov;17(11):1141-7.
2. Fukunaga A, Oda Y, Imamura S, Mizuno M, Fukumoto T, Washio K. Cholinergic Urticaria: Subtype Classification and Clinical Approach. *Am J Clin Dermatol.* 2022 Sep 15:1-14.
3. Altrichter S, Salow J, Ardelean E, Church MK, Werner A, Maurer M. Development of a standardized pulse controlled ergometry test for diagnosing and investigating cholinergic urticaria. *J Dermatol Sci.* 2014;75(2):88-93.

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Connecting Allergy and Dentistry: we need to build bridges

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Dear Editor,

An article published in the March 2024 issue of the Journal of The American Dental Association, titled “Gingival hypersensitivity reactions to toothpastes”, recently caught our attention. It is worth noting that JADA is a high-impact journal, indexed in the Scopus database (CiteScore 5.0) and published by the prestigious American Dental Association. The article itself is a case series and literature review¹. It stood out to us because it showed us that it is not only our specialty of allergology—nor exclusively the medical profession—that is interested in allergic diseases. We’re forgetting the dentists!

The aforementioned article includes 11 patients from a Spanish referral center, the majority of whom were women (72.7%) with hypersensitivity to “cinnamon”. The most frequently diagnosed lesion was gingival redness with itching or mild discomfort. Toothpaste was implicated in the pathogenesis of the symptoms, as discontinuing it led to the disappearance of the lesions. Several different toothpastes were implicated. The authors contextualize that dental practitioners may encounter type I (IgE-mediated) and type IV (T-cell-mediated) hypersensitivity reactions. Delayed hypersensitivity reactions are most common, and are usually known as contact stomatitis.¹ Remarkably, in the referral-center setting at which the authors work, even with strong clinical suspicion and probable intention to publish, patch testing was only performed in approximately half of the cases, and in many cases with toothpaste alone. The most pertinent question is: how would we react to cases like these in Brazil?

It is acknowledged that hypersensitivity reactions to dentifrices are unusual. This is because toothpaste is continuously diluted in water and saliva during tooth-brushing.¹ However, it is important to note that toothpaste formulations are quite complex, containing multiple ingredients. These include mild abrasives, fluorides, humectants, flavorings, artificial sweeteners, thickening agents, dyes, and surfactants.² These formulations also vary widely depending on the manufacturer. Therefore, when involvement is suspec-

ted, testing with the patient’s toothpaste is essential. This maxim applies to the management of contact dermatitides in general: testing must be performed with the patient’s own product! However, allergists know that testing with undiluted toothpaste alone can cause false-positive reactions. Renowned expert Anton de Groot advises that a semi-open or occlusive test be carried out initially with undiluted toothpaste. However, as noted above, if this test is positive, it does not conclusively demonstrate an allergy. The toothpaste should be additionally tested in serial dilutions (100%, 50%, and 20%, diluted in petroleum jelly or water) and/or tested in controls. Challenge and rechallenge may also be useful to demonstrate whether a positive test is clinically significant.² The allergist is the professional who is most qualified for (and familiar with) performing such dilutions for patch testing procedures.

However, patient counseling can only be considered complete when each ingredient is tested on its own in an attempt to identify the offending chemical trigger.² The Spanish study cited the article that endorsed the launch of the standard Latin American series adapted for patch testing in Brazil.³ This series unquestionably represented a major step forward in updating our old Brazilian standard battery. As an example of the importance of this adaptation, a recent study identified the substances most often associated with sensitization in patients with oral diseases. Sodium tetrachloropalladate was the most commonly implicated substance, with a remarkable positivity rate of over 27% among tested patients. For comparison purposes, nickel sulfate came second with 23% positivity.⁴ This chloropalladate salt, which represents the element palladium, is also in the Latin American series. The adapted series also includes propolis, a leading cause of allergic cheilitis. The North American Contact Dermatitis Group (NACDG) lists propolis as one of the most prevalent such substances, with an 8.6% positivity rate.⁵ There is also growing concern regarding propolis in Europe, and it has already been incorporated into the European baseline series.⁶ Reports of perioral lesions caused by propolis first emerged in Brazil with the advent of the Latin American series.⁷ We believe there were no previous reports of such a diagnosis because this substance is not regularly tested in our country. Allergists need to show dentists that we are used to performing patch tests with this series, which can mean elucidating the specific etiologic agent implicated in a case of oral pathology.

In addition, we currently have very good supplemental patch test series available for use in situations such as this. The dental series, which is made to order by an established manufacturer of extracts for patch testing, is very similar to an equivalent series available in Europe,⁸

which shows we are no longer limited to standard batteries alone (Table 1). An analysis of this series shows that acrylates and certain metals commonly used in dentistry predominate. These substances greatly broaden diagnostic possibilities for dentists who treat patients with hypersensitivity reactions.

A review of the current specialized literature shows many cases that demonstrate the importance of supple-

mental specialist series. For instance, one published case reports an 8-year-old child who presented with a 1-year history of cheilitis. Topical treatments were tried but improvement was only seen during use; when discontinued, the lesions recurred. The patient denied using lipstick and the like. His condition caused anxiety in the family. Intraoral examination revealed 4 metal crowns. Laboratory tests were within normal limits. A patch test was then performed,

Table 1

Patch test battery, dental series^a

Série dental	Concentração	Veículo
1. Methyl methacrylate	2%	Petroleum jelly
2. Triethylene glycol dimethacrylate	2%	Petroleum jelly
3. Diurethane dimethacrylate	2%	Petroleum jelly
4. Ethylene glycol dimethacrylate	2%	Petroleum jelly
5. Bisphenol A diglycidyl dimethacrylate	2%	Petroleum jelly
6. <i>N,N</i> -Dimethyl- <i>p</i> -toluidine	5%	Petroleum jelly
7. Benzophenone 3 (Oxybenzone)	10%	Petroleum jelly
8. 1,4-Butanediol dimethacrylate	2%	Petroleum jelly
9. Bisphenol A dimethacrylate	2%	Petroleum jelly
10. Potassium bichromate	0.5%	Petroleum jelly
11. Cobalt chloride	1%	Petroleum jelly
12. 2-Hydroxyethyl methacrylate (2-HEMA)	2%	Petroleum jelly
13. Nickel sulphate	5%	Petroleum jelly
14. Eugenol	2%	Petroleum jelly
15. Colophon	20%	Petroleum jelly
16. Formaldehyde	2%	Water
17. <i>p</i> -Tolyldiethanolamide	2%	Petroleum jelly
18. Copper sulfate	2%	Petroleum jelly
19. Methyl hydroquinone	1%	Petroleum jelly
20. Palladium chloride	2%	Petroleum jelly
21. Aluminum chloride	2%	Petroleum jelly
22. Camphorquinone (bornanedione)	1%	Petroleum jelly
23. (Dimethylamino)ethyl methacrylate	0.2%	Petroleum jelly
24. 1,6-Hexanediol diacrylate	0.1%	Petroleum jelly
25. Drometrizole (2(2'-hydroxy 5'-methylphenyl) benzotriazole)	1%	Petroleum jelly
26. Tetrahydrofurfuryl methacrylate	2%	Petroleum jelly
27. Tin	50%	Petroleum jelly
28. Sodium tetrachloropalladate	3%	Petroleum jelly
29. Carvone	5%	Petroleum jelly
30. Glutaraldehyde	0.2%	Petroleum jelly

^a IPI ASAC BRASIL® patch test battery: dental series.

which was consistent with nickel sensitivity. The patient denied any contact with metal instruments. Therefore, the decision was made to replace the alloy crowns with composite resin ones; within 2 weeks, there was complete remission of the patient's condition.⁹

Cases of sensitivity to acrylates are even more common. One published example is a 41-year-old Japanese woman who used a gingival protection product during teeth whitening. A second treatment session occurred a week later. The next day, the patient developed gingival ulcerations with purpura and lip edema. A clinical diagnosis of contact dermatitis was made and she underwent patch testing, which was positive for two acrylates and three methacrylates. The gingival protection agent contained 2-hydroxyethyl methacrylate. The absence of symptoms during the initial treatment, followed by a severe reaction after the second application, suggests that the patient was sensitized during her first contact with the product. Cross-reactivity between methacrylates is to be expected.¹⁰

The oral cavity should be carefully studied by a physician or dentist whenever any type of lesion is discovered on the oral mucosa or tongue. The lips and perioral region should not be overlooked. This investigation should include a detailed history and immunoallergic workup. When properly indicated, patch testing should be performed with a standard series followed by a dental series as well as the patient's own products.

We must strengthen our ties with the dental profession. We need dentists to be both familiar with our specialty and aware that we are able to help them address these symptoms when they present. Indeed, we know that dentists are often the first to notice such conditions in their patients. Allergists, in turn, need our Society to act by making this connection—for instance, by promoting lectures for dentists across the states of Brazil, demonstrating our expertise and the excellent work we already do and are in the constant pursuit of improving.

It's time to build bridges...

References

1. López-Pintor RM, González-Serrano J, Ivaylova Serkedzhieva K, Serrano Valle J, de Arriba L, Hernández G, et al. Gingival hypersensitivity reactions to toothpastes. *J Am Dent Assoc.* 2024;155(3):213-226.e3. doi:10.1016/j.adaj.2023.11.003.
2. de Groot A. Contact Allergy to (Ingredients of) Toothpastes. *Dermatitis.* 2017;28(2):95-114. doi:10.1097/DER.000000000000255.
3. Belluco PES, Giavina-Bianchi P, Belluco RZF, Novaes MRCG, Reis CMS. Prospective study of consecutive patch testing in patients with contact dermatitis using an adapted Latin American baseline series. *Eur Ann Allergy Clin Immunol.* 2023;55(05):235. doi:10.23822/EurAnnACI.1764-1489.250.
4. Al-Gawahiri M, Rustemeyer T, Franken SM, van Zuuren EJ, Ipenburg NA. Frequency and clinical relevance of contact allergy in dental patients. *Contact Dermatitis.* 2024;90(1):66-73. doi:10.1111/cod.14440.
5. Dekoven JG, Warshaw EM, Reeder MJ, Atwater AR, Silverberg JI, Belsito D V, et al. North American Contact Dermatitis Group Patch Test Results: 2019-2020. *Dermatitis.* 2023;34(2):90-104. doi:10.1089/derm.2022.29017.jdk
6. Wilkinson M, Gonçalo M, Aerts O, Badulici S, Bennike NH, Bruynzeel D, et al. The European baseline series and recommended additions: 2019. *Contact Dermatitis.* 2019;80(1):1-4. doi:10.1111/cod.13155.
7. Belluco PES, Belluco RZF, Reis CMS. Allergic contact cheilitis caused by propolis: case report. *Einstein (Sao Paulo).* 2022;20:eRC6151. https://doi.org/10.31744/einstein_journal/2022RC6151.
8. Chemotechnique Diagnostics. Patch Test Products & Reference Manual. 2024 [Internet]. Available from: <https://www.chemotechnique.se/ckfinder/userfiles/files/Katalog%202024%20w%20cover2.pdf>.
9. Zeng Q, Wang S, Cheng L, Mu J, Yang J, Zhou H. Allergic contact cheilitis caused by nickel from stainless steel crowns in primary molars: An easily overlooked intraoral allergen in children? *Contact Dermatitis.* 2023;89(6):505-7. doi:10.1111/cod.14413.
10. Hayakawa M, Baba Y, Kouno M. Allergic Contact Stomatitis Caused by (Meth)acrylates in a Gingival Protection Product Used During Teeth Whitening. *Dermatitis®.* 2024;35(1):96-8. doi:10.1089/derm.2023.0180.

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The role of the ASBAI's Academic League Committee in medical training

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Dear Editor,

The Brazilian Undergraduate National Curriculum Guidelines for Medicine require Higher Education Institutions to adapt their curriculum frameworks to cover all pillars of education during the training process, in accordance with the needs of the academic community.¹

In the quest to acquire skills for future professional performance, it is important that students have the opportunity to experience and learn care pertinent to disease prevention and health promotion, in order to develop an active, critical, innovative, and evidence-based viewpoint.^{2,3}

In recent years, there has been a considerable increase in the number of academic leagues operating in undergraduate medical schools in Brazil, with the same occurring in the Allergy and Immunology medical specialty. Although there is no consensus in the literature on the definition of academic league, both the Brazilian National Executive Board of Medical Students and the Brazilian Association of Academic Leagues seem to agree that an academic league is a student association that adopts the university tripod as a reference: teaching, research, and extension.^{4,5}

Therefore, the importance of academic leagues for health training is highlighted, including the Allergy and Immunology specialty, since the participation of medical students in these leagues helps broaden their view of health care as professionals. Following this premise, in September 2021 the Brazilian Association of Allergy and Immunology (ASBAI) created the ASBAI Program for Allergy and Immunology Academic Leagues. The Program aims to bring together students who express an interest in advancing their knowledge of the Allergy and Immunology specialty while still in medical school.⁶

The activities developed in the Program are coordinated by the Academic League Committee, which

is subordinate to the Teaching and Service Accreditation Committee. The Academic League Committee consists of expert associates who coordinate Immunoallergy academic leagues in their institutions. The league members play a key role in the development of activities that adopt the university tripod (teaching, research, and extension) as a reference. These activities include discussion of clinical cases through webinars [teaching], preparation of guides on the management of allergic and immunologic diseases for general practitioners, primary care physicians, and emergency physicians [teaching/extension], preparation of information material for the general population [extension], and encouragement of research.

Brazil is a country of continental size with a health system that operates in a heterogeneous and complex manner, requiring a broader vision capable of incorporating individuals in all their dimensions. The gathering of students from various parts of the country around the learning of Allergy and Immunology must ensure a dialogue between the different forms of knowledge.

Finally, the ASBAI Program for Allergy and Immunology Academic Leagues has occupied a major place in the teaching-learning process of undergraduate students. In this respect, a constant dialogue between the participants in this process is necessary to recognize learning needs and enhance these complementary strategies for health training, especially the growth of the Allergy and Immunology specialty.

References

1. Brasil, Ministério da Educação, Conselho Nacional de Educação. Resolução nº 3, de 20 de junho de 2014. Institui Diretrizes Curriculares Nacionais do Curso de Graduação em Medicina e dá outras providências. Diário Oficial da União; 23 jun 2014. Seção 1, p. 8-11.
2. Franco CAGS, Cubas MR, Franco RS. Currículo de medicina e as competências propostas pelas diretrizes curriculares. *Rev Bras Educ Med.* 2014;38(2):221-30.
3. Misael JR, Santos Júnior CJ dos, Wanderley FAC. Ligas acadêmicas e formação médica: validação de um instrumento para avaliação e percepção discente. *Rev Bras Educ Med.* 2022;46(1):e014.
4. Direção Executiva Nacional dos Estudantes de Medicina (DENEM). Coordenação Científica. Ligas acadêmicas [Internet]. Julho 2014. Available from: <http://www.denem.org.br/cartilhas/Cartilha-Ligas-Acade%CC%82micas-CoCien.pdf>.
5. Associação Brasileira de Ligas Acadêmicas (ABLAM). [Internet]. Available from: www.ablam.org.br/diretrizes-nacionais/.
6. Associação Brasileira de Alergia e Imunologia (ASBAI). Programa da ASBAI para Ligas Acadêmicas de Alergia e Imunologia [Internet]. Available from: www.asbai.org.br/programa-da-asbai-para-ligas-academicas-de-alergia-e-imunologia/.

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An update on the treatment of hereditary angioedema in Brazil

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Dear editor,

Given the recent changes in treatment of hereditary angioedema (HAE) in Brazil, we understand that it is extremely important to update the information of the latest Brazilian Guidelines for Hereditary Angioedema (2022).¹

HAE is characterized by recurrent edema of the subcutaneous and submucosal tissues. It affects the face, extremities, genitals, and gastrointestinal and respiratory tracts, and can even lead to death when affecting the upper airways.² Angioedema results from an uncontrolled release of bradykinin, which binds to its receptor on the vascular endothelium, resulting in plasma leakage. Growing knowledge about the mechanisms involved in the pathogenesis of HAE has enabled the development of new therapies.³

Drug treatment for HAE is divided into on-demand and short- and long-term prophylaxis. The goal of long-term prophylaxis should be to completely control the disease and normalize the patient's quality of life. Several drugs have been approved for long-term HAE prophylaxis, with national and international guidelines classifying them as first- or second-line therapies according to their safety profile and evidence of efficacy. Brazilian and international guidelines, both updated in 2022, include intravenous and subcutaneous plasma-derived C1 inhibitor (pdC1INH) and lanadelumab as first-line therapies for long-term prophylaxis. Although the international guidelines also include berotralstat among the main therapies for long-term prophylaxis, the Brazilian guidelines do not, since, at the time of publication, this drug had not been approved by the Brazilian National Health Surveillance Agency.^{1,3}

Berotralstat is a small synthetic molecule that specifically inhibits plasma kallikrein. Its pharmacokinetic profile allows a single daily oral dose.⁴ It was licensed in December 2020 by the U.S. Food and Drug Administration, in April 2021 by the European Medicines Agency, and was approved in Brazil in April 2024. It is recommended at a

dose of 150 mg per day in patients 12 years and older who have HAE with C1INH deficiency (HAE-C1INH). Berotralstat demonstrated response from the first month of treatment and, after 6 months, it significantly reduced the monthly frequency of HAE attacks compared to placebo (1.31 versus 2.65; $p < 0.001$). Quality of life scores, although improved, did not statistically differ from placebo. In the phase 3 study of berotralstat, gastrointestinal events, including abdominal pain, vomiting, and diarrhea, were among the most frequently reported adverse effects, although most symptoms were mild and transient. The drug is not recommended during pregnancy and breastfeeding.⁵

Unlike other currently available treatment options, berotralstat is an oral medication, which may help overcome the challenges associated with parenteral medications and improve the quality of life of patients with HAE. A relevant fact about long-term prophylaxis with berotralstat is that it is effective in preventing attacks in patients who have HAE with normal C1INH (HAE-nC1INH) and in those with HAE due to variants in *F12* (AEH-FXII).⁴

Although first-line medications for long-term prophylaxis are available in Brazil, access remains a significant challenge. Most patients with HAE are treated at reference centers associated with the Unified Health System, and <25% of Brazilians have access to supplementary health insurance, making this scenario even more challenging. All first-line medications for long-term prophylaxis of HAE are very expensive and none are incorporated into the Unified Health System, and only second-line therapies available, with no short-term changes expected. Recently, patients with access to supplementary health insurance achieved a victory when lanadelumab was incorporated into the National Supplementary Health Agency list, with coverage being mandatory for adults and adolescents (+12 years) with HAE-C1INH, while pdC1INH, as a blood product, may be covered.

Regarding access to attack treatment, 2 major advances have occurred: the National Commission for the Incorporation of Technologies into the Unified Health System recommended incorporating icatibant and intravenous pdC1INH. This recommendation is reserved for treatment of attacks of HAE-C1INH types I and II, according to an as yet unpublished Ministry of Health protocol.

Despite recent improvements, groups of patients still lack HAE treatment options. The only option for long-term prophylaxis among pregnant and breastfeeding women is pdC1INH (classified as category C by the U.S. Food and Drug Administration). It can also be used for short-term prophylaxis and to treat attacks in this population.

Icatibant is not approved for on-demand treatment in pregnant and breastfeeding women, despite its good safety profile.⁶ The only long-term HAE prophylaxis for children under 12 years of age is intravenous pdC1INH, except for subcutaneous pdC1INH, which can be used in patients 8 years and older. For attacks in this age group, intravenous pdC1INH and icatibant can be used. Pregnant and breastfeeding women and children can use tranexamic acid, but it is less effective for attack prevention and involves thrombosis risk, especially in pregnant women. There is still no approved therapy for HAE-nC1INH.¹

As stated in the latest Brazilian Guidelines for Hereditary Angioedema, several drugs have been developed in recent decades, while several others are in development or are undergoing clinical trials.¹ The authors hope that as treatment possibilities expand, access to these resources be achieved.

References

1. Campos RA, Serpa FS, Mansour E, Alonso MLO, Arruda LK, Aun MV, et al. Diretrizes brasileiras de angioedema hereditário 2022 - Parte 2: terapêutica. Arquivos de Asma, Alergia e Imunologia. 2022;6(2):170-96.
2. Minafra FG, Cunha LAO, Mariano RG de S, Goebel GA, de Lima LS, Pinto JA. Investigation of Mortality of Hereditary Angioedema in a Reference Center in Brazil. J Allergy Clin Immunol Pract. 2022;10:1805-12.
3. Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022;77:1961-90.
4. Johnson F, Stenzl A, Hofauer B, Heppt H, Ebert E-V, Wollenberg B, et al. A Retrospective Analysis of Long-Term Prophylaxis with Berotralstat in Patients with Hereditary Angioedema and Acquired C1-Inhibitor Deficiency-Real-World Data. Clin Rev Allergy Immunol. 2023;65:354-64.
5. Zuraw B, Lumry WR, Johnston DT, Aygören-Pürsün E, Banerji A, Bernstein JA, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: A randomized, double-blind, placebo-controlled phase 3 trial. J Allergy Clin Immunol. 2021;148:164-172.e9.
6. Šimac DV, Štimac T, Novak S. Is Icatibant Safe for the Treatment of Hereditary Angioedema During Pregnancy? Curr Allergy Asthma Rep. 2022;22:135-40.

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