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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Decipher me or I will devour you – Unraveling the enigma of chronic urticaria

Decifra-me ou te devoro – desvendando o enigma da urticária crônica

Fábio Chigres Kuschnir[1]

Decipher me or I will devour you! This was the ultimatum that the sphinx of Thebes, in Ancient Greece, launched to travelers who intended to enter its domains. For those who did not solve the enigma proposed by the mystical creature, the outcome was tragic. Keeping due proportions, chronic urticaria (CU) has always been one of the great challenges of our specialty.

For doctors, specialists or not, the lack of robust evidence on the underlying pathophysiological mechanisms and the large number of possible triggers generated a large number of tests, important dietary restrictions and different therapeutic proposals, many of which focused on the use of high doses of first-generation antihistamines. Most of the time, these strategies proved to be ineffective in the adequate control of the so-called chronic idiopathic urticaria (ICU).[1]

For patients, in addition to the high socioeconomic cost and impact on quality of life due to the symptoms, limitations and side effects imposed by the treatment, it was common to observe an anxious pilgrimage to different medical services in search of the "cure" and origins of the disease.

As the knowledge in molecular mechanisms of ICU increased, especially from the studies of patients undergoing therapy with anti-IgE (omalizumab), it was possible to partially unravel the "enigma" and confirm the hypothesis that a significant portion of cases of the disease was due to auto reactivity and/or autoimmunity, resulting in a nomenclature change to spontaneous chronic urticaria (CSU) in those cases with no specific trigger.[2-4]

These findings had a profound impact on the management of chronic urticaria and angioedema, enabling the development of new subclassifications based on disease biomarkers, as well as changes in clinical, laboratory and therapeutic approaches, widely disseminated through national and international guidelines.[5-6]

In this issue of *Arquivos Brasileiros de Asma, Alergia e Imunologia* (AAAI), the Scientific Department of Urticaria of the Brazilian Association of Allergy and Immunology presents a practical guide in a question/answer format on chronic urticaria in children, the elderly and pregnant women, patient groups considered even more challenging, due to the scarcity of studies in these groups.[7]

Also in this issue of the AAAI, the same Scientific Department addresses in a practical and objective way different aspects of acute urticaria which, despite its high prevalence, is still surrounded by myths, mainly on the part of patients and general practitioners, generating misconduct and fruitless searches by causal agents.[8]

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By revealing some of these "riddles", the two documents help in the diagnostic and therapeutic approach and in the decision-making regarding the challenging urticaria cases that we face in our daily lives.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

The new hereditary angioedema guidelines: what is its role?

As novas diretrizes de angioedema hereditário: qual é o seu papel?

Anete Sevciovic Grumach[1]

Progress in the knowledge and diagnosis of rare diseases has been extraordinary in recent years. In parallel, the interest in establishing treatments for these situations also showed a noticeable improvement. Guidelines on hereditary angioedema (HAE) have been published for over 20 years. Initially, these documents were developed from the experience of specialists and without a methodological system.[1,2] However, there was a need to establish specific guidelines for patients with hereditary angioedema, whose risk of death from asphyxia was from 25 to 40%. There was no way to ignore a clinical entity that was increasingly diagnosed and which had no appropriate therapeutic resources. It is important to highlight that plasma-derived C1 inhibitors have been available in European countries for decades, despite limited supply in most countries, including some developed countries.[3]

The recognition of the kinin-bradykinin system as the main mechanism involved in edema represented a significant change in the treatment of HAE. The need to treat attacks and reduce or even eliminate HAE mortality has boosted the development of drugs to treat the disease. The guidelines are beginning to take shape, with comparative studies demonstrating the effectiveness of newer treatments over conventional ones, such as plasma infusion or the use of plasmin inhibitors. Protocols with more adequate methodology are also included, although the recommendations are not yet necessarily supported by an adequate level of certainty in the evidence.[4] The main objective of expert panel recommendations is to advise clinicians on the best possible and acceptable way to approach a given decision making in the area of diagnosis, management or treatment.[5]

The treatment of angioedema attacks has been expanded with access to new therapeutic resources. Self-administration and early application of medications reduced emergency room visits, or even hospitalization, significantly reducing the duration of attacks. Considering that there would be adequate drugs for attacks, crisis prophylaxis became the new goal to be achieved. For this reason, several studies have demonstrated the effectiveness of new drugs and the impact on quality of life. It is important to emphasize that patients with properly treated hereditary angioedema have the same survival rate as the general population, and the disease does not cause relevant adverse effects, allowing a productive life. According to a recent publication that evaluated the situation of HAE management in 28 countries, there are inequalities in the services and treatments around the world, and access to appropriate treatments is still restricted to developed countries.[3] Mortality from hereditary angioedema in our country, recorded by the Association of patients with HAE (ABRANGHE), still impacts the profile of our patients (ABRANGHE personal communication).[6,7]

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There are numerous ways to synthesize available biomedical information[8] so that health care professionals can make decisions from heterogeneous sources. Clinical practice guidelines are documents that generally cover the context-specific information needed to make explicit and ideally transparent recommendations.[4,8] Low- and middle-income countries have been slowly and progressively adjusting to the standards of developed countries, but always striving for a global approach to the patient. It is difficult to ignore advances in patient assessment with the use of quality of life questionnaires, action plans and diagnostic tests. Clinical practice guidelines are the most important documents for incorporating scientific evidence into health decision-making, however, it is necessary to recognize some limitations of this process, mainly in developing countries. However, not knowing the evolution in the treatment of hereditary angioedema would be to deny the relevant role of new therapeutic resources.

With the advances described, consensus was largely replaced by guidelines, incorporating scientific evidence.[9,10] Clinical practice guidelines are not cookbooks as they may have limitations in their availability and applicability in the local context. However, they serve as an update so that the clinical diagnostic and therapeutic protocols (PCDT), essential instruments for the implementation of new resources, are reviewed. The Ministry of Health has used the instrument called AGREE II (Appraisal of Guidelines for Research & Evaluation II) that evaluates six domains: the scope and purpose, participation of those involved, rigor in its elaboration, clarity and specificity of the recommendations and applicability of the proposal.[11-13] Thus, the expectation is that the guidelines published here in the "Archives of Asthma, Allergy and Immunology" will contribute to a better diagnosis and treatment of the patient with hereditary angioedema, reaching the main recommendation of the latest guidelines of the World Allergy Organization, which is the normalization of the patient's life.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

2022 Brazilian guidelines for hereditary angioedema – Part 1: definition, classification, and diagnosis

Diretrizes brasileiras do angioedema hereditário 2022 – Parte 1: definição, classificação e diagnóstico

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ABSTRACT

Hereditary angioedema is an autosomal dominant disease characterized by recurrent attacks of edema that affect the subcutaneous tissue and the submucosa, involving several organs. The main affected sites are the face, upper and lower limbs, gastrointestinal tract, and upper airways. Because health professionals lack knowledge about this condition, there is a significant delay in diagnosis, compromising the quality of life of affected individuals. Furthermore, delayed diagnosis may result in increased mortality from asphyxia due to laryngeal edema. The erratic nature of the attacks with variations in clinical course and severity of symptoms among different patients and in one patient throughout life constitutes a challenge in the care of patients with hereditary angioedema. The main type of hereditary angioedema results from more than 700 pathogenic variants of the *SERPING1* gene with functional or quantitative deficiency of the C1 inhibitor protein, but in recent years other mutations have been described in six other genes. Important advances have been made in the pathophysiology of the disease, and new drugs for the treatment of hereditary angioedema have been developed. In this context, the Brazilian Study Group on Hereditary Angioedema (GEBRAEH) in conjunction with the Brazilian Association of Allergy and Immunology (ASBAI)

RESUMO

O angioedema hereditário é uma doença autossômica dominante caracterizada por crises recorrentes de edema que acometem o tecido subcutâneo e o submucoso, com envolvimento de diversos órgãos. Os principais locais afetados são face, membros superiores e inferiores, as alças intestinais e as vias respiratórias superiores. Em decorrência da falta de conhecimento dessa condição por profissionais de saúde, ocorre atraso importante no seu diagnóstico, comprometendo a qualidade de vida dos indivíduos afetados. Além disso, o retardo no diagnóstico pode resultar em aumento da mortalidade por asfixia devido ao edema de laringe. A natureza errática das crises com variação do quadro clínico e gravidade dos sintomas entre diferentes pacientes, e no mesmo paciente ao longo da vida, se constitui em desafio no cuidado dos doentes que têm angioedema hereditário. O principal tipo de angioedema hereditário é resultante de mais de 700 variantes patogênicas do gene *SERPING1* com deficiência funcional ou quantitativa da proteína inibidor de C1, porém nos últimos anos outras mutações foram descritas em seis outros genes. Ocorreram avanços importantes na fisiopatologia da doença e novas drogas para o tratamento do angioedema hereditário foram desenvolvidas. Nesse contexto, o Grupo de Estudos Brasileiro em Angioedema

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updated the Brazilian guidelines on hereditary angioedema. Greater knowledge of different aspects resulted in the division of the guidelines into two parts, with definition, classification, and diagnosis being addressed in this first part.

Keywords: Angioedema, hereditary angioedema, diagnosis, classification, differential diagnosis

Hereditário (GEBRAEH) em conjunto com a Associação Brasileira de Alergia e Imunologia (ASBAI) atualizou as diretrizes brasileiras do angioedema hereditário. O maior conhecimento dos diversos aspectos resultou na divisão das diretrizes em duas partes, sendo nessa primeira parte abordados a definição, a classificação e o diagnóstico.

Descritores: Angioedema, angioedema hereditário, diagnóstico, classificação, diagnóstico diferencial.

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Hereditary angioedema: a look at the best care

In recent decades, there has been an important advance in knowledge about the pathophysiology and access to the molecular diagnosis of angioedema, which has allowed the identification of new forms associated with hereditary angioedema (HAE).[1] In addition, these advances have enabled the development of new, effective and safe drugs for the treatment of HAE. As a consequence, there was greater dissemination of the disease, which resulted in a greater number of patients identified, although national surveys still show a significant delay in the diagnosis of HAE, resulting in greater morbidity and mortality.[2]

The unpredictable and potentially fatal character of HAE negatively impacts the quality of life of affected individuals and their families.[2-4] Although this condition is characterized by the presence of symptoms only in periods of an angioedema crisis, other aspects influence the quality of life that are present in asymptomatic periods, emphasizing the need for continuous support for affected individuals.[3] Therefore, the support and guidance provided to patients and family members by the Brazilian Association of HAE Carriers (ABRANGHE) contribute to minimizing the burden and disseminating knowledge about the disease.

In this context, the first Brazilian guidelines for the diagnosis and treatment of hereditary angioedema were prepared by specialists from the Brazilian Association of Allergy and Immunology (ASBAI) in 2010 and updated in 2017, with the active presence of the Brazilian Study Group on Hereditary Angioedema (GEBRAEH).

Updating the Brazilian guidelines aims to disseminate knowledge about HAE, establish norms regarding its diagnosis and treatment in Brazil, following the best evidence and recommendations of international guidelines, with a view to better patient care. The most recent international guidelines indicate that the main goals of HAE treatment should be to achieve total control of the disease and provide a

normal life for the patient.[5] In addition, since the last update of the guidelines, in 2017, new treatments have been developed, as well as new forms of administration of existing drugs were approved by ANVISA, justifying the need for this update.

The 2022 Brazilian guidelines for the diagnosis and treatment of hereditary angioedema will be presented in two parts. In the first part, the definition, classification and diagnosis of HAE will be addressed and, in the second part, the therapeutic approach. A non-systematic literature review was performed with the selection of consensuses/guidelines and relevant articles from the MEDLINE database using PubMed. In addition, controversial points were debated among the participating authors.

What is hereditary angioedema?

Angioedema is a transient, circumscribed, asymmetrical, deforming, non-inflammatory, non-pruritic, sometimes painful, edema located in the subcutaneous layer of the skin and/or in the submucosa of some organs.[6,7]

HAE was first described in 1882 by Quincke, originally as "angioneurotic" edema, due to its association with psychological or psychiatric disorders.[8-10] In 1888, Osler established its hereditary nature, however, the first biochemical alteration associated with the disease, the deficiency of the C1 esterase inhibitor (C1-INH), was only identified 75 years later, when HAE was defined as a quantitative or qualitative deficiency of the C1 inhibitor (HAE-C1-INH).[11-13]

HAE is a rare, potentially fatal and underdiagnosed genetic disease, characterized by recurrent attacks of edema that can affect both the dermis and subcutaneous tissue as well as internal organs, predominantly the digestive system and upper respiratory tract.[14-15] It is characterized by angioedema without the presence of wheals, unlike histaminergic angioedema, where approximately 90% of patients have these skin lesions.[16] Approximately one third of patients with recurrent angioedema without wheals may be diagnosed with HAE.[17-18] Currently, two main groups of HAE are recognized: angioedema with C1-INH deficiency (HAE-C1-INH), and HAE with normal C1-INH (HAE-nC1-INH).The average worldwide prevalence of HAE-C1-INH has been estimated at approximately 1:67,000 (1.5 per 100,000 population), while HAE-nC1-INH is rarer, estimated to occur in 1:400,000 individuals.[19-20]

What are the causes of hereditary angioedema?

C1-INH is a glycoprotein encoded by the *SERPING1* gene, located on chromosome 11, and which has more than 700 mutations already described in HAE-C1-INH1. C1-INH is a member of the serpin or serine protease inhibitor super family; it acts as a suicidal inhibitor that irreversibly imprisons the target protein in an inactive, highly efficient complex.[21,22] Pathogenic variants in the *SERPING1* gene result in a quantitative reduction in the production of C1-INH, mainly by the hepatocyte, and in a decrease in its functional activity, causing HAE-C1-INH type I, responsible for 85% of cases. In HAE-C1-INH type II, there is the production of a dysfunctional protein without alteration in the quantitative levels of C1-INH, identified in 15% of the remaining cases.[23-25]

The inheritance pattern in HAE-C1-INH is autosomal dominant. In 25% of patients, a *de novo* mutation occurs, without an evident family history of the disease.[26-28] In HAE-C1-INH, the mutation occurs in one of the two copies of the *SERPING1* gene, with rare published cases of homozygosity. Mutations resulting in HAE-C1-INH type I can occur anywhere in the *SERPING1* gene, while mutations responsible for HAE-C1-INH type II occur in exon 8, where the loop of the C1-INH reactive center is located, giving rise to a dysfunctional protein.[28] In HAE-C1-INH type I, plasma levels of C1-INH should be close to 50%, however, patients with this type of HAE have levels that vary between 5% and 30% of normal plasma levels. This discrepancy can be explained by the finding that the C1-INH product of the mutated *SERPING1* gene forms an aggregate with the normal C1-INH, and this aggregate is retained in the endoplasmic reticulum, configuring a dominant negative mechanism.[24,28] Biochemical penetrance, with laboratory alterations, approaches 100%, but the clinical expression and severity of the disease are highly variable.[28]

In 2000, patients and families with angioedema were first described who manifested symptoms similar to those of patients with HAE-C1-INH, however, with normal quantitative and functional levels of C1-INH. This type of HAE was initially described as HAE type III, however this nomenclature is no longer used, and this type of HAE is currently designated as HAE with normal C1-INH (HAE-nC1-INH).[29] The inheritance pattern in HAE-nC1-INH is also autosomal dominant.[28]

What is the mechanism involved in hereditary angioedema?

C1 is the first component of the classical complement pathway and forms a complex by binding to one molecule of C1q, two of C1r and two of C1s. This complex has slow auto activation, however, when binding to an immune complex, C1 acquires its full activity. C1-INH inhibits the activated form of C1, stabilizing it and decreasing its activation. Each activated molecule of C1r and C1s irreversibly binds to a molecule of C1-INH.[30,31]

Initially, C1-INH was recognized only for its activity in inhibiting the complement system, both in classical and lectin pathways, without which it would result in an overly activated system. Subsequently, C1-INH was also associated with the inhibition of several proteases, including plasma kallikrein, coagulation factors XII (FXII) and XI, and plasmin. Therefore, in addition to inhibiting the complement system, C1-INH participates in the regulation of the contact systems and kallikrein/kinin, coagulation, and fibrinolysis.[25,31-33] Further studies have revealed that C1-INH deficiency in HAE-C1-INH results in overproduction of bradykinin (BK) that binds to the B2 receptor (BDKRB2), playing an important role in angioedema.[34-36] The development of new treatments, such as the B2 receptor antagonist of BK and kallikrein inhibitors, reinforced the role of BK as the main mediator in HAE-C1-INH.[37,38]

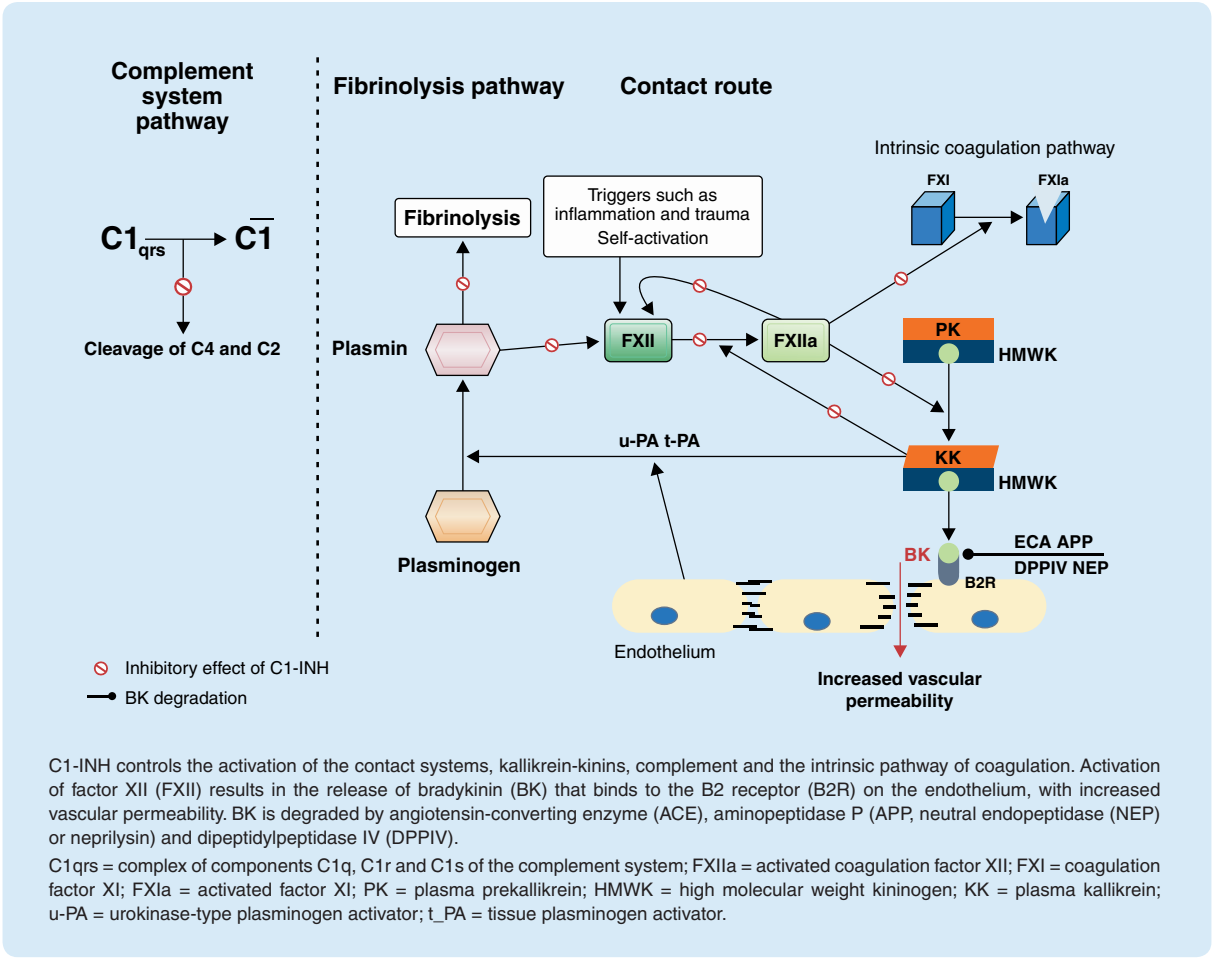
Commonly used synonymously, and despite exhibiting overlap and interactions, the terms plasma contact systems (SC) and kallikrein-kinin (SCC) are different. The SC refers to the proteolytic system initiated by the auto activation of factor XII (FXII), while the SCC consists of kallikrein that cleaves high molecular weight kininogen (HMWK) and thereby releases a vasoactive nonapeptide, BK.[39] Activation of FXII, with generation of FXIIa, is initiated by negatively charged surfaces, or macromolecules. Subsequently, FXIIa activates more FXII, in a process of self-activation. The next substrate in the cascade is prekallikrein, which will be converted to its active form, kallikrein, which in turn degrades HMWK, releasing BK. By binding to its B2 receptor, which is constitutively expressed on endothelial cells, BK interferes with endothelial junctions, increasing vascular permeability and inducing angioedema. BK also stimulates the production of nitric oxide by endothelial cells, which, consequently, triggers vasodilation by contracting the cytoskeleton. It is worth noting that the activation of FXII occurs close to the endothelial wall, determining the activation of the cascade that results in the production of BK that binds, in a paracrine way, to the B2 receptor on the endothelium. Additionally, kallikrein directly activates FXII and also acts on the fibrinolytic system, converting plasminogen into plasmin which, in turn, activates more FXII, forming a retroactivation cycle (Figure 1).[22,25,31,40-43]

Plasma BK has an extremely short half-life as it is readily degraded by various peptidases (Figure 1). Angiotensin-converting enzyme (ACE) is the most important peptidase for BK degradation. Dipeptidyl peptidase IV (DPPIV, neutral endopeptidase (NEP) or neprilysin) and aminopeptidase P (APP) are other peptidases that act in the same process. BK is transformed by these enzymes into des-Arg-BK, which is its inactive form.[40,44]

Among the systems inhibited by C1-INH, SC and SCC have greater relevance for the genesis of HAE-C1-INH. C1-INH inhibits the auto activation of FXII to FXIIa, the conversion of prekallikrein to kallikrein, the activation of FXII by kallikrein, and the proteolytic cleavage of HMWK with the release of BK. With all these steps inefficiently inhibited in the HAE-C1-INH, there will be an exaggerated release of BK.[25,30]

In recent years, the role of the local endothelium has gained importance in the attempt to explain the local nature of angioedema. In response to various stimuli, such as infection, trauma, and stress, the endothelium releases vasoactive substances that modulate both vasodilation and vasoconstriction, as well as vascular permeability. Plasma prekallikrein circulates in complex with HMWK and this complex can be recruited to the surface of the endothelium. Thus, the endothelium plays a key role in inducing the angioedema crisis. The mechanism responsible for inducing this process in a certain part of the organism, and not in another, and the fact that the crisis is localized and not systemic is still unknown. In addition, C1-INH has already been shown to bind to adhesion molecules on the endothelium wall, in addition to the complement system, making its inhibitory action more efficient. In summary, the endothelium, through the action of some stimuli, can become locally activated, initiating the process that culminates in the release and compartmentalized action of BK.[25]

In HAE-nC1-INH, mutations in the gene *F12* coding for FXII were described in a number of patient families, and this type of HAE was designated as HAE-FXII.[45] Among the four mutations in the *F12* gene that cause HAE-FXII, all located in exon 9, the missense mutation c.983C>A, which leads to the substitution of the amino acid threonine for lysine at position 328 of the FXII



C1-INH controls the activation of the contact systems, kallikrein-kinins, complement and the intrinsic pathway of coagulation. Activation of factor XII (FXII) results in the release of bradykinin (BK) that binds to the B2 receptor (B2R) on the endothelium, with increased vascular permeability. BK is degraded by angiotensin-converting enzyme (ACE), aminopeptidase P (APP, neutral endopeptidase (NEP) or neprilysin) and dipeptidylpeptidase IV (DPPIV).

C1qrs = complex of components C1q, C1r and C1s of the complement system; FXIIa = activated coagulation factor XII; FXI = coagulation factor XI; FXIa = activated factor XI; PK = plasma prekallikrein; HMWK = high molecular weight kininogen; KK = plasma kallikrein; u-PA = urokinase-type plasminogen activator; t_PA = tissue plasminogen activator.

Figure 1
C1 inhibitor (C1-INH) sites of action in contact systems, kallikrein-kinins, complement and intrinsic coagulation pathway

protein (p.Thr328Lys), has been the most frequently found.[20] Pathogenic variants in the *F12* gene make FXII more susceptible to activation by plasmin and other proteases.[20,28,46] The thrombin that is generated after trauma can activate FXII and explain angioedema after this stimulus.[47] As already described, FXII plays a central role in the initial phases of SC and SCC activation, and in the increase of BK[25] release.

However, not all patients with HAE-nC1-INH had mutated here that of the *F12*, that is, most remained with the HAE of *unknown cause* (HAE-U).[48] With the advent of new full-exome sequencing technologies, mutations in five genes other than *F12* have been described in families of HAE-nC1-INH1 patients (Table 1). A mutation in heterozygous and autosomal dominant transmission in the plasminogen gene (*PLG*) has been described and, to date, the mechanism of angioedema is still unclear.[49] In the same year, a mutation in the angiopoietin 1 gene (*ANGPT1*) he was identified. This mutation broadens the pathophysiological spectrum of angioedema, as it involves a gene unrelated to SC and SCC. Mutation of *ANGPT1* results in the synthesis of decreased amounts of *ANGPT1* in plasma and a decreased binding to its Tie2 receptor (*tunica interna* endothelial cell kinase 2). The binding of *ANGPT1* to Tie2 is important for the stabilization and reduction of vascular permeability.[50] Another mutation in the kininogen 1 gene (*KNG1*) was described in 2019 and the mechanism of angioedema is still unknown, but it may be related to the process of BK[51] formation. Subsequently, a mutation with possible gain of function in the myoferlin gene (*MYOF*) was associated with a new subtype of HAE-nC1-INH. Myoferlin is an endothelial cell membrane protein and modulates signal transduction via vascular endothelial growth factor (VEGF). The interaction of myoferlin

Table 1
Types of hereditary angioedema with normal C1-INH with identified pathogenic variants[1,20,53]

Type of HAE-nC1-INH	Gene	cDNA change	Change in protein	Chromosome	First description
HAE-FXII	*F12*	c.983C>A[a]	p.Thr328Lys	5	Dewald & Bork (2006)
HAE-FXII	*F12*	c.983C>G	p.Thr328Arg	5	Dewald & Bork (2006)
HAE-FXII	*F12*	c.971_1018+24del72	indel	5	Bork et al. (2011)
HAE-FXII	*F12*	c.892_909dup	p.Pro298_Pro33dup	5	Kiss et al. (2013)
HAE-PLG	*PLG*	c.988A>G	p.Lys330Glu	6	Bork et al. (2018)
HAE-ANGPT1	*ANGPT1*	c.807G>T[b]	p.Ala119Ser	8	Bafunno et al. (2018)
HAE-KNG1	*KNG1*	c.1136T>A[b]	p.Met379Lys	3	Bork et al. (2019)
HAE-Myoferlin	*MYOF*	c.651G>T[b]	p.Arg217Ser	10	Arian et al. (2020)
HAE-HS3OST6	*HS3ST6*	c.430A>T[b]	p.Thr144Ser	16	Bork et al. (2021)

[a] Mutation found in more than 90% of patients with HAE-FXII.
[b] Mutations described in only a single family.

with VEGF signaling pathways may be related to the release of nitric oxide which, in turn, is an important mediator of vascular permeability.[52] The most recently described mutation was that of the heparan sulfate-glucosamine 3-O-sulfotransferase 6 (*HS3ST6*) gene. It is suspected that this mutation leads to incomplete synthesis of heparan sulfate, affecting the structure of proteoglycans, and the consequent change in the interaction of HMWK with endothelial cells.[53]

Understanding the influence of estrogen, endogenous and/or exogenous on HAE-C1-INH, both in types I and II and in HAE-FXII, is still incomplete. The HAE-C1-INH is negatively impacted by estrogen, and the HAE-FXII was once considered estrogen-dependent, since some patients with an *F12* mutation have clinical manifestations only after pregnancy or with the use of contraceptives containing this hormone.[54-56] Estrogen stimulates the release of some cytokines and the heat shock protein called Hsp90, which in endothelial cells can convert prekallikrein into kallikrein, which cleaves HMWK, releasing BK. Additionally, kallikrein activates FXII either directly or by inducing the degradation of plasminogen to plasmin, which in turn activates FXII. Therefore, estrogen, by stimulating the release of Hsp90, induces the activation of FXII, mainly in HAE-FXII.[57] The promoter region of *F12* contains an estrogen-response element and has been shown to increase transcription of FXII mRNA in response to the hormone. It is likely that estrogen also contributes to increased BK B2 receptor expression. The action of BK is mediated by nitric oxide, and estrogen is a regulator of the release of this substance, contributing to BK-mediated angioedema. Finally, estrogen can decrease the degradation of BK by interfering with the activity of the angiotensin-converting enzyme.[33,58,59]

Therefore, so far, mutations in seven different genes have been described in patients with HAE, the most frequent being in the *SERPING1* gene followed by mutations in the *F12* gene related to HAE-C1-INH and HAE-FXII, respectively.[20] Other mutations identified in HAE patients and families involve genes encoding proteins that participate in BK production pathways, such as *SERPING1*, *F12*, *KNG1* and possibly *PLG* (fibrinolytic system).[20] Mutations in genes involved in the regulation of vascular permeability at the endothelium level, such as *ANGPT1* and *MYOF*, or in the endothelial regulation of the kinin system, such

as *HS3ST6*, have also been described in patients with HAE-nC1-INH, revealing new pathogenic pathways that may become therapeutic targets.[1,20,53] Thus, hereditary angioedema can also be classified based on the new mechanisms described:

– Bradykinin angioedema: HAE-C1-INH (types I and II), HAE-FXII, HAE-PLG, HAE-KNG;
– Angioedema due to vascular endothelium dysfunction: HAE-ANGPT1, HAE-MYOF and HAE-HS3ST6.

What are the typical clinical manifestations of hereditary angioedema?

General features

HAE symptoms can start at any age, however, in most patients they start in the first or second decade of life. Studies show the onset of symptoms in 75% of patients with HAE-C1-INH up to 15 years of age.[2,26,60-64] In general, in 50% of HAE-C1-INH cases, the onset of symptoms occurs around 10 years of age, with an increase in the frequency and severity of crises at puberty.[65] In the HAE-nC1-INH, most cases are triggered in adolescence, as reported in a Brazilian cohort, in which 72% of patients (n = 197) had their first crisis between the second and third decades of life.[66,67]

HAE is manifested by recurrent and unpredictable episodes of angioedema, in any part of the body.[68-70] The frequency and severity of HAE crises varies between patients and throughout the life of the same patient.[5,68,69,71,72] It is described that 5% of individuals with HAE are asymptomatic, and 25% develop sporadic symptoms.[69,73-75] The frequency of attacks is individual and varies from sporadic episodes to more than one attack per week. This wide variation in phenotypic expression is not correlated with plasma concentrations of C1-INH, and it is likely that other genetic and/or environmental factors may influence seizure frequency.[76]

A peak of symptoms is observed between 12 and 24 hours, spontaneously regressing in two to five days. THE Edema onset is usually slow and gradual, and usually occurs around eight hours. However, in places such as the abdomen and larynx, angioedema can develop more quickly.[68-70] In hereditary angioedema wheals do not occur and there is no response to treatment with antihistamines, corticosteroids and adrenaline.[6,7]

HAE-C1-INH types I and II do not differ in terms of clinical symptoms. Although the HAE attacks both sexes, tends to be more severe and frequent in women, due to the role of estrogen in the pathogenesis of the disease. The clinical presentation of HAE-nC1-INH is similar to HAE-C1-INH, but the symptoms are less frequent, and other differences are also described.[66,72]

The course of the disease tends to be more severe the earlier the onset of symptoms.[69,77] Likewise, a worsening in the frequency and severity of seizures is observed after puberty, both in women and in men.[65] In some older patients, the symptoms become milder, however, the angioedema attacks rarely stop completely.[65,68]

Triggering factors

Angioedema episodes can occur spontaneously, but in up to 91% of cases they are induced by physical, psychological, infectious, drug or hormonal factors.[5,78-80] Emotional stress is reported by HAE-C1-INH patients as the most frequent triggering factor for crises.[80,81] Mechanical trauma, even if mild, is the second most frequent trigger in the HAE-C1-INH, and angioedema characteristically begins in the traumatized area.[82] Angioedema can be triggered by dental, surgical or diagnostic procedures, usually occurring around 4 to 36 hours after the intervention.[83,84] Infections in general, especially viral infections, are considered a relevant trigger of HAE crises, especially in children.[82,85] Situations in which there is an increase in estrogen levels, such as the use of oral contraceptives, hormone replacement therapy during menopause, pregnancy and menstruation, are of potential risk for triggering crises in the HAE-C1-INH.[86]

Several drugs that interfere with BK metabolism have been described as associated with an increased risk of angioedema attacks. In the vast majority of cases, the mechanism involves inhibition of BK degradation, resulting in an elevation of its serum level and, consequently, angioedema.[40] Drugs used in the treatment of arterial hypertension with action on the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme (ACE) inhibitors and, with lower risk, angiotensin II receptor blockers (ARBs), were associated with acquired angioedema, however, can also trigger HAE.[40,87]

Likewise, gliptins that inhibit the DPPIV enzyme, used as oral hypoglycemic agents, reduce BK

catabolism and are potential triggers for the development of crises.[40,87] Neprilysin inhibitors, another class of drugs used in the treatment of arterial hypertension and heart failure, such as sacubitril, can cause angioedema, especially when used in combination with RAAS inhibitors.[40,87,88] Inhibitors of the intracellular protein mTOR, immunosuppressants used in the treatment of cancer, represent an additional risk for patients with HAE-C1-INH.[89]

Other less frequent triggers of angioedema attacks are described by patients, such as exposure to extreme temperatures, alcohol consumption, ingestion of some foods, and fatigue.[80,90,91]

Prodromes

Prodromes are reported in several patients with HAE-C1-INH, preceding the crisis by one to 24 hours.[81,92,93] One third of patients present with macular, erythematous-serpiginous, fleeting and non-pruritic skin lesions, usually on the trunk and limbs, known as erythema marginatum, or also serpiginous erythema.[94] In children, erythema marginatum is described as an independent phenomenon, without subsequent angioedema, and often as the initial manifestation of HAE-C1-INH.[95] Non-specific symptoms such as asthenia, thirst, hunger, nausea, mental fatigue, mood swings, depression, anxiety, irritability, aggression, muscle aches, tingling or tightness in the affected area, as well as flu-like symptoms as well have been reported as prodromal symptoms.[81,93,94]

Erythema marginatum has not been reported as a prodrome in patients with HAE-nC1-INH, however other nonspecific symptoms such as fatigue, chest pain and palpitations have been observed in some cases.[20] Some patients with HAE-nC1-INH have skin lesions that resemble ecchymosis, however, there are few cases described.[96-99]

The prodromal manifestations allow the early initiation of treatment in case of crisis and, thus, reduce the morbidity and mortality associated with HAE-C1-INH. However, complaints are very variable and, to date, there is no scientific evidence of their predictive value.[92,93] The presence of erythema marginatum, the most characteristic prodrome of HAE-C1-INH, has been associated with a delay in the diagnosis of the disease, as it is often confused with urticaria.[100]

Location

The three most characteristic sites of involvement of HAE are: subcutaneous, abdomen and larynx.[2,68-70] Subcutaneous involvement is the most frequent, affecting 95% of patients with HAE-C1-INH, highlighting the extremities, genitalia and face as the most common sites involved. The abdomen is the second most common site of involvement, occurring in up to 93% of cases. In crises, several sites can be affected simultaneously, a characteristic that distinguishes HAE from other causes of angioedema without urticaria.[2,6,68-70]

Abdominal pain due to intestinal loop edema can be intense and spasmodic, lasting from many hours to several days. Often, these symptoms can be confused with an acute surgical abdomen, resulting in unnecessary appendectomies and exploratory laparotomies in up to one third of patients, both in the HAE-C1-INH and in the HAE-nC1-INH.[101,102] Edema of the mucosa of the gastrointestinal tract can cause compression of the lumen and a clinical picture of temporary paralytic ileus, causing nausea and vomiting. Watery diarrhea due to accumulation of fluid in the lumen of the edematous bowel is also common. Leakage of fluid into the peritoneal cavity can result in ascites with increased volume of the abdomen, often identified by ultrasound as fluid in the abdominal cavity.[103] Hemoconcentration, arterial hypotension and even hypovolemic shock can occurin these patients secondary to substantial fluid loss to the interstitium or cavity.[69]

The involvement of the larynx, more precisely in the supraglottic region, occurs in 50% of patients, and at least one episode occurs during the patient's lifetime.[2,68-70] Laryngeal edema is more frequent between 11 and 45 years of age, and rare before the third year of life.[104,105] Although less frequent that skin and abdominal symptoms, laryngeal edema is potentially fatal, particularly in untreated patients. Another important aspect is that there may be edema of regions above the larynx, such as the base of the tongue and oropharynx, which may also impede the passage of air and result in asphyxia and hence the term upper airway edema, rather of laryngeal edema, has been used.[73,78,106] Has been described high frequency of tongue edema in patients with mutation in the gene encoding plasminogen (HAE-PLG).[20] The most frequent onset of laryngeal angioedema is approximately eight hours, nonetheless, may have a sudden onset and cause acute airway obstruction.[104,105] It is worth noting that patients with

facial edema are considered at risk for upper airway edema. Although less frequent than cutaneous and abdominal symptoms, lethal laryngeal edema may be the first presentation of HAE-C1-INH.[104,105]

Unusual clinical manifestations of HAE-C1-INH, such as linear blisters, severe headache, dysuria, and acute pancreatitis have also been described in the medical literature.[107-109]

What tests confirm the diagnosis?

Every individual with clinical suspicion of HAE or who has a family history of similar symptoms, should undergo laboratory tests to confirm HAE-C1-INH. The measurement of the serum level of C4 can be used to screen for HAE (Figure 2). In quantitative deficiency or dysfunction of C1-INH, stabilization of the C1 complex is low, becoming partially activated and C4, its preferred substrate, depleted. In most patients with HAE-C1-INH types I and II, C4 is continuously decreased in plasma, but there is the possibility of normal C4 levels.[79] In these situations, C4 measurement is recommended in the crisis period, if the clinical history is suggestive and the analysis of C1-INH levels is not available.[5,110] Quantitative (by radial immunodiffusion or turbidimetry/nephelometry) and functional (by chromogenic assay) assessment of C1-INH are recommended for definitive diagnosis. Most patients (85%) have quantitative C1-INH below 50% of the normal range, establishing the diagnosis of HAE-C1-INH type I.[79] When the C1-INH concentration is normal (or even high, in some cases), the C1-INH functional test is essential. The diagnosis of HAE-C1-INH type II is characterized by normal or elevated quantitative C1-INH and reduced functional activity of C1-INH, corresponding to approximately 15% of patients with HAE-C1-INH.[111] In Brazil, the C4 test is widely available in clinical analysis laboratories, while the other tests are performed only in more specialized laboratories. It is important to emphasize that the collection and manipulation of samples can be limiting factors for the broad access to the evaluation of C1-INH, as degradation and consumption of complement components can occur very easily.[112] Thus, the biochemical measurements necessary for the diagnosis of HAE-C1-INH, especially the functional assessment of C1-INH, can generate false-positive results, and it is advisable to carry out at least two measurements collected on different days.[5,111,113]

In acquired angioedema due to C1-INH deficiency (AEA-C1-INH), C4 and C1-INH concentrations, as well as functional assessment, may be reduced. In this case, the C1q dosage must be performed and is reduced in approximately 70% of the cases. Clinical features such as symptoms of later onset in adulthood and absence of a family history of recurrent angioedema suggest the diagnosis.[114,115.] Also, considering that a percentage of patients with AEA-C1-INH may have normal plasma levels of C1q, genetic evaluation of the *SERPING1* gene is recommended for the differential diagnosis. In cases with de novo mutations or questionable clinical history, genetic evaluation may also be necessary.[116]

In children under one year of age, plasma levels of C1-INH may be below the values considered normal due to immunological immaturity, recommending the genetic analysis of *SERPING1* to aid in the diagnosis of HAE-C1-INH.[77,117]

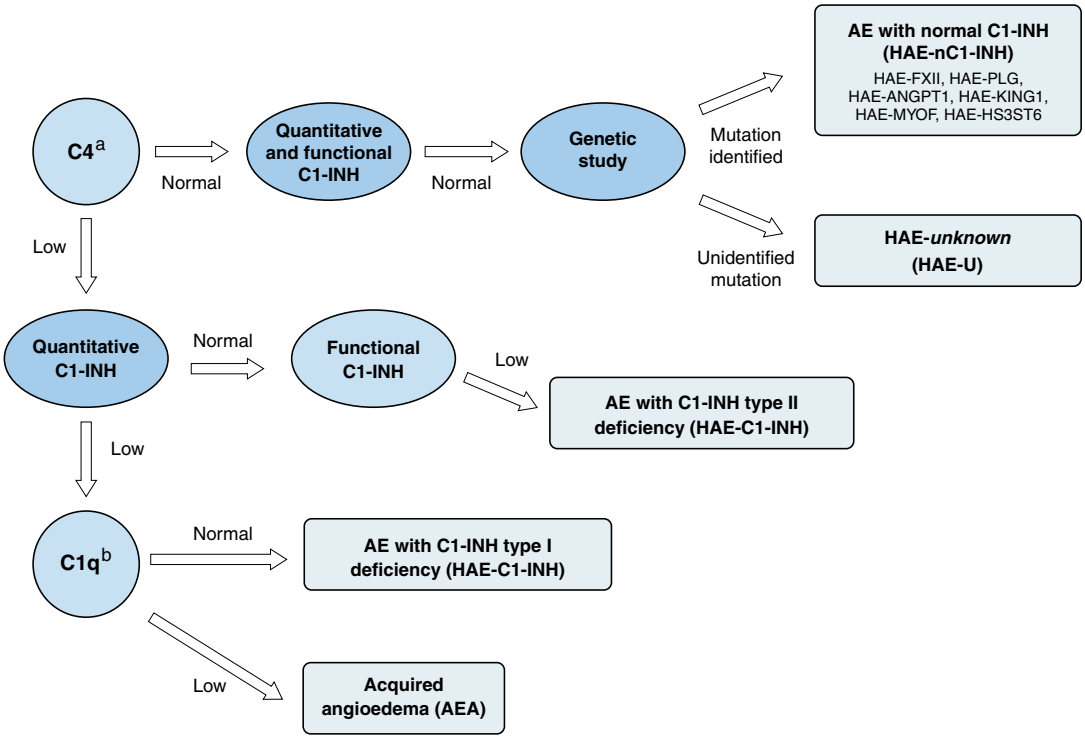
SERPING1 genotyping can be performed by Sanger sequencing or next-generation sequencing, and must cover the eight exons of the gene, including its splicing sites. In the absence of pathogenic variants, the presence of large deletions and insertions should be evaluated using techniques such as multiplex ligation-dependent probe amplification (MLPA) or long-range PCR, although these tests are not widely available.[28] The pathogenicity assessment of new variants identified in *SERPING1* should follow the international guidelines established by the American College of Medical Genetics and Genomics (ACMG) for HAE.[20,118] Although not essential for the diagnosis of symptomatic patients, the determination of the mutations that cause HAE-C1-INH helps in family screening and early prevention, even in asymptomatic carriers.

For cases of suspected HAE and consistent and normal results of C4 and C1-INH, the HAE-nC1-INH should be investigated, for which there are no biochemical markers available, and the only alternative is genetic diagnosis.[1,20]

In patients with HAE, it is estimated that the delay in diagnosis is still high, and national studies document that this delay in diagnosis varies between 14 and 18 years.[2,26,60-64]

What are the diagnostic criteria for HAE?

Some criteria to standardize the diagnosis of HAE have been proposed (Table 2).[72] Among them, some are required for the diagnosis, while others constitute a strong indication, but are not necessary,



[a] If C4 normal, repeat during the angioedema crisis.

[b] Request depending on clinical history.

AE = angioedema, HAE = hereditary angioedema, AEA = acquired angioedema, HAE-U = hereditary angioedema of unknown cause, HAE-FXII = hereditary angioedema due to Factor XII gene mutation, HAE-PLG = hereditary angioedema due to plasminogen gene mutation , HAE-ANGPT1 = hereditary angioedema due to an angiopoietin 1 gene mutation, HAE-KNG1 = hereditary angioedema due to a kininogen 1 gene mutation, HAE-MYOF = hereditary angioedema due to a myoferlin gene mutation, HAE-HS3ST6 = hereditary angioedema due to the mutation in the 3OST6 heparan sulfate gene.

Figure 2
Algorithm for the diagnosis of hereditary angioedema[1,5,14,72]

being, therefore, supporting criteria. For example, the detection of a mutation in the *SERPING1* gene in HAE-C1-INH is not necessary for the diagnosis and is therefore a supporting criterion. The characteristic of non-inflammatory subcutaneous angioedema lasting more than 12 hours and the presence of abdominal pain of undefined organic etiology, lasting more than six hours, in addition to laryngeal edema, are important characteristics in HAE.[14]

These criteria are not absolute and clinical history is predominant, especially in locations where laboratory tests are not available. In HAE-nC1-INH, a therapeutic test can help to establish the diagnosis.[72]

In Figure 3, we suggest a list of warning signs and an acronym to encourage diagnostic suspicion and promote awareness of HAE-C1-INH.

What is not hereditary angioedema?

Two main pathophysiological mechanisms of angioedema are described: by activation of mast cells and/or basophils, resulting in the release of histamine and other mediators (histaminergic angioedema); and by excess BK (bradykinin-mediated or non-histaminergic angioedema), as seen in HAE-C1-INH, AEA-C1-INH, and angioedema induced by ACE

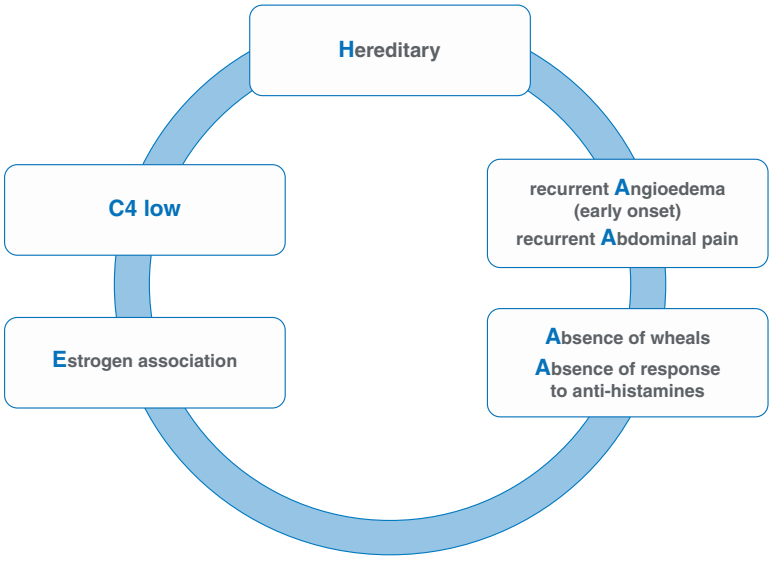
inhibitors or gliptins, drugs involved in BK metabolism (Figure 4).[8,17,119] Therefore, the main differential diagnoses of HAE are the other types of angioedema, especially those with chronic or recurrent presentation. Knowledge about the pathophysiological mechanisms, clinical characteristics and response to drugs used during the crisis contribute to the suspicion of other causes of angioedema. In addition to clinical aspects, laboratory evaluation helps in the discrimination between histamine-mediated and bradykinin-mediated angioedema (Table 3).

The most frequent type of recurrent angioedema is histaminergic, which has some characteristics that differentiate it from HAE, including the presence of wheals, improvement with antihistamines, and triggering of symptoms by the use of nonsteroidal anti-inflammatory drugs (NSAIDs). However, histaminergic angioedema can present without urticaria, and NSAIDs are among the main causes of angioedema, even in those patients who do not have urticaria.[9] Current guidelines for the treatment of chronic spontaneous angioedema/urticaria highlight the fact that some patients will not respond to conventional doses of antihistamines and may need to be increased in dose, reaching up to four times the daily recommended doses to control symptoms. Therefore, to confirm or rule out the histaminergic nature of angioedema, a therapeutic trial of antihistamines using four times the recommended dose for a period of time of

Table 2
Criteria for the diagnosis of hereditary angioedema

Weight	Criterion
HAE-C1-INH	
Required	History of recurrent angioedema in the absence of wheals, without the use of medications that may trigger angioedema
Required	Decreased antigenic or functional C1-INH (< 50% of normal)
Required	Decreased C4 levels (baseline or measured in crisis)
Support	Detection of a pathogenic variant in the *SERPING1* gene (not required for diagnosis) Family history of recurrent angioedema Age of onset < 40 years
HAE-nC1-INH	
Required	History of recurrent angioedema, in the absence of wheals, without the use of medications that may trigger angioedema
Required	Antigenic and functional C4, C1-INH levels unchanged or close to normal values
Required (one of 2)	1) Demonstration of a mutation associated with the disease OR 2) Family history of recurrent angioedema and lack of efficacy of high-dose second-generation antihistamine therapy for at least a month or an expected interval of three or more attacks of angioedema, whichever is longer
Support	1) History of rapid and lasting response to a drug that inhibits bradykinin AND 2) documented visible angioedema; or in patients with abdominal symptoms, evidence of intestinal wall edema documented by CT or MRI

HAE-C1-INH = hereditary angioedema with C1 esterase inhibitor deficiency, HAE-nC1-INH = hereditary angioedema with normal C1 esterase inhibitor, MRI = MRI, CT = CT scan.
Adapted from Busse PJ et al.[2].



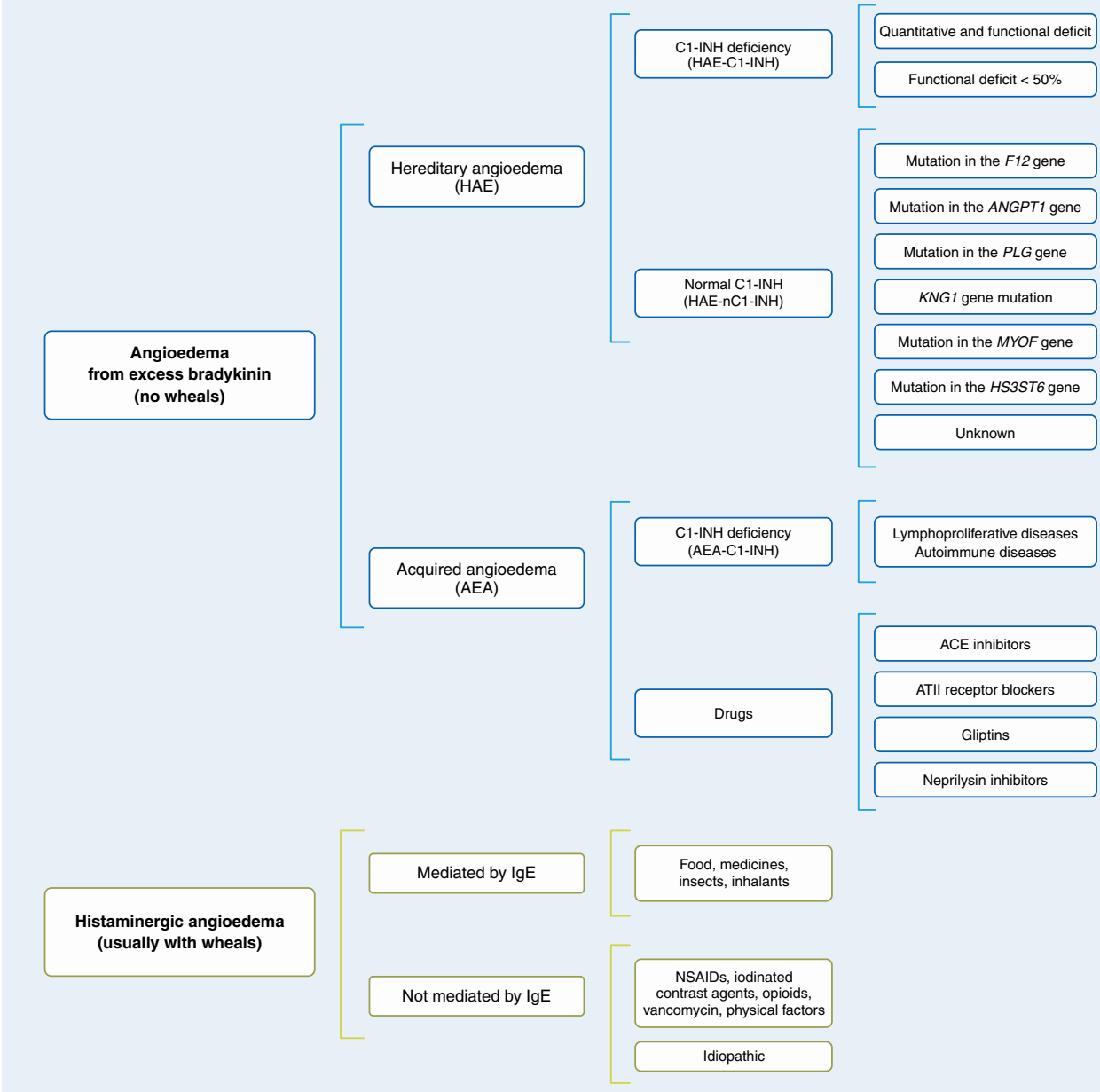
HAAAAE = Heridarity, recurrent Angioedema, recurrent Abdominal pain, Absence of wheals, Absence of response to antihistamines, association with Estrogen.
Adapted from: Giavina-Bianchi P et al.[14].

Figure 3
Warning signs for the diagnosis of HAE-C1-INH[14]

approximately six weeks is sufficient to assess your response to treatment. The safety of increasing the dose of antihistamines, including bilastine, cetirizine, levocetirizine, desloratadine, ebastine, fexofenadine and rupatadine, has been demonstrated.[16,120] Although BK-mediated angioedema is less frequent, the risk of mortality in this type of angioedema is 45 times greater than that of histaminergic angioedema.[121]

Regarding the acquired forms of BK-mediated angioedema, it is very important to ask the patient about the use of ACE inhibitors. As ACE is the main enzyme involved in BK degradation, its inhibition leads to increased serum concentrations of this mediator, and can cause angioedema. Up to 0.7% of individuals using ACE inhibitors have recurrent angioedema, with an increased risk among Afro-descendants, smokers, the elderly and females.[17,44] ACE-induced angioedema most often involves the face, tongue, oropharynx and larynx, however sporadic cases of abdominal episodes have been reported. The mean time for the onset of symptoms of angioedema is 1.8 years, however symptoms occur in 25% of cases within the first month of using the medication. They can also occur up to 10 years after the introduction of treatment.[122] ACE inhibitors should be discontinued in all patients with recurrent angioedema, even if the angioedema has been triggered after several years of drug use. Although ACEI-induced angioedema attacks may resemble those of HAE, patients will have normal levels of C4 and C1q, in addition to normal quantitative and/or functional levels of C1-INH (Table 4). More rarely, angiotensin II receptor blockers (ARB) and gliptins can induce angioedema.[123]

AEA-C1-INH is an even rarer type of angioedema than HAE, with an estimated prevalence of 1.5:1,000,000 individuals, without genetic inheritance.[114,115] In this type of angioedema, the onset of symptoms occurs later, there is no family history of angioedema, and the disease is due to the consumption of C1-INH or the production of C1-INH neutralizing autoantibodies,



HAE = hereditary angioedema, C1-INH = C1 inhibitor, *F12* = coagulation factor XII, *ANGPT1* = angiopoietin-1, *PLG* = plasminogen, *KNG1* = kininogen 1, *MYOF* = myoferlin, *HS3ST6* = heparan sulfate 3ST6, ACE = angioetensin, ATII = angiotensin II, IgE = immunoglobulin E, NSAIDs = non-steroidal anti-inflammatory drugs.

Figure 4
Classification of angioedema[1,7,8, 17,119]

associated with lymphoproliferative or autoimmune diseases, respectively. As a consequence, C1-INH activity is low, the complement system is activated, and C1q is generally reduced, a particular feature that may help in the differential diagnosis. In addition to C1-INH function below 50% of normal, C1-INH antigen levels are often reduced, although the presence of cleaved C1-INH can result in normal C1-INH antigenic levels

Table 3
Characteristics of recurrent angioedema regarding the mediator, clinical and laboratory aspects[1,7,20,119]

	HAE-C1-INH (types I and II)	HAE-nC1-INH	HAE-C1-INH	Histaminergic AE
Mediator	Bradykinin	Bradykinin	Bradykinin	Histamine
Clinical condition	Family history Trauma Early start Serpiginous erythema may be a prodrome	Family history Trauma Later Women Language (HAE-PLG) Hematoma can occur	Underlying disease Later	No family history Spontaneous Any age Urtica in 90% of cases Preferred location on face/lips
Laboratory tests	C4 low C1-INHq low/normal or increased C1-INHf low	C4 normal C1-INHq normal C1-INHf normal Molecular test for variant search	C4 low C1-INHq low C1q low	C4 normal C1-INHq normal C1-INHf normal

AE = angioedema, HAE-C1-INH = hereditary angioedema with C1 Inhibitor deficiency, HAE-nC1-INH = hereditary angioedema with normal C1 Inhibitor, HAE-PLG = hereditary angioedema due to plasminogen gene mutation, C1-INHq = quantitative C1-INH, C1-INHf = functional C1-INH.

in about 20% of patients. As there is a great overlap of AEA-C1-INH associated with autoantibodies and lymphoproliferative diseases, its classification as the same disease is suggested.[124,125]

Idiopathic non-histaminergic angioedema should be considered when there is no heredity, all known causes of angioedema have been excluded, and symptoms persist despite treatment with high doses (up to four times the standard dose) of second-generation non-sedating antihistamines.[17] There is evidence that BK may be the mediator involved in idiopathic non-histaminergic angioedema. However, the evidence is not definitive, considering that other vasoactive mediators derived from mast cells or other cells, including cysteinyl-leukotrienes, prostaglandins, and platelet activating factor may play a role.[119] On the other hand, the involvement of mast cells/basophils does not exclude the participation of BK, as there is evidence that mast cells can increase vascular permeability by releasing heparin, which, in turn, induces the formation of BK. There are also indications of the participation of BK release in spontaneous chronic urticaria, with or without angioedema.[126,127] Among patients considered to have idiopathic non-histaminergic angioedema still there may be individuals with HAE-nC1-INH, with no family history and no known mutation, as well as some patients with histaminergic angioedema without wheals and resistant to antihistamines.[9,16,17,119] Therefore, the identification of the different forms of bradykinin-mediated angioedema can be better defined through specific laboratory and molecular aspects (Table 4).

Final considerations

HAE is an autosomal dominant genetic disease associated with recurrent angioedema that affects the subcutaneous tissue and submucosal tissue, mainly of the digestive tract and upper respiratory tract.[5,71,72]

Table 4
Laboratory and molecular features of bradykinin-mediated angioedema[119]

	HAE-C1-INH				
	HAE type I	HAE type II	HAE-nC1-INH	AEA-C1-INH	AEA-iECA
C1-INH	< 50%	Normal or increased	Normal	< 50%	Normal
Functional C1-INH	< 50%	< 50%	Normal	< 50%	Normal
C4	Low	Low	Normal	Low	Normal
C1q	Normal	Normal	Normal	Low (70% of cases)	Normal
Mutation	*SERPING1*	*SERPING1*	*FXII, PLG, ANGPT1, KNG1, MYOF, HS3ST6*	No	No
Ac anti-C1-INH	No	No	No	50% of cases	No

HAE = hereditary angioedema, HAE-C1-INH = hereditary angioedema with C1 inhibitor deficiency, HAE-nlC1-INH = hereditary angioedema with normal C1 inhibitor, AEA-C1-INH = acquired angioedema with C1 inhibitor deficiency, AEA-ACEi = angioedema acquired by angiotensin converting enzyme inhibitor, C1-INH = C1 inhibitor, anti C1-INH Ab = anti C1-INH antibody.

There are seven types of HAE defined by distinct pathogenic genetic variants: HAE-C1-INH, HAE-FXII, HAE-PLG, HAE-ANGPT1, HAE-KNG1, HAE-MYOF and HAE-HS3ST6. The most frequent mutations occur in the *SERPING1* gene, followed by mutations in the *F12* gene related to HAE-C1-INH and HAE-FXII, respectively.[20,53]

In many individuals with HAE, genetic variants causing the disease are not yet known, and these patients are diagnosed with HAE-U (HAE-unknown).[1]

Bradykinin is the main mediator associated with the clinical manifestations of HAE. The action of this mediator occurs due to the greater activity of the contact system and kallikrein-kinins system in most patients, while alterations in the endothelium have been described in others.[1,25,40,79]

Symptoms are most often triggered by stress situations, mechanical trauma, infections and medications, particularly estrogens, due to their actions to stimulate the contact system. Some patients have prodromal symptoms.[5,7]

Clinical manifestations are similar in the different types of HAE, being generally more frequent in HAE-C1-INH. Laryngeal edema is the most serious symptom that, although less frequent, can be the cause of death by asphyxia. HAE-C1-INH usually appears in childhood, and HAE-nC1-INH forms in adults.[20,105]

The initial screening test for the diagnosis of HAE is the serum C4 level. Then, the quantitative and functional measurement of C1-INH should be performed. In some cases with suspected AEA-C1-INH, it is necessary to measure C1q. In the absence of C1-INH alterations, the genetic study should be performed mainly in the absence of family history, or to characterize a specific type of HAE-nC1-INH.[5,71,72]

HAE can be confused with idiopathic histaminergic angioedema and also with recurrent angioedema with the use of drugs, especially ACE inhibitors, or with AEA-C1-INH.[7,17]

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Conflict of interests

Régis A. Campos, Faradiba S. Serpa, Maria Luisa O. Alonso, Pedro Giavina-Bianchi, Herberto José Chong-Neto, Eli Mansour, Eliana Toledo, Anete S. Grumach and Solange O.R. Valle received financial and/or honorary support from Takeda and CSL Behring. Anete S. Grumach is a CNPq productivity fellow and has also consulted for Catalyst. The following authors received financial and/or honorary support from Takeda: Camila L. Veronez, Jane da Silva, Marcelo V. Aun, L. Karla Arruda. The other authors deny conflicts of interest.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

2022 Brazilian guidelines for hereditary angioedema – Part 2: therapy

Diretrizes brasileiras de angioedema hereditário 2022 – Parte 2: terapêutica

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ABSTRACT

The treatment of hereditary angioedema begins with the education of patients and their families about the disease, as it is essential to know the unpredictability of attacks as well as their triggering factors. Drug treatment is divided into attack therapy and prophylaxis of clinical manifestations. Attacks should be treated as early as possible with the bradykinin receptor antagonist icatibant or C1-inhibitor concentrate. An action plan needs to be established for all patients with attacks. Long-term prophylaxis of symptoms should preferably be performed with first-line drugs such as C1-inhibitor concentrate or the anti-kallikrein monoclonal antibody lanadelumab. Attenuated androgens are the second line of treatment. In short-term prophylaxis, before procedures that can trigger attacks, the use of C1-inhibitor concentrate is recommended. There are some restrictions for the use of these treatments in children and pregnant women that should be considered. New drugs based on advances in knowledge of the pathophysiology of hereditary angioedema are under development and are expected to improve patient quality of life. The use of standardized tools for monitoring quality of life and controlling disease activity is essential in the follow-up of these patients. The creation of associations of patients and families of patients with

RESUMO

O tratamento do angioedema hereditário tem início com a educação dos pacientes e familiares sobre a doença, pois é fundamental o conhecimento da imprevisibilidade das crises, assim como os seus fatores desencadeantes. O tratamento medicamentoso se divide em terapia das crises e profilaxia das manifestações clínicas. As crises devem ser tratadas o mais precocemente possível com o uso do antagonista do receptor de bradicinina, o icatibanto ou o concentrado de C1-inibidor. É necessário estabeler um plano de ação em caso de crises para todos os pacientes. A profilaxia de longo prazo dos sintomas deve ser realizada preferencialmente com medicamentos de primeira linha, como concentrado do C1-inibidor ou o anticorpo monoclonal anti-calicreína, lanadelumabe. Como segunda linha de tratamento temos os andrógenos atenuados. Na profilaxia de curto prazo, antes de procedimentos que podem desencadear crises, o uso do concentrado de C1-inibidor é preconizado. Existem algumas restrições para uso desses tratamentos em crianças e gestantes que devem ser consideradas. Novos medicamentos baseados nos avanços do conhecimento da fisiopatologia do angioedema hereditário estão em desenvolvimento, devendo melhorar a qualidade de vida dos pacientes. O uso de ferramentas padronizadas para

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hereditary angioedema has played a very important role in the care of these patients in Brazil.

Keywords: Hereditary angioedema, therapeutics, emergency treatment, quality of life, biological therapy.

monitorização da qualidade de vida, do controle e da atividade da doença são fundamentais no acompanhamento destes pacientes. A criação de associações de pacientes e familiares de pacientes com angioedema hereditário tem desempenhado um papel muito importante no cuidado destes pacientes no nosso país.

Descritores: Angioedema hereditário, tratamento farmacológico, tratamento de emergência, qualidade de vida, tratamento biológico.

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How to treat patients with hereditary angioedema?

The treatment of hereditary angioedema (HAE) involves multiple aspects related to health education, pharmacotherapy and the use of tools to assess the control, disease activity and quality of life of the patient. These actions provide individualized treatment plans that contribute to achieving the main objective of treatment, which is to fully control the disease and provide a normal life.[1]

The strategy involving the careful treatment of crises and their prevention is essential for the adequate management of patients, seeking to reduce the significant morbidity and mortality associated with HAE. The drug treatment of HAE consists of the use of drugs for crises and short- or long-term prophylaxis.[2,3] In recent decades there has been a better understanding of the pathophysiology of the disease, which has led to the development of new therapies.[4] However, access to these therapies in Brazil is still restricted, and patients continue to use inappropriate treatments, both for crises and for prophylaxis, which contributes to unfavorable outcomes.

What are the actions related to health education?

Appropriate education can provide patients and/or their families with HAE management skills. Once diagnosed, patients and family members should be oriented about the disease, with the objective of helping them in the best decisions to be made.[3,5,6] During childhood, guidance is also necessary for teachers, caregivers, as well as family doctors and pediatricians.[7-9] Clarifications about the course of HAE and the triggering factors of the crises are the most important initial measures for the patient and his family to have a better quality of life and to prevent serious complications. Other aspects that deserve attention

due to the possibility of affecting the severity of the disease are psychosocial issues.[10-13]

Health professionals involved in monitoring patients with HAE can help them make decisions about treatment and other conditions that deserve special attention, using a process called "shared decision-making" (CDT).[6,13,14] In line with the BDD concept, the latest international HAE guidelines consider the use of this process mainly with regard to the choice of therapy, making HAE management sensitive to the preferences of patients and family members.[2,3] The information shared with the patient must be impartial and balanced, insofar as it includes the reasons why or not to use a certain treatment.[6]

The patient must receive a written document with information about the disease and the conduct to be adopted in case of a crisis[10] (Appendix 1). A report on the disease, therapeutic options, monitoring, prohibited drugs and contact of the specialist physician in HAE must be provided to other assistant physicians and emergency teams.[2,3,15] Sports and hobbies with impactful movements and risk of trauma should be avoided. Regular dental follow-up can avoid extractions and surgical procedures, which are important triggers of crise.[10]

Immunizations are indicated for the prevention of infections that are also potential triggers of crises.[3,16] Considering that HAE is classified as a primary immunodeficiency, that is, an innate error of immunity (ICD10: D84.1), patients can have access to the vaccination schedule administered by the Special Immunobiological Centers (CRIEs) of the Ministry of Health.[17]

Influenza vaccination should be indicated annually, as some patients may have attacks triggered by respiratory infections. Vaccines against hepatitis A and B viruses (HAV and HBV) should be indicated to reduce the chance of infections and the theoretical risk of transmission of HBV by blood products, used in the treatment of HAE crises. Thus, serology for HBV, HCV and HIV is recommended, especially in patients who have been exposed to blood products. Vaccination against COVID-19 should be performed, although there are recent reports of angioedema attacks after the administration of these vaccines.[3,16,18,19]

Another relevant issue is the need to research the disease in family members and provide guidance on the pattern of inheritance and genetic counseling.[10] All first-degree relatives, even if asymptomatic, should be investigated for the possibility of HAE.[10,12,20]

How should long-term prophylaxis be performed?

The objective of long-term prophylaxis is to reduce the frequency and severity of crises with the main focus on improving the patient's quality of life and reducing mortality.[1,3] Treatment must always be personalized, and the indication must be based on the frequency and severity of crises, quality of life and access to medication.[21] There is no established limit for the number of attacks that would indicate the need for continued use of medication. It should be considered that an attack with upper airway obstruction in one patient may have a different weight than a greater number of mild attacks involving extremities in another patient.

Long-term prophylaxis does not necessarily imply permanent uninterrupted use. Dose adjustments and frequency of use must be individualized, guided by the clinical evolution of the patient.[3]

The drugs currently available in Brazil for long-term prophylactic treatment are: attenuated androgens, plasmin inhibitors (antifibrinolytic agents), C1 inhibitor concentrate (C1-INH) and kallikrein inhibitors (Table 1). The most recent international consensus established as first-line drugs for the long-term treatment of HAE, C1-INH concentrates and kallikrein inhibitors.[2,3,15,22] However, in Brazil, these drugs are not yet available in the Unified Health System (SUS), which offers access only to the attenuated androgen danazol, nor incorporated in the List of Procedures of the National Health Agency (ANS), which regulates supplementary health.

Attenuated androgens (AA) used for long-term prophylaxis include danazol and oxandrolone, which increase plasma levels of C1-INH and C4, being effective in reducing the frequency of angioedema attacks.[3] The most relevant adverse effects of AA and usually dose-dependent are hepatotoxicity, virilization and alteration of the plasma lipid profile. Virilizing effects include menstrual cycle irregularity, voice changes, and hirsutism. Psychological effects such as mood swings, loss of libido, anxiety and depression can occur. Other adverse reactions described include weight gain, acne, myopathies, arterial hypertension and hematuria. These adverse effects are reversible when the drug is discontinued.[23-25] Danazol is the only AA registered with the National Health Surveillance Agency (ANVISA), the optimal dose to minimize adverse effects being ≤ 200 mg/day.[3,15,26] Patients using AA should be monitored with blood count,

Table 1
Drugs available in Brazil for long-term treatment of patients with hereditary angioedema[2-4,15]

Drug	Mechanism of action	Half life	Way of use	Dose (adult)	Dose (child)	Comments
Tranexamic acid	Inhibits plasminogen activation	2-8 hours	VO, IV	1000-6000 mg/day	30-50 mg/kg/day	It does not work in crises. Effective in 1/3 of patients
Danazol	Increases hepatic synthesis of C1-INH; enhances aminopeptidase function	7-12 hours	VO	200 mg/day (maximum)[a]	2.5 mg/kg/day	See drug interactions and contraindications. It does not work in crises.
pdC1-INH	Replacement of C1-INH	32.7-62 hours	IV	1000 IU or 20 IU/kg[b]	1000 IU or 20 IU/kg	Approved ≥ 12 years
pdC1-INH	Replacement of C1-INH	50-70 hours	SC	60 IU/kg, 2x/week	60 IU/kg, 2x/wk	Approved ≥ 8 years
Lanadelumab	Kallikrein inhibition	2 weeks	SC	300 mg/2 weeks for 6 months. Space for 4 weeks with improvement	Same as adults	Approved ≥ 12 years

[a] TheMaximum dose established by consensus.
[b] Fixed dose according to pivotal study and variable dose according to studies published later.

liver function, lipid profile, creatine phosphokinase, alpha-fetoprotein, and urinalysis every six months and abdominal ultrasound annually to screen for hepatocellular adenoma or carcinoma. AAs are contraindicated during pregnancy and breastfeeding, before puberty, and in patients with prostate cancer or liver, kidney or heart failure.[25]

The literature is scarce on the use of the antifibrinolytic tranexamic acid in the long-term prophylaxis of AEH.[27-29] This drug competitively inhibits plasminogen activation, with a reduction in the transformation of plasminogen to plasmin and a decrease in fibrinolysis. It has lower efficacy than danazol and less toxicity, and its use is reserved for patients with intolerance or contraindication to danazol, as well as in patients younger than 12 years.[4] Tranexamic acid is used at a dose of 30-50 mg/kg/day, divided into 2-3 doses, with a maximum dose of 6.0 g/day.[3] The main concern with the use of antifibrinolytics is the risk of thrombosis, although this adverse reaction has not been reported.[28,29] The onset of the therapeutic effect is approximately 48 hours after its administration.[27]

Plasma-derived (pdC1-INH) or human recombinant (rhC1-INH) C1 inhibitor concentrates are drugs used to replace C1-INH deficiency. They act on all systems regulated by this glycoprotein, controlling the production of bradykinin.[3,4] pdC1-INH is obtained by separating C1-INH from purified human plasma by a combination of processes such as cryoprecipitation, ion exchange chromatography, ultrafiltration, nanofiltration, polyethylene glycol precipitation,

pasteurization and, finally, lyophilization.[3,30] This process guarantees the safety of the treatment in relation to the transmission of infectious diseases such as hepatitis and acquired immunodeficiency syndrome.[30-37] The plasma half-life of pdC1-INH is greater than 30 hours, therefore, it is safe and effective for long-term prophylaxis, with few adverse events.[32,38-40]

In Brazil, two products are approved by ANVISA: Berinert SC® (subcutaneous use) and Cinryze® (intravenous use). Randomized double-blind studies of Cinryze® have demonstrated its efficacy and safety.[30,41,42] The pivotal study with Cinryze® used a fixed dose of 1,000 IU intravenous (IV) every 3-4 days, however, later, another retrospective study showed better efficacy with the use of doses according to the patient's weight (20 IU/ kg/dose).[30,41,42] The risk of thromboembolism resulting from the prophylactic use of pdC1-INH was observed by the FDA (US Food and Drug Administration).[43] Later studies did not confirm this occurrence, suggesting that patients could have other associated predisposing factors.[44,45]

The prophylactic use of Berinert SC®, twice a week, significantly reduced the frequency of seizures.[46] The most frequent adverse effect was a mild reaction at the application site. The subcutaneous (SC) use of pdC1-INH facilitates self-administration and is available as Berinert® SC 2000/3000 IU (ANVISA).[47] The SC formulation contains 1500 IU in 3 mL of solution, compared to the IV formulation which contains 500 IU in 10 mL. SC administration results in more consistent plasma levels between applications compared to IV administration.[39] The recommended dose is 60 IU/kg of weight, for patients over eight years of age, twice a week (every three or four days), to be applied to the abdomen.[46,48]

Not yet available in our country, rhC1-INH (Ruconest®) is obtained from the milk of transgenic rabbits and, therefore, is contraindicated in patients with known or suspected allergy to rabbits or products derived from them.[32,49] Clinical studies have demonstrated the efficacy and safety of rhC1-INH, without thrombotic adverse events.[49,50] The plasma half-life is shorter due to its glycosylation, approximately 3 hours, which makes its use in long-term prophylaxis difficult, however, a study demonstrated this possibility when administered once a week for eight weeks.[40,51] The recommended dose is 50 U/kg IV for adults weighing less than 84 kg, and a dose of 4200 U (two vials) for adults weighing more.[50] Patients who do not wish to be treated with blood products for religious, moral or other reasons may receive recombinant C1-INH.[52]

Lanadelumab (Takhzyro®) is part of the group of kallikrein inhibitor drugs and is an anti-plasma kallikrein monoclonal antibody for SC use, released for patients over 12 years of age.[53] The pivotal phase 3 (HELP), double-blind, randomized, placebo-controlled study evaluated the drug administered subcutaneously at three different doses (150 mg every four weeks; 300 mg every four weeks and 300 mg every two weeks) or placebo. There was a significant difference in the reduction of seizures for the three doses used in relation to placebo, with better results when used at a dose of 300 mg every two weeks.[53] It is worth noting that the therapeutic effect occurred after the first dose and remained throughout the clinical trial.[54] This study was followed by an open-label phase with a dose of 300 mg, which proved the long-term efficacy and safety of the drug when in 97.7% of the treatment days there were no angioedema attacks.[14] The most frequently reported adverse events were local reactions and dizziness, with no serious events being reported.[14,54] A dose of 300 mg SC every 14 days is recommended and after six months without crises, the interval between doses can increase to four weeks.[55] A recent real-life study showed that the administration interval can be gradually increased before reaching this six-month period, always verifying the clinical response.[56]

The safety profile of the different drugs should always be considered when choosing long-term prophylaxis in the treatment of HAE-C1-INH (Table 2).

Long-term prophylaxis for patients with HAE-nC1-INH has not been studied in randomized, placebo-controlled clinical trials.[2] However, smaller open-label studies and case series reports have suggested strategies that can be used. The two main therapies used are antifibrinolytics and hormone therapy. There are reports for long-term prophylaxis in HAE-nC1-INH using pdC1-INH and lanadelumab, but only in specific situations, usually in the absence of response to other options.[2] Some women with HAE-nC1-INH with worsening symptoms during pregnancy benefited from the use of pdC1-INH.[57]

The first step in the treatment of AEH-nC1-INH consists of suspending the use of exogenous estrogens, which is often enough to make the patient asymptomatic.[58] Other options include the use of progestins or even AA.[59-61] Tranexamic acid has been used with good response, probably due to the inhibition of plasmin formation.[61]

How should short-term prophylaxis be performed?

Short-term prophylaxis is indicated for patients undergoing medical or surgical procedures that mainly involve the cervicofacial region, at risk of angioedema of the upper respiratory tract, such as more invasive dental treatment (tooth extraction), tonsillectomy, facial surgery, endoscopy, bronchoscopy and surgical procedures that require tracheal intubation.[54,62-65] It was found that among patients diagnosed with AEH-C1-INH who underwent tooth extraction, 21% developed local angioedema after the procedure.[65] Dentists are unaware of the AEH and patients face difficulties in obtaining dental care.[66]

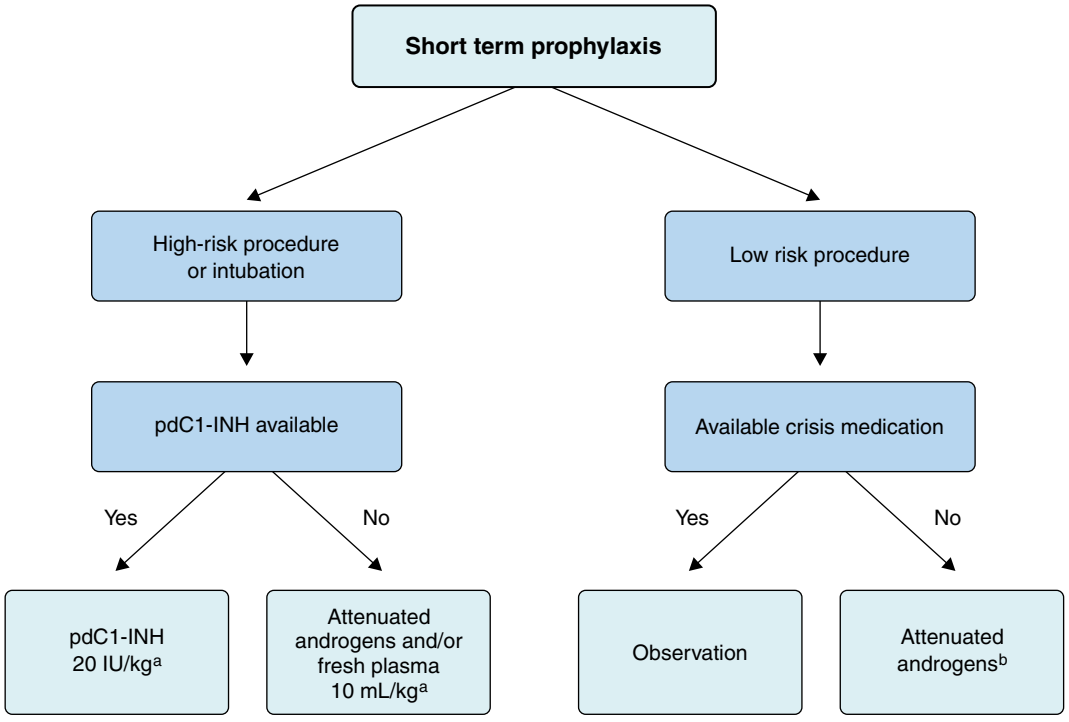
Table 2
Adverse effects and contraindications of prophylactic drugs for hereditary angioedema available in Brazil[2-4,15]

Medication	Adverse effects	Contraindications	Comments
Danazol	Hormonal: seborrhea, acne, hirsutism, menstrual irregularity, virilization, libido alteration, voice alteration. Alkylation at position 17 alpha: hepatotoxicity, increased transaminases, hepatic adenoma, hepatocarcinoma. Others: weight gain, change in lipoprotein profile, increased risk of atherogenesis, increased blood pressure, epiphyseal closure	Children (Tanner I-IV), pregnancy, breast cancer, prostate cancer, nephrotic syndrome, and changes in liver function	Interaction with other drugs: statins (rhabdomyolysis), increases carbamazepine concentration, increases insulin resistance, increases prothrombin time in warfarin users
Tranexamic acid	Muscle necrosis (asthenia, myalgia, increased CPK, increased aldolase), dizziness and postural hypotension, nausea, diarrhea and abdominal pain, muscle cramps, dysmenorrhea, pruritus, theoretical risk of thrombosis	Thrombophilia	Increased risk of thrombosis
Plasma-derived C1 inhibitor (pdC1-INH)	Theoretical risk of transmission of infectious agents, thrombosis (extremely high off-label doses), anaphylaxis (very rare), neutralizing anti-C1-INH antibodies		
Lanadelumab	Mild local reactions, hypersensitivity reactions, interference with clotting tests (APTT prolongation)		

CPK = creatine phosphokinase.

For minor dental procedures, no routine prophylaxis is necessary if crisis treatment is immediately available.[66] In non-dental surgeries, the risk of perioperative crisis varies from 5.7 to 30.5%.[63] The unpredictability of HAE crises triggered by procedures makes the current international consensus suggest that short-term prophylaxis should be considered individually.[2,15] The risk associated with the procedure to be performed, the availability of crisis treatment and the occurrence of a previous episode in similar circumstances should be verified.[15,21] In some situations, when the risk of the procedure to be performed is minimal and there is availability of crisis treatment, one may choose not to indicate short-term prophylaxis. In these cases, at the slightest sign of the onset of symptoms, crisis treatment should be instituted[21] (Figure 1).

pdC1-INH is the first-line treatment for short-term prophylaxis, and should be used one to six hours before the procedure, at a dose of 20 U/kg.[33,41,67,68] Fresh plasma can be used in procedures with high risk or need for intubation, when pdC1-INH is not available, however, there are no comparative studies evaluating the different drugs.[69] The suggested dose of fresh plasma is 10 mL/kg (2-4 units for an adult), one to six hours before the procedure[70] (Figure 1). AAs can also be used when the risk related to the surgery is relatively low.[71] Danazol is administered orally, three times a day, at a dose of 2.5 to 10 mg/kg/day with a maximum of 600 mg/day, starting 5 to 7 days before and maintaining it for 2 to 3 days after the procedure.[2,15,71-73] AEH crisis was found in 12% of patients after tooth extraction, even when receiving short-term prophylaxis,[65] which reinforces the need for



pdC1-INH = plasma-derived C1-INH concentrate.

[a] 1 to 6 hours before the procedure.

[b] For danazol 2.5 to 10 mg/kg, up to 200 mg/ 8-12 hours 5 days before and 2-3 days after the procedure.

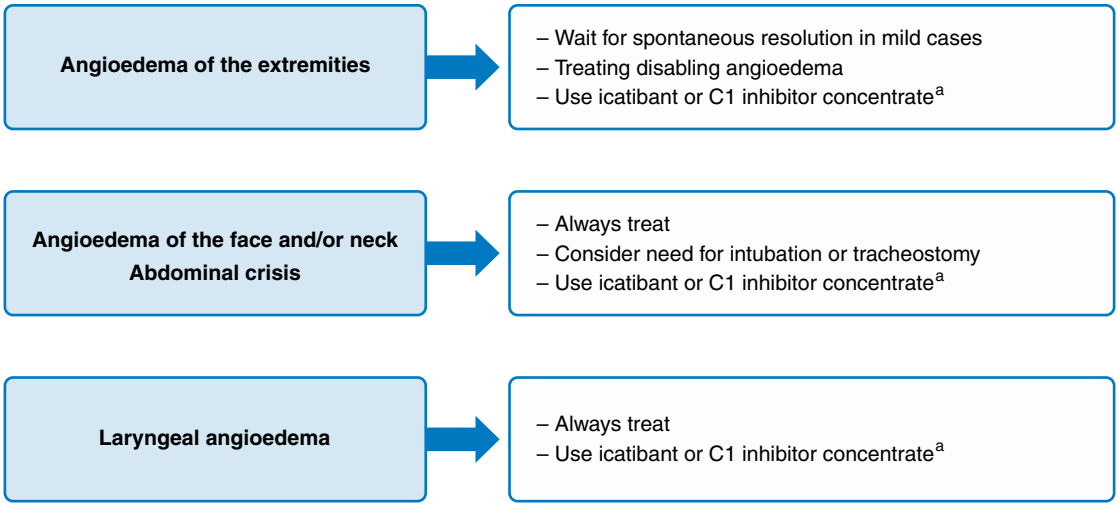
Figure 1
Short-term prophylaxis of hereditary angioedema with C1-INH deficiency[21]

crisis medication availability. There are no published data on short-term prophylaxis in AEH-nC1-INH. Therefore, the same protocol used in the AEH-C1-INH is recommended.[2]

How should hereditary angioedema attacks be treated?

The patient and/or caregiver should be instructed to treat the crisis, considering the potential for severity/location and possible disability. Early treatment of crises is essential and patients must have access to therapy and be trained to self-administer the medication.[2,3,15,74] Treating the crisis only in the medical service requires displacement and results in delayed initiation of therapy, which can contribute to inappropriate approaches and unfavorable outcomes. Although there is a consensus that attacks of abdominal, facial, labial and upper respiratory tract location should be treated early due to their potential for severity, when disabling extremity attacks also deserve attention and rapid treatment[2] (Figure 2). In case of an attack involving the larynx, delay in treatment can be fatal.[75] Thus, it is recommended that HAE patients have at least two doses of the drug to use at home in cases of eventual crises.[3,10,76,77]

In the emergency room, the first step in approaching patients with HAE crisis affecting the upper airways, tongue and/or uvula is to maintain a patent airway. In unstable patients, with imminent risk of asphyxia, orotracheal intubation (OTI) should not be delaye.[78] It is important to emphasize that, in the initial phase of airway obstruction, no drop in oxygen saturation is observed. Emergency room monitoring is indicated and, in cases of hypotension or dehydration, fluid replacement should be applied. When patients present with severe abdominal crises, in addition to specific therapy, symptomatic treatment with administration of fluids, antiemetics and analgesics is indicated. Antispasmodics and narcotics may be needed to treat severe pain.[79]



[a] Available in Brazil: C1-INH concentrate and icatibant (Fyrazyr®). In all situations, if C1 inhibitor concentrate or icatibant is not available, use fresh frozen plasma.

Figure 2
Recommendations for the treatment of hereditary angioedema crisis, according to the affected area[18]

The drugs used for the treatment of crises act by preventing the action of bradykinin on endothelial cells or increasing the levels of C1-INH, and, consequently, reducing the levels of bradykinin.[21] For crisis management, four types of treatments can be used: pdC1-INH, rhC1-INH, bradykinin B2 receptor antagonist (icatibant) and kallikrein inhibitor (ecalantide).[2,3,50,80] In Brazil, so far, there are three products approved by ANVISA for use in HAE crises: two pdC1-INH (Berinert® and Cinryze®)[47,81] and icatibant (Firazyr®)[82] (Table 3).

PdC1-INH and rhC1-INH are effective and safe for the treatment of HAE attacks in all age groups.[42,67,80] Berinert® is a pasteurized and nanofiltered product, indicated for IV administration at a dose of 20 IU/kg, regardless of the severity of the crisis.[42] In pivotal studies, the median time to onset of symptom relief was 0.46 hours and to complete resolution 15.5 hours. In addition, only 1.1% of patients required a second dose to control symptoms, with a time of four hours between the first and second doses, if necessary.[42] The other nanofiltered pdC1-INH concentrate (Cinryze®) was used at fixed doses (500 U or 1,000 U) in patients with angioedema of the extremities and in abdominal crises.[83] As with Berinert®, Cinryze® self-administration significantly reduced the duration and severity of attacks, in addition to the need for analgesics. A dose of 1000 U is recommended for the treatment of crises and can be repeated one hour later, if necessary.[41,49] However, there is evidence that fixed doses may not be sufficient to control seizures, and a dose of 20 IU/kg is more effective.[83] Additional dose was required in more than 60% of patients with laryngeal edema crisis who received fixed doses of pdC1-INH.[83]

RhC1-INH (Ruconest®) is not approved for self-administration, as it is not available in Brazil. The recommended dose is an IV injection of 50 U/kg for adults weighing less than 84 kg and at a dose of 4200U (two vials) for those weighing 84 kg or more.[84]

Icatibant acetate (Firazyr®) is a synthetic molecule, similar to bradykinin, which acts as a competitive and selective antagonist of the bradykinin B2 receptor.[85,86] HAE attacks resolve more quickly with early use of icatibant compared to late use, therefore, administration within the first six hours after the onset of symptoms is recommended.[87] In Brazil, icatibant acetate is licensed for home self-administration. Home use is safe, and the most common adverse events are erythema and pain at the injection site, with spontaneous resolution.[88] The recommended dose is 30 mg for adults and 0.4 mg/kg in the age group from 2 to 17 years, subcutaneously, exclusively in the abdominal region, with additional injections being possible every 6 hours, up to a maximum of three times in 24 hours.[85]

Ecallantide (Kalbitor®) is a kallikrein inhibitor approved for use in the United States and not available in Brazil. The recommended dose is 30 mg SC, and it is not approved for self-administration at home, as anaphylaxis has been observed in approximately 3% of patients.[89]

The use of fresh frozen plasma should be reserved for situations in which no other seizure drugs are available. This treatment strategy has only been used in observational studies and has not been tested in clinical trials for efficacy and safety in HAE attacks. In addition, the administration of plasma offers not only the replacement of C1-INH, but also the substrates on which this inhibitor acts, which may not have adequate efficacy and even worsen the condition. Other risks of the use of plasma consist of the occurrence of transfusion reactions, transmission of pathogens, in addition to volume overload.[90] The recommended dose is two to four units for adults and 10 to 15 mL/kg for children.[21]

The need to seek a health service for plasma administration makes it impossible for many patients to receive rapid treatment.[90] In some situations, the angioedema crisis can be very serious and require rapid response therapy and, in addition, in some regions of Brazil, access to plasma transfusion is not possible, which emphasizes the need to provide an effective therapy. and capable of self-administration.

To date, there are no studies comparing the efficacy of drugs used to treat HAE crisis in randomized clinical trials. Therefore, we suggest using the available option, in the shortest possible time between the beginning of the crisis and its application to obtain better effectiveness.

How should hereditary angioedema in childhood and adolescence be managed?

About 90% of patients present their first HAE symptoms before the age of 20 years.[91] A recent Brazilian multicenter study evaluated 95 pediatric patients with HAE-C1-INH and showed a lower mean age at onset of symptoms (3.3 years), with almost all symptomatic patients (96.2%) having their first symptoms. before age 12.[92] AEH-nC1-INH

generally begins in adolescence or adulthood, and its manifestation before the first decade of life is rare.[93]

In the pediatric age group, there is an average delay of four to eight years in the diagnosis of HAE.[91,92] Some of the main factors involved in this delay include: difficulty for the child to verbalize their symptoms, misdiagnosis of symptoms (eg, recurrent abdominal pain is common in childhood), symptoms may be less intense than in adults, delay in the investigation by parents due to denial of their own disease or fear of the result, screening tests with C4 with low accuracy in the pediatric age group, absence of family history and little

Table 3
Characteristics and guidelines for the drugs available in Brazil for the treatment of hereditary angioedema crisis[4,47,82]

Features/guidelines	Medication	
	Icatibant (Firazyr®)	**Plasma-derived C1-INH concentrate (Cinryze® / Berinert®)**
Age group	≥ 2 years	≥ 12 years / No age limit
Presentation	10 mg/mL of icatibant (syringe with 3 mL of the solution)	500 IU lyophilized powder/ 500 IU lyophilized powder
Dose	0.4 mg/kg up to 18 years 30 mg over 18 years or 65 kg	1,000 IU / 20 IU/kg
Route of administration	Subcutaneously, slowly. Preferably in the abdominal region	Intravenous / Slow intravenous or infusion (4 mL/minute)
Self administration	Yes	Yes / Yes
Solution appearance	Colorless and clear	Colorless to slightly blue / Colorless and clear
Storage temperature	2 °C to 8 °C	2 °C to 8 °C / Ambient (15 °C to 30 °C)
Storage after fractionated dose use or reconstitution	Not recommended	Not recommended / After reconstitution, only in the vial
Storage time	Not recommended	Immediate use after reconstitution / Maximum 8 hours at room temperature
Adverse effects	Local reactions (itching, pain, swelling, and erythema in active ischemic heart disease acetate to administration area)	Theoretical risk of transmission of infectious agents to thrombosis (very high off-label doses). Anaphylaxis (very rare). Formation of anti-C1-INH neutralizing antibodies

recognition of the disease by pediatricians. In general, pediatricians are the first physicians to evaluate a child with HAE, however they are responsible for only 3% of diagnoses of this disease.[94] Thus, it is very important to educate these professionals, highlighting warning signs for the diagnosis of HAE in children: positive family history, presence of recurrent abdominal pain and trauma as a triggering factor for angioedema crises.[95]

The drug treatment of HAE in childhood and adolescence uses the same strategies as adults, however, it is important to note that few clinical trials specifically target the pediatric age group, particularly in children under 12 years of age.[9]

In Brazil, so far, there are three products approved by ANVISA for the treatment of angioedema crises in this age group: two pdC1-INH (Berinert® and Cinryze®) and icatibant (Firazyr®).

pdC1-INH for IV use is effective and safe in the treatment of all forms of HAE attacks due to C1-INH deficiency in children and adolescents. Recent research with the use of pdC1-INH in the pediatric age group for a prolonged period has confirmed its efficacy and safety.[96] Berinert® is indicated for IV administration at a dose of 20 IU/kg, regardless of the severity of the crisis and without age restrictions. Another nanofiltered pdC1-INH, Cinryze® is approved for adolescents over 12 years of age at fixed doses (500 U or 1000 U).[10,97]

The safety and efficacy of icatibant (Firazyr®) have been studied in children.[98] Most patients started to resolve symptoms within an hour and the most common adverse event was reaction at the application site with spontaneous resolution. The recommended dose is 0.4 mg/kg in the age group from 2 to 17 years, over 12 kg, subcutaneously, exclusively in the abdominal region, with additional injections being possible every 6 hours, up to a maximum of three injections within 24 hours. It is presented in 3 mL pre-filled syringes containing 10 mg/mL icatibant. Doses can be adapted by weight [12 to 25 kg = 10 mg (1 mL); 26 to 40 kg = 15 mg (1.5 mL); 41 to 50 kg = 20 mg (2 mL); 51 to 65 kg = 25 mg (2.5 mL); >65 kg = 30 mg (3 mL)].

Fresh frozen plasma should be used at a dose of 10 mL/kg IV, only in emergency situations and in the absence of licensed drugs for crisis, due to side effects and its low efficacy with risk of paradoxical worsening.[98] Other options not available in Brazil, but used in other countries for the treatment of crises, include ecallantide (SC kallikrein inhibitor, over 12 years old) and Ruconest® (intravenous recombinant C1-INH concentrate, over 12 years old).[15,99]

Therefore, for the treatment of seizures in patients under 12 years of age, pdC1-INH for IV use (Berinert®), icatibant (Firazyr®) may be used in patients over two years of age, and fresh plasma in any age.

Tranexamic acid is indicated for long-term prophylaxis of children with HAE under 12 years of age, despite its low efficacy, given the impossibility of treatment with more effective drugs in use in adolescents and adults.[3,100] Lanadelumab (Takhzyro®) is currently only approved in patients over 12 years of age, showing high efficacy and a good safety profile, as demonstrated in the extension study in which 21 patients under 18 years of age were evaluated.[14] AAs should not be used in the pediatric age group, especially before puberty.[25,101] Other options approved by ANVISA with high efficacy and good safety profile include: IV pdC1-INH (Cinryze®, ≥ 12 years) and SC (Berinert® SC, ≥ 8 years) (Table 1). Adolescents with HAE may benefit from the use of continuous progestin from menarche, as it can help in the control of crises, since they inhibit the endogenous estrogen cycle, particularly in the HAE-nC1-INH.[101]

pdC1-INH (Berinert SC®) and lanadelumab (Takhzyro®) have significantly changed long-term prophylaxis as they are both safe, self-administered and released by subcutaneous infusion, which is an important advantage for use in children and teenagers.[2] However, additional studies are still needed to assess efficacy and safety in younger children.

Thus, for long-term prophylaxis in children under 8 years of age, tranexamic acid is currently available. Patients between 8 and 12 years of age can receive pdC1-INH SC (Berinert®), and those 12 years and older can receive long-term prophylaxis like adult patients, considering AA in those with Tanner stage V.

For short-term prophylaxis, the same pharmacotherapy strategies used in adults are recommended. It is important to point out that AA are not indicated for long-term prophylaxis in children before puberty, but they can be used for a short period before risky procedures.[3]

How should HAE be addressed during pregnancy, delivery, postpartum and lactation?

Anatomy, physiology and hormonal changes caused by pregnancy can influence the manifestations

and affect the course and treatment of HAE.[3] Estrogen is a trigger for seizures because it is related to the control of bradykinin production.[102] Thus, symptoms can become more frequent and more severe during pregnancy, after delivery and lactation.[8,59,103,104] During pregnancy, the disease may improve, worsen or there may be no impact on the frequency and severity of attacks, which makes it difficult to predict the evolution of patients.[105-107] Despite the divergent results, the tendency is for symptoms to worsen during the first trimester of pregnancy, when serum estrogen levels are higher and long-term prophylaxis with drugs contraindicated in pregnancy has to be discontinued. The second trimester has been described as the period of lowest disease activity due to permanently high levels of the other hormones. In the third trimester, increased production of placental estrogens and prolactin can increase the frequency and intensity of seizures.[103]

The frequency of seizures during previous pregnancies has no predictive value for the evolution of HAE in later pregnancies. Symptomatic patients are more likely to have premature labor or miscarriage due to bradykinin activity, which leads to uterine smooth muscle contraction.[103] An increase in the frequency and severity of seizures has been described in pregnant women with early onset of symptoms or who present trauma as an important triggering factor.[107] Pregnant women with HAE-C1-INH whose fetus has the same deficiency have a higher frequency of seizures in the gestational period than those whose fetuses are healthy.[108] It is believed that other factors not yet determined may lead to angioedema crises in pregnant women.[108] Pregnant women with AEH-nC1-INH generally have a greater number of seizures during pregnancy, particularly in AEH-FXII.[57,109-111]

The main triggers of crises in this period are stress and physical trauma.[112,113] The seizures occur in a location similar to that of the non-gestational period, and there may be a predilection for the abdomen, which makes the differential diagnosis difficult.[103] In these situations, abdominal ultrasound is useful in the diagnostic evaluation. In general, seizures are mild and rarely life-threatening.[113]

As for the mode of delivery, vaginal delivery is preferable to cesarean section. When there is an obstetric indication for cesarean delivery, epidural anesthesia is the best choice.[114] It is highly recommended that the hospital where the delivery will take place has trained personnel to care for HAE patients and that medication is available, both for prophylaxis and for the management of a possible crisis.[103]

Genetic counseling should be offered to patients with HAE, since there is a 50% chance that the offspring will also have the disease.[103]

When planning pregnancy, women who have been using long-term AA prophylaxis should discontinue treatment at least one month before conception. Androgens are not recommended during pregnancy, as they cross the placental barrier and can result in fetal virilization, leading to female pseudohermaphroditism.[3,15] It is recommended to carry out a beta-HCG measurement before starting AA administration in women of childbearing age.[15] Tranexamic acid also crosses the placental barrier and can cause side effects for the fetus, but to a lesser extent than those caused by AA.[3,8,15,103]

The treatment of crises during pregnancy includes the prescription of symptomatic drugs (analgesics), hydration and use of specific medication, when indicated.[103] The therapy of choice in the management of crises during pregnancy, childbirth, postpartum and breastfeeding is pdC1-INH in the same dosage as non-pregnant women.[2,3,15] Other drugs effective in crisis management, such as icatibant and recombinant C1-INH, were used during this period, with a good safety and efficacy profile.[115-117] There are no data on the use of ecallantide, and this drug is classified as Category C in pregnancy by the FDA.[103] Fresh frozen plasma can be administered in cases of severe crisis where pdC1-INH is not available.

In cases of HAE-C1-INH, when long-term prophylaxis is necessary, the first-line drug is pdC1-INH IV at a dose similar to that of non-pregnant women.[3,15,46,118] The pdC1-INH has been used for over two decades, with evidence of efficacy and safety in this population, being classified as category C by the FDA.[2] In women with HAE-nC1-INH, there are isolated reports that show efficacy and safety of pdC1-INH concentrate.[57,119] The SC administered pdC1-INH has not yet been sufficiently evaluated, but there are reported cases of use in pregnant women, with no evidence of risk to the fetus.[120,121]

When pdC1-INH is not available, tranexamic acid may be indicated, but its effectiveness has not been proven.[3] The dosage is similar to that prescribed for non-pregnant women. Although there are no data that corroborate a greater risk due to the prothrombotic effect, it is recommended to use it with caution in patients with a personal and/or family history of

thromboembolism.[122] There are currently no data available on the use of lanadelumab during pregnancy and therefore it should not be used.

Short-term prophylaxis during pregnancy should be considered in any procedure performed, particularly in interventions with risk of crises such as chorionic villus sampling, amniocentesis and surgically induced abortion.[3] The first-choice treatment is also the administration of pdC1-INH, 1 to 6 hours before the procedure, at a dose of 20 U/kg of weight or 1000 IU, depending on the drug.[15,103] The need for short-term prophylaxis for delivery is unclear. Most international consensuses suggest that prophylaxis should be indicated in cesarean delivery, but that in vaginal delivery, just having crisis medication available in the delivery room would be enough.[2,3,15] Prophylactic administration of pdC1-INH concentrate is also indicated in cases of need for intubation and for difficult deliveries requiring forceps or in patients without disease control during the third trimester.[2,3,103] There are isolated reports showing the efficacy of using pdC1-INH for short-term prophylaxis in the delivery of women with AEH-nC1-INH.[123] When short-term prophylaxis is indicated and pdC1-INH is not available, fresh frozen plasma and/or tranexamic acid can be administered.[3]

In the puerperium, crises usually occur immediately after delivery or within 48 hours after delivery, and can have serious consequences.[103,123] During this period, some women may experience angioedema of the vulva and infusion sites, as well as urethral obstruction and abdominal crises, and observation of the patient is recommended for 72 hours after delivery.[32,103,123] Studies show that, regardless of the type of delivery, crises are rare, even in the absence of prophylaxis.[106,107] After hospital discharge, the recommendations for home follow-up of postpartum women are the same as those given to non-pregnant women with HAE.[103]

During lactation, there may be an increase in the frequency and severity of HAE crises, interfering with breastfeeding.[124] Higher concentrations of prolactin appear to be responsible for the temporary increase in seizures after delivery.[107] AA and antifibrinolytics are excreted in human milk and, therefore, should be avoided during this period.[46,90] Even so, we can consider the use of tranexamic acid in the absence of pdC1-INH as prophylaxis.[32,90] Another therapeutic option for prophylaxis during lactation is the use of progesterone alone, without estrogen.[102] Even at low doses, progesterone alone is the contraceptive of choice during lactation, even in the early postpartum period[125] and has prophylactic potential in the management of AEH.[114]

The use of available drugs for the treatment of HAE with or without C1-INH deficiency is limited during pregnancy, childbirth, postpartum and lactation, but there are safe and available options. The pdC1-INH is the recommended first-line option in the management of these patients, both in prophylaxis and in the treatment of crises.[3]

Drugs for the therapeutic approach of HAE in pregnancy according to FDA categorization are summarized in Table 4.

Therefore, according to the latest international consensus, the treatment of AEH-C1-INH, including special groups (children, pregnant women and nursing mothers), includes first and second choice therapeutic options (Table 5).

What are the prospects in the treatment of hereditary angioedema?

In the last decades, the treatment of HAE has evolved from the use of nonspecific drugs for prophylaxis and treatment of crises (such as attenuated androgens, tranexamic acid and frozen plasma) to the use of specific drugs considered first-line. First-line drugs target the replacement of C1-INH and, more recently, molecules aimed at controlling plasma kallikrein-kinins system proteins.[1-3,15]

With the availability of effective and safe drugs for the treatment of angioedema attacks, most drugs under development work for long-term prophylaxis. Several studies are also being conducted with the aim of expanding the age group and adding other indications for existing products. Most new drugs in development currently target factor XII, plasma kallikrein and the B2 kinin receptor (B2R). The new prophylactic therapies aim to provide greater dosage convenience, with an increase in the interval between IV or SC applications, and to develop drugs for oral administration.

Among the new drugs already available in other countries, berotralstat (BCX7353) (BioCryst Pharmaceuticals, Inc) has been approved by the FDA and EMA (European Medicines Agency). It is a small synthetic molecule that inhibits plasma kallikrein, administered orally, which has been shown to be safe and effective in long-term prophylaxis. In the latest international consensus on hereditary angioedema,

together with the plasma-derived C1-INH concentrate and lanadelumab, this molecule was considered one of the first options for long-term prophylaxis due to its efficacy and its oral administration.[3] Some side effects have been described: abdominal pain, vomiting, diarrhea and low back pain.[127] These reactions occur soon after the start of treatment, becoming less frequent with time and are usually self-limiting.[128]

At least six new drugs intended for HAE prophylaxis or treatment of seizures are in phase 1, 2 and 3 clinical trials (Table 6). Among these medications, three act by inhibiting plasma kallikrein, with oral administration, two of which are intended for long-term prophylaxis and one for the treatment of angioedema crises.[129-134] Donidarsolen (IONIS PKK-LRx) is a new drug for the treatment of AEH-C1-INH based on the use of a second-generation antisense oligonucleotide, which targets the gene encoding plasma prekallikrein with significant clinical efficacy, safety and tolerance in long-term prophylaxis.[135-137] Garadacimab® (CSL312, CSL Behring) is a subcutaneously administered monoclonal antibody that targets factor XIIa, in development for long-term prophylaxis in HAE-C1-INH, showing an average reduction of monthly HAE attacks above 90%.[138] The drug PHA-022121® (Pharvaris) proved to be a potent antagonist of the bradykinin B2 receptor (B2R) with oral administration and is currently being evaluated for the treatment of seizures and long-term prophylaxis in patients with HAE-C1-INH.[139-141]

The perspectives of gene therapy for AEH-C1-INH have become closer using adenoviral vectors (AAV) in the expression of normal copies of the gene encoding C1-INH.[142-144] In another innovative approach, NTLA-2002®, still in the pre-clinical phase, was based on the use of the "clustered regularly interspaced short palindromic repeats" (CRISPR)/Cas^9 system in the in vivo edition of the prekallikrein gene, generating a process of gene knockout.[145]

Considering the new treatments already approved and some of the perspectives of therapy for HAE-C1-INH, most of the contact pathway and fibrinolysis can

Table 4
Medications used in the approach tohereditary angioedemaduring pregnancy[126]

Scientific name	Commercial name	Indication in the HAE	Category (FDA)
Danazol	Ladogal®	Prophylaxis	X
Tranexamic acid	Transamin®	Prophylaxis	B
	Hemoblock®	Prophylaxis	
pdC1-INH	Berinert®	Crisis	C
pdC1-INH	Cinryze®	Prophylaxis	C
rhC1-INH [a]	Ruconest®	Prophylaxis	B
		Crisis	
Icatibanto	Firazyr®	Crisis	C
Ecalantid [a]	Kalbitor®	Crisis	C
Lanadelumab	Takhzyro®	Prophylaxis	Not defined

[a] Medicines not approved by ANVISA for use in Brazil.
HAE = hereditary angioedema, FDA = Food and Drug Administration, pdC1-INH = plasma-derived C1 inhibitor concentrate, rhC1-INH = recombinant C1 inhibitor.

Table 5
AEH-C1-INH treatment strategies approved in Brazil for different patient populations according to the recommendations of the latest international consensus[2,3,15]

Population	Treatment line	Treatment strategies		
		Prophylaxis		Crisis
		Long term	Short term	
Adults and elderly	First	pdC1-INH (SC, EV) Lanadelumab Berotralstat [a]	pdC1-INH EV	pdC1-INH EV Icatibanto
	Second	Attenuated androgens [b] Tranexamic acid	Attenuated androgens Plasma	Plasma
Children and teenagers	First	pdC1-INH EV pdC1-INH SC > 8 years Lanadelumab > 12 years	pdC1-INH EV	pdC1-INH EV Icatibanto > 2 years
	Second	Tranexamic acid Attenuated androgens after puberty	Attenuated androgens Plasma	Plasma
Pregnant women	First	pdC1-INH (SC [a], EV)	pdC1-INH EV	pdC1-INH EV
	Second	Tranexamic acid	Plasma	Plasma

[a] Not approved in Brazil.
[b] Maximum dose of 200 mg (danazol).
pdC1-INH = plasma-derived C1 inhibitor concentrate, IV = intravenous, SC = subcutaneous.

now be controlled, which may result in a lower action of bradykinin, with improvement or prevention of attacks of angioedema (Figure 3).

What are the tools for monitoring the quality of life, activity and control of hereditary angioedema?

HAE crises can cause not only physical damage, but also psychological damage, such as fear of death from asphyxia during laryngeal crises, fear of not having the specific medication in case of crisis, fear of not having a doctor who knows your disease in case of care of urgency, guilt for transmitting the disease to their children, among many others.[146] In addition, the unpredictable and potentially fatal aspect of the disease often leads to anxiety, depression, stress or the risk of other mental disorders, with marked impairment of the quality of life of patients and their families.[147-156]

In the last three decades, it has become common to objectively assess quality of life (QoL) in various diseases, but the impact of HAE on the QoL of affected patients has only recently been studied.[157,158]

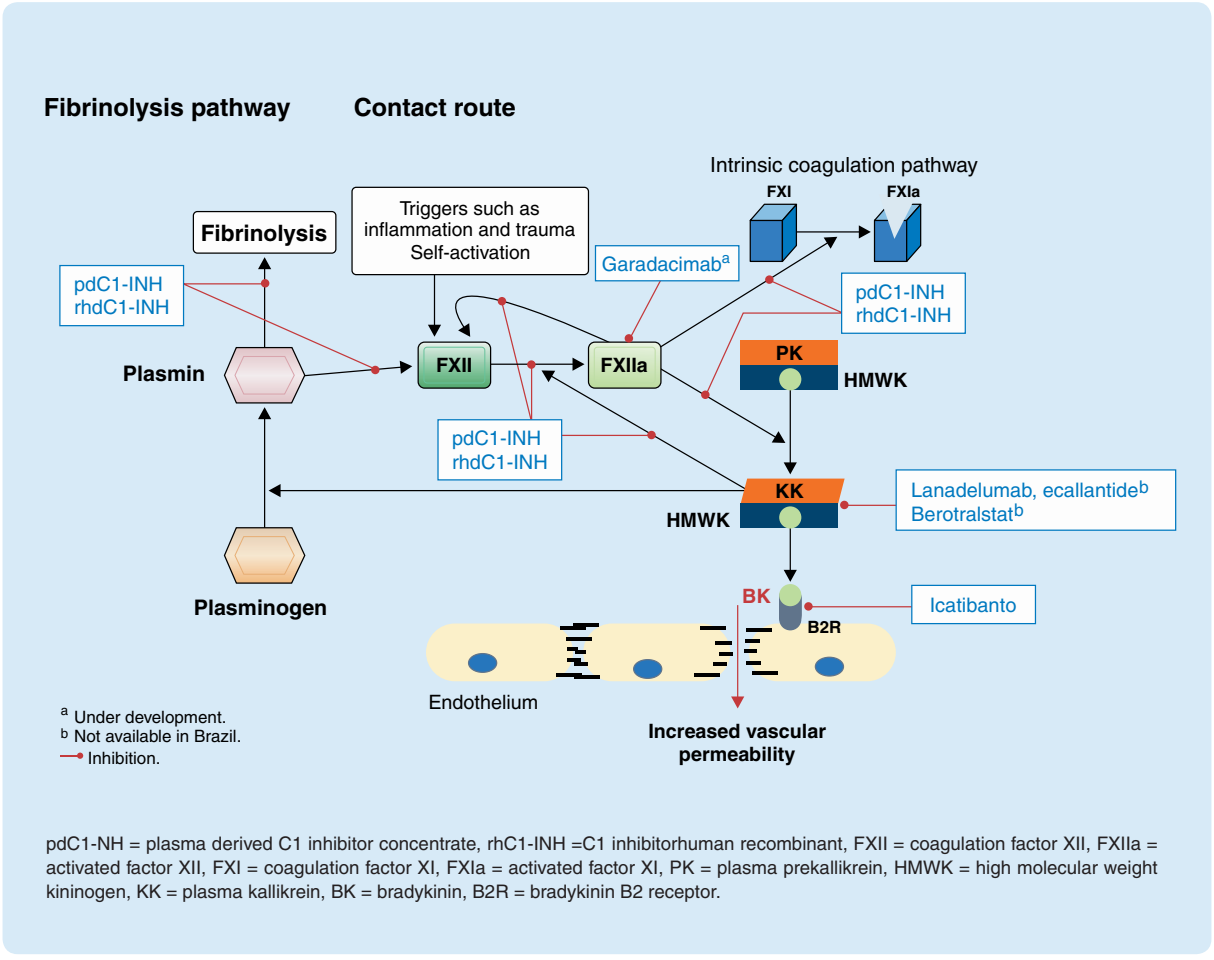
It is well established that HAE profoundly affects the quality of life of those affected, both in the physical, psychological and social spheres.[22] Objectively measuring the QoL of these patients can contribute to improve the therapeutic approach and assess the response to the instituted treatment.

There are two questionnaires to assess the QoL of HAE patients over 18 years of age. The Hereditary Angioedema Quality of Life questionnaire (HAE-QoL) addresses seven domains: physical and health aspects, disease-related stigmas, social and emotional aspects, concern for offspring, perceived control over the disease, mental health and treatment difficulties, with score from 25 to 135, where 25 is the worst general health status, and 135 the best.[119-161] The Angioedema Quality of Life questionnaire (AE-Qol) is a symptom-specific questionnaire for any type of recurrent angioedema, and covers four dimensions:

Table 6
New treatments for hereditary angioedema in phase 1, 2 and 3 clinical studies*

Treatment	Administration	Name	Mechanism	Study phase
PLP	Oral	ATN-249® (Attune Pharmaceuticals)	CP inhibitor	Phase 1 completed[a]
		KVD824® (KalVista Pharmaceuticals)	CP inhibitor	Phase 1 completed[a]
	Subcutaneous	Garadacimab® (CSL Behring)	Anti-factor XII monoclonal antibody	Phase 2 finished and phase 3 recruiting[b]
		IONIS-PKK-LRx® (IONIS Pharmaceuticals)	Antisense oligonucleotide for CP	Phase 2 finished and phase 3 recruiting[b]
PLP and crisis	Oral	PHA-022121® (Pharvaris)	Antagonist B2 receptor	Phase 2 recruiting[b]
Crisis	Oral	KVD900® (Kalvista Pharmaceuticals)	CP inhibitor	Phase 2 completed[b]

* Second access in February/2022.
[a] Registered with the Australian New Zealand Clinical Trials Registry.
[b] Source: US National Library of Medicine – ClinicalTrials.gov.
B2R = bradykinin B2 receptor, PLP = long-term prophylaxis, CP = plasma kallikrein.



pdC1-NH = plasma derived C1 inhibitor concentrate, rhC1-INH =C1 inhibitorhuman recombinant, FXII = coagulation factor XII, FXIIa = activated factor XII, FXI = coagulation factor XI, FXIa = activated factor XI, PK = plasma prekallikrein, HMWK = high molecular weight kininogen, KK = plasma kallikrein, BK = bradykinin, B2R = bradykinin B2 receptor.

Figure 3
Site of action in the fibrinolysis and contact pathways of different therapies for hereditary angioedema with C1-INH2-4 deficiency

functional capacity, fatigue, fear and eating, with a score from 0 to 100, where zero corresponds to the best general health status, and 100 for the worst.[162] The AE-QoL has been used in clinical studies to evaluate the effect of new therapies for AEH.[163]

The Angioedema Activity Score (AAS) was the first instrument developed to assess angioedema activity. It is validated for all forms of recurrent angioedema, including HAE, where patients document the presence or absence of angioedema in the last 24 hours. If angioedema is present, five additional questions must be answered, each with a score of 0 to 3 points. According to the period of time the symptoms were recorded, the minimum and maximum scores for AAS consist of: 0 to 15 (AAS: daily); 0 to 105 (AAS7: weekly) and 0 to 420 (AAS28: monthly).[164]

Recently, the Angioedema Control Test (AECT) was developed, which is the first tool to assess disease control in patients with any type of recurrent angioedema.[165] It consists of four questions, related to frequency, quality of life, unpredictability of the disease, and treatment, with a score from 0 to 16, where 16 is total control, with a score ≥ 10 meaning good control, and < 10 the lack of control. In Brazil, the EGTC is in the process of validation.

All these tools make it possible to measure the quality of life, activity and control of the HAE and help in the management of the disease, as they allow a broader and more objective understanding, helping to adjust the treatment of patients with HAE. However, there is a need to standardize the use of these tools in children and their caregivers.

How do hereditary angioedema patient associations work and what are the functions?

The first associations of patients with chronic diseases appeared in the 1950s and, since then, there has been a growing movement to strengthen these institutions. In the last decades, this movement was based on the assertions that these patients are a group that faces similar obstacles, the shared experiences constitute a different knowledge from that of health professionals and that it was legitimate for the patient to have the right to have an opinion in decisions about his illness. Strategies to value patients and caregivers can improve health outcomes, leading to effective decision making, management of disease complications, better health behavior, strengthening of support groups and efficient use of health services.[166]

In this context, associations of patients with hereditary angioedema (HAE) were created in several countries, with the aim of giving greater visibility and disseminating information about the existence of this disease, offering broad support to patients, family members and caregivers of patients with HAE. These institutions defend the idea that, in all parts of the world, patients with HAE should have access to all the necessary resources to control their symptoms, and with that, guarantee an adequate quality of life that allows them to carry out their activities in work, school and the improvement of interpersonal relationships.[3]

Internationally, Hereditary Angioedema International (HAEi) is a global, non-profit network of patient associations that was created with the aim of improving the lives of individuals with HAE. HAEi, which currently has 93 member countries, provides its member organizations with specially designed tools and technical assistance to promote disease education and support activities that meet the unique needs of HAE patients and their families. In addition, it also works to encourage clinical research in the generation of several new drugs for the treatment of HAE, in partnership with Angioedema Reference and Excellence Centers (ACARE) to further improve the quality of clinical care and patient care.[13]

In Brazil, the Brazilian Association of Hereditary Angioedema (Abranghe) was founded in April 2010 through the initiative of HAE patients. Abranghe has also been working to provide support and represent the interests of HAE carriers. This association offers information about the disease, main reference centers specializing in HAE in the country, provides educational materials and participates in national and international events. In addition, it registers patients with a confirmed diagnosis of the disease and provides them with an identification card. Contact with Abranghe can be made by phone, email or social media.[167]

It should be noted that an important role of patient associations is to raise awareness among managers regarding the recognition of HAE as a disabling and potentially fatal chronic condition. Therefore, these entities can assist in the elaboration of public policies to improve access to diagnostic and therapeutic means, thus aiming to reduce morbidity and mortality and provide a more dignified life to these patients. As an example of these policies, Ordinance GM/MS n°199 of 01/30/2014 instituted the national policy of comprehensive care for people with rare diseases, approved the guidelines for comprehensive care for people with rare diseases in the SUS and instituted financial incentives for funding the diagnosis of these diseases.[168]

Access to treatment, considered expensive, has still been a major challenge faced by associations that fight for the rights of HAE patients. Within the scope of the SUS, in almost all Brazilian states, access to medicines occurs most of the time, by judicialization. In the private service, health operators rarely release the drugs indicated for prophylaxis and for crisis. This demonstrates that these policies still need to be improved so that everyone is guaranteed access to treatment.

It is the role of HAE patient associations to educate patients and caregivers, inform the general population about the disease and raise awareness of HAE-related problems, in order to gain social legitimacy and give visibility to their demands. It is also vitally important that leaders and associations understand the complexities, laws, guidelines and processes involved in accessing medicines, as this will lead to immeasurable benefits for patients with this disease.[169]

Final considerations

Specialists from the Brazilian Association of Allergy and Immunology (ASBAI) and the Brazilian Study Group on Hereditary Angioedema (GEBRAEH) have updated these guidelines for HAE therapy, with the aim of helping health professionals in the identification and management of this disease. The HAE is currently less neglected, but it is still necessary to continue progressing with a critical eye on the new challenges and striving for better care for HAE patients.

All medicines approved for HAE in Brazil so far can be self-administered at home, which is a fundamental aspect in our country, because in many places access to health units is precarious, and early treatment of a crisis is very important, whether for presenting better results, as well as reducing the patient's suffering.

New drugs for long-term prophylaxis such as pdC1-INH SC and lanadelumab, with specific actions on the kinin-kallikrein system, have the potential to significantly reduce the number of seizures, in addition to being administered subcutaneously, contributing to significant improvement in the quality of life of patients. Although the cost of these drugs is high, some patients with severe and very frequent attacks, and who do not improve even with the use of attenuated androgens, need access to them. It should be emphasized that the use of preventive therapies for seizures does not replace the need for access to medication for the treatment of seizures.

Other drugs will emerge with the potential to further improve the care of these patients. The specialist in Allergy and Immunology plays a key role in this process, requiring a more up-to-date and comprehensive knowledge of hereditary angioedema.

Important challenges remain patient access to the newest and most effective drugs, and drug release to pediatric patients.

Final guidelines for the treatment of hereditary angioedema with C1 inhibitor deficiency are summarized in Table 7.

Table 7
Guidelines for the treatment of hereditary angioedema with C1-INH deficiency in Brazil

Treatment strategies	Prevent seizures, prescribe medication for prophylaxis (short and long term) and treatment of seizures (on demand).
Crisis prevention	Treat infections early, control stress, provide guidance on the use of drugs that can trigger crises, prescribe vaccination to prevent infections, among others.
Short term prophylaxis	Indicate before procedures such as dental treatment or endoscopy. Plasma-derived C1 inhibitor concentrate (first-line treatment) may be used. If there is no access, attenuated androgens (second-line treatment) are suggested. In the absence of concentrateC1 inhibitorderived from plasma, fresh frozen plasma may be prescribed.
Long term prophylaxis	Indicate the C1 inhibitor concentrate, subcutaneously (preferably) or intravenously to be applied every 3 or 4 days, or the antikallikrein monoclonal antibody (lanadelumab) to be applied subcutaneously every 2 weeks (treatments of first line). In Brazil, first-line drugs are approved by ANVISA. However, only the attenuated androgen danazol (second-line treatment) is available in the SUS, which should be prescribed at the maximum recommended dose (200 mg/day) as suggested by international consensus.

Table 7 *(continuation)*
Guidelines for the treatment of hereditary angioedema with C1-INH deficiency in Brazil

Choice of long-term prophylactic treatment strategy	Evaluate clinical and laboratory criteria. Consider contraindications to the use of attenuated androgens, such as pregnancy, breastfeeding, severe liver, kidney or heart failure; porphyria; androgen-dependent tumor; abnormal vaginal bleeding not yet diagnosed, active thrombosis or thromboembolic disease, history of both events and concomitant use with simvastatin.
Sustainability of the Brazilian Health System for long-term prophylaxis	Indicate the use of androgen – at the maximum recommended dose (200 mg/day) as suggested by international consensus (second-line treatments). According to the response to treatment, contraindication or adverse events to the use of androgens, which must be evaluated by reference centers, the use of C1 inhibitor and lanadelumab (first-line treatments) is considered. Response to treatment is evaluated by disease control, time to reduction of signs and symptoms, quality of life and adverse events.
Crisis treatment	Indicate icatibant (bradykinin B2 receptor antagonist) or plasma-derived C1 inhibitor concentrate (first-line treatments). In Brazil, these two drugs are approved by ANVISA, but not available in the SUS. In the absence of first-line drugs, fresh frozen plasma may be prescribed. All seizures must be treated, however, seizures that affect the extremities are at lower risk. Despite advances in HAE treatment in recent years, access to treatment is very limited in Brazil.

ACTION PLAN FOR PATIENTS WITH HEREDITARY ANGIOEDEMA

_____has a diagnosis of hereditary angioedema.

Hereditary angioedema (HAE) is characterized by recurrent episodes of edema in different parts of the body, which may occur simultaneously or not, such as lips, eyelids, larynx, hands, and feet, as well as bouts of abdominal pain, with or without nausea, vomiting, and diarrhea due to intestinal loop edema. Abdominal pain is typically intense and may simulate acute abdomen.

SIGNS AND SYMPTOMS OF HAE:

Cutaneous edema	Typically involves feet and hands.
Abdominal edema	Characterized by severe abdominal pain, nausea, vomiting, and diarrhea.
Glottic/airway edema	Compromises breathing and requires immediate medical evaluation. The following may be present: voice alteration and difficulty swallowing.
Prodromes (warning signs of HAE attack onset)	Tingling sensation, redness, tiredness, or nausea.

This type of angioedema is non-allergic and therefore does not respond to antihistamines, corticosteroids, and adrenaline.

If a patient experiencing a HAE attack arrives at your health center, **one** of the following medications should be administered:

Medication	Dosage and administration	Storage and handling	When to re-treat
Icatibant injection (Firazyr®) Patients ≥ 2 years	Dose:_____ (_____) Route: subcutaneous. Region: abdomen.	Storage: 2ºC to 8ºC. Do not freeze.	Additional doses may be administered at intervals of at least 6 hours. Do not administer more than 3 doses in 24 hours.
Plasma-derived human C1-inhibitor – pdC1INH (Berinert®) No age restrictions.	Dose: 20 UI/kg Route: intravenous. Flow rate: 4 mL/min. 1 vial/ampoule: 500 UI.	Storage: 15ºC to 30ºC. Do not freeze. The vial should be stored in the original package to protect from light.	An additional dose may be administered after 1 hour.
Plasma-derived human C1-inhibitor – pdC1INH (Cinryze®) Patients ≥ 12 years	Dose: 1,000 UI Route: intravenous. Flow rate: 4 mL/min. 1 vial/ampoule: 500 UI.	Storage: 2ºC to 8ºC. Do not freeze. The vial should be stored in the original package to protect from light.	An additional dose may be administered after 1 hour. In laryngeal attacks, a second dose may be administered before 1 hour, if necessary.

If none of these medications are available, supportive care should be conducted, and frozen fresh plasma (FFP) should be administered – 10 mL/kg, maximum of 2 to 4 units of FFP, which contains approximately 200 mL/unit.

If the patient shows signs of upper airway obstruction and asphyxia (dyspnea, stridor, hoarseness, difficulty swallowing, sensation of tightness in the throat, drop in O2 saturation level), early orotracheal or nasopharyngeal intubation should be strongly considered.

For questions, please contact us via phone: (__).

Sincerely,
Physician's name and regional medical board number:
Name of follow-up health center:

Observations:_____
_____
_____

Appendix 1
Action plan for patients with hereditary angioedema

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Conflict of interests

Régis A. Campos, Faradiba S. Serpa, Maria Luisa O. Alonso, Herberto J. Chong-Neto, Pedro Giavina-Bianchi, Anete S. Grumach, Eli Mansour, Eliana Toledo and Solange O. R. Valle received financial and/or honorary support from Takeda and CSL Behring. Anete S. Grumach is a CNPq productivity fellow and has also consulted for Catalyst. The following authors received financial and/or honorary support from Takeda: L. Karla Arruda, Marcelo V. Aun, Jane da Silva and Camila L. Veronez. The authors Maine L. D. Bardou, Ana Flávia Bernardes, Fernanda L. Campinhos, Rosemeire N. Constantino-Silva, Sérgio D. Dortas-Junior, Mariana P. L. Ferriani, Joanemile P. de Figueiredo, Lais S. Gomes, Ekaterini Goudouris, Marina T. Henriques, Antônio A. Motta, Therezinha R. Moyses, Fernanda L. Nunes, Jorge A. Pinto, Ana Júlia R. Teixeira, Nelson A. Rosario-Filho, Norma de Paula M. Rubini, Almerinda Maria do Rêgo Silva and Dirceu Solé deny conflicts of interest.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Practical guide to urticaria for special patient groups

Guia prático de urticária para grupos especiais de pacientes

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ABSTRACT

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

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

RESUMO

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

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

Introduction

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

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

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

Children

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* Adapted from Magerl et al. [51]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Seniors

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 2
Complementary diagnostic evaluation of recurrent angioedema without urticaria

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pregnant and lactating women

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

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

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

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

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

*Adapted from Ventura et al.[55]

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

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

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

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

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

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

4. Is it safe to use omalizumab during pregnancy?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

Conflict of interests

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

Table 4
Cutaneous manifestations of pregnancy-specific dermatoses*

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

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

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

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

* Adapted from Lehrhoff et al.[71]

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Practical guide to acute urticaria

Guia prático de urticária aguda

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ABSTRACT

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

Keywords: Urticaria, angioedema, diagnosis, therapeutics.

RESUMO

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

Descritores: Urticária, angioedema, diagnóstico, terapêutica.

Introduction

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

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

What are the main triggers of acute urticaria?

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

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

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

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

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

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

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

Table 1
Main causes of acute urticaria

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

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

What are the possible etiopathogenic mechanisms involved in acute urticaria?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

What are the main infectious agents related to acute urticaria?

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

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

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

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

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

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

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

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

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

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

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

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

Are there predictors of severity for AU?

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

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

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

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

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

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

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

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

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

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

What should be the initial therapeutic approach for acute urticaria?

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

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

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

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

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

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

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

Should acute urticaria be treated with oral or injected medication?

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

When to use corticosteroids in the treatment of acute urticaria?

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

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

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

When to use adrenaline in the treatment of acute urticaria?

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

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

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

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

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

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

Table 3
Second-generation antihistamines

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

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

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

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

Conclusion

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

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

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

Conflict of interests

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

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Non-IgE mediated food allergy: food protein-induced allergic proctocolitis – An update

Alergia alimentar não IgE mediada: proctocolite induzida por proteínas alimentares – Atualização

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ABSTRACT

An increase in the worldwide prevalence of food allergies has been observed in the past decades, currently affecting 6% of children. This increase has been associated with the interaction between genetic, environmental, and immune response factors and can be observed in IgE, non-IgE, and mixed mediated reactions. Non-IgE mediated food allergies result from delayed-type hypersensitivity and mostly affect the gastrointestinal tract, such as food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), food protein-induced enteropathy (FPE), and celiac disease. These reactions can be differentiated by their clinical presentation, severity, age at onset, and natural history. Among non-IgE-mediated allergic reactions to food, allergic proctocolitis is the most frequent. It usually develops in the first year of life and has excellent prognosis. Although it has a benign course, allergic proctocolitis is challenging for health care professionals because it often presents with hematochezia, requiring an accurate differential diagnosis. Knowledge and management of allergic proctocolitis is of paramount importance for medical practice in allergy and immunology. Its diagnosis is based on clinical history followed by elimination diet, especially cow's milk, with subsequent oral food challenge, which may usually be performed at home. Accurate diagnosis is important to avoid unnecessary elimination diets. For this review, PubMed database was searched for recently published literature reviews and studies on the diagnosis and treatment of non-IgE mediated allergies, with a focus on allergic proctocolitis.

Keywords: Food hypersensitivity, infantile diarrhea, gastrointestinal hemorrhage, milk hypersensitivity, breastfeeding.

RESUMO

Nas últimas décadas observa-se aumento na prevalência mundial de alergia alimentar, que já acomete aproximadamente 6% das crianças, atribuído à interação entre fatores genéticos, ambientais e alterações na resposta imunológica e pode envolver reações mediadas por IgE, não mediadas e mistas. As formas não IgE mediadas decorrem de reação de hipersensibilidade tardia, mediada por linfócitos T e afetam prioritariamente o trato gastrointestinal, como a Síndrome da enterocolite induzida por proteína alimentar (FPIES), Síndrome da proctocolite alérgica induzida por proteína alimentar (FPIAP), Síndrome da enteropatia induzida por proteína alimentar (FPE) e doença celíaca. As características destas reações podem ser diferenciadas por sua apresentação clínica, gravidade, idade de início e história natural. Entre as reações alérgicas aos alimentos não IgE mediadas, a proctocolite alérgica é a mais frequente. Geralmente ocorre no primeiro ano de vida e apresenta excelente prognóstico. Embora costume ter um curso benigno, traz grande preocupação aos cuidadores por frequentemente cursar com quadro de hematoquezia exigindo diagnóstico diferencial adequado. O conhecimento e manejo da proctocolite alérgica é de suma importância para a prática médica em Alergia e Imunologia. Seu diagnóstico é baseado na história clínica seguindo-se dieta de exclusão, especialmente do leite de vaca, com subsequente provocação oral, que geralmente pode ser realizada no domicílio. O diagnóstico preciso é importante, para se evitar dietas de exclusão desnecessárias. Nesta revisão foram utilizados artigos publicados nos últimos anos, com busca realizada através da base PubMed envolvendo revisões, diagnóstico e tratamento de alergias não IgE mediadas, com foco em proctocolite alérgica.

Descritores: Hipersensibilidade alimentar, diarreia infantil, hemorragia gastrointestinal, hipersensibilidade ao leite, aleitamento materno.

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Introduction

Allergic reactions to foods have been the subject of intense discussion and research among experts. In the last two decades, an increase in prevalence has been observed, with data varying between different studies, probably due to differences in their methodology, including different definitions of food allergy (AA) and eating habits in the geographical areas studied.[1] Its occurrence and clinical expression depend on the interaction between genetic and environmental factors and changes in the immune response. It affects approximately 6% of children, being more common in children under 3 years of age. In adults, a prevalence of 3.5% is estimated.[1,2] The associated family history of atopy is still the greatest risk indicator for its onset. A recent study in Brazil found that among the 604 patients with a report of AA, 4% had a confirmed diagnosis of food allergy.[3] Another study in Brazil showed an incidence of cow's milk protein allergy (CMPA) of 2.2% and a prevalence of 5.4% in children aged ≤ 24 months.[4] The knowledge and management of this condition becomes, therefore, of paramount importance for clinical practice in Allergy and Immunology.

Food allergy with gastrointestinal manifestations results from continuous exposure to food protein, which promotes inflammation by different immunological mechanisms. It can have different forms of presentation, depending on the mechanism and the location predominantly involved.

Classification

Allergic reactions to food are exacerbated immune responses to food ingestion that occur in a susceptible host.[5] These reactions can be classified, according to the type of immune response to the ingested antigens, into immunoglobulin E (IgE)-mediated, non-IgE-mediated, and mixed reactions[6] (Figure 1).

IgE-mediated reactions are usually manifested by symptoms that occur shortly after ingestion of food, usually involving the skin (urticaria, angioedema), respiratory tract (cough, wheezing, nasal congestion), cardiovascular system (hypotension), and may also present like anaphylaxis.[1]

Mixed reactions involve IgE antibodies, T lymphocytes and cytokines. They manifest as eosinophilic gastropathies (eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis), atopic dermatitis, and asthma.[7]

Non-IgE-mediated allergic reactions to foods occur without the participation of specific IgE and are due to a delayed-type hypersensitivity reaction mediated by T lymphocytes.[5,8] They are expressed by pathologies that affect various organs, such as the gastrointestinal tract, like Food Protein Induced Enterocolitis Syndrome (FPIES), Food Protein Induced Allergic Proctocolitis Syndrome (FPIAP), Food Protein Induced Enteropathy Syndrome (FPE), and celiac disease. The skin can be affected in cases of food contact dermatitis and dermatitis herpetiformis, in addition to the lungs in Heiner syndrome or pulmonary hemosiderosis (Figure 2). The expression of symptoms and severity depends on the segment of the gastrointestinal tract affected.[9] Celiac disease and iron deficiency anemia induced by cow's milk allergy are also classified as non-IgE-mediated reactions, but will not be discussed in this review.[6]

Presentation of non-IgE-mediated allergies

The main gastrointestinal manifestations of non-IgE-mediated food allergy have similar and overlapping clinical expressions, but which can be differentiated based on their typical clinical features, severity, age of onset, and natural history.[10]

Table 1 shows a comparative chart between the three main forms of non-IgE mediated food allergy: FPIES, FPIAP and FPE.

Food protein-induced proctocolitis syndrome - FPIAP

FPIAP, also called allergic proctocolitis, is a form of food allergy not mediated by IgE, which appears in the first six months of life, being more frequent between the first and fourth weeks after birth.[13] It often manifests as blood and mucus in the stool in healthy infants. More rarely, vomiting and diarrhea may occur. Onset is usually insidious, with a prolonged latent period after introduction of food, although onset may rarely be acute, within 12 hours of first contact.[14]

It is a benign and transient condition, which does not interfere with the child's growth even when the causal food remains in the diet and bleeding continues, although it can progress to anemia.[14]

In 60% of cases of hematochezia in infants, the cause is allergic proctocolitis.[15] It can affect breastfeeding children. In fact, approximately 60% of cases of proctocolitis occur in breastfeeding infants.[16] Cow's milk (VL) is the main causal food, although several foods, such as soy, egg, wheat and others,

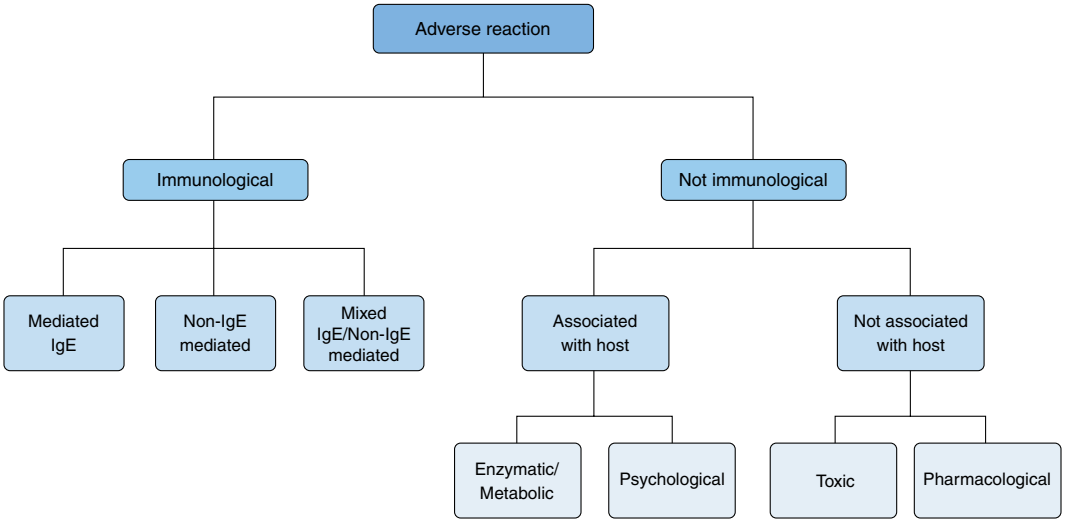

Figure 1
Classification of adverse food reactions

can be excreted in breast milk after ingestion by the mother and consequently can be considered as possible agents. Infants fed formulas containing LV or soy may also have allergic proctocolitis; including extensively hydrolyzed VL formulas, which can lead to symptoms in up to 10% of cases.[16]

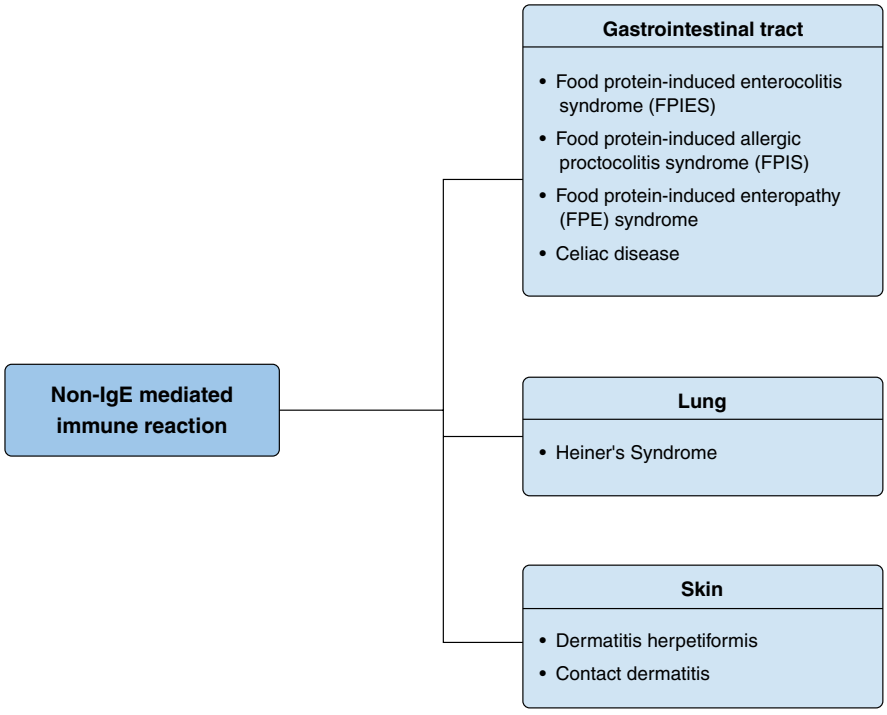

Figure 2
Non-IgE-mediated immune-mediated adverse food reactions
Adapted from: Sampson HA.[8]

Table 1
Comparison of major non-IgE-mediated gastrointestinal allergic syndromes

Features	FPIES	FPIAP	FPE
Typical age of onset	Days to 12 months	Days to 6 months	2 to 24 months
Symptoms			
Vomit	Prominent	No	Intermittent
Diarrhea	Severe	No	Moderate
Blood in the stool	Severe	Moderate	Rare
Edema	Acute, serious	No	Moderate
Shock	15-20%	No	No
Deficit weight-stature	Moderate	No	Moderate
Most typical presentation	Late and repetitive vomiting	Blood in the stool	Chronic diarrhea
Main foods involved	Milk, soy, rice	Milk, soy	Milk, soy, wheat, egg
Multiple awareness	> 50% milk/soy in some populations	40% milk/soy	Rare
Feeding at onset of symptoms	Formula	> 50% exclusive breastfeeding in some studies	Formula
Resolution age	> 3 years	1-2 years	1-3 years
Prick test with food	Negative*	Negative	Negative
Food specific IgE	Negative*	Negative	Negative
Total IgE	Normal	Normal	Normal
Peripheral blood eosinophilia	No	Occasional	No
Biopsy			
Villous lesion	Not uniform	No	Crypts of varying size
Colitis	Prominent	Focal	No
Mucosal erosion	Occasional	Occasional, linear	No
Lymph node hyperplasia	No	Common	No
Eosinophils	Prominent	Prominent	Few
Food challenge test	Vomiting in 4 to 6 hours, diarrhea in 5-8 hours	Rectal bleeding in 6-72h	Vomiting, diarrhea or both in 40-72h

FPIES = Food Protein Induced Enterocolitis Syndrome, FPIAP = Food Protein Induced Allergic Proctocolitis Syndrome, FPE = Food Protein Induced Enteropathy Syndrome.

* Positive prick test and/or specific IgE may be present at initial diagnosis or at follow-up (atypical FPIES).

Adapted from Caubet et al.[11] and Leonard AS[12].

Food protein-induced enterocolitis syndrome - FPIES

FPIES occurs predominantly in infants between 2 and 7 months of age, associated with the introduction of milk formulas and solid foods.[11] Rarely occurs in exclusively breastfed children, older children and adults.[17] In 65 to 80% of cases, FPIES is caused by a single food, mainly VL or soy. Other agents involved include egg and cereals, particularly rice and oats.[18]

The clinical expression of FPIES is influenced by the protocol of introduction of solid foods in the infant, frequency and type offood allergen introduced in the diet, in different geographic regions.[18]

FPIES is divided into two phenotypes: acute and chronic. The acute form is the most common and usually occurs by accidental ingestion, or re-exposure to the causal food after a period of restriction diet. It is manifested by uncontrollable vomiting, lethargy and pallor, which begin 1 to 4 hours after ingestion of the food involved.[19] In 15% of cases, it can progress to severe systemic symptoms that include hypothermia, hypotension, and may progress to hypovolemic shock.[20] Diarrhea can occur within 5 to 10 hours and often represents a more severe form of FPIES. The acute form is also seen in older children or adults when the causal food is not a staple food and is consumed only occasionally. In adults, it is usually associated with the ingestion of crustaceans.[12] Children with FPIES triggered by LV and soy proteins usually become tolerant around 2 to 3 years of age, whereas forms triggered by solid foods tend to have a longer evolution.[11,18]

Chronic FPIES is infrequent and is characterized by the persistence of symptoms, which, despite being less intense than those of the acute form, can be severe. The most reported symptoms are vomiting, diarrhea (with or without blood), lethargy, dehydration, abdominal distension and failure to thrive. In these situations, a differential diagnosis with inflammatory bowel diseases should be sought.[12,19]

Food protein-induced enteropathy syndrome - FPE

PEF is characterized by chronic diarrhea and recurrent abdominal pain, which can progress to weight loss and growth retardation in up to 20% of cases. Bloody stools are usually absent, but occult blood may be present in 5% of patients.[21] It starts between 2 and 9 months of age, associated with the introduction of VL formula, and less frequently of soy, egg and wheat. PEF is a transient disorder with resolution around 1 to 3 years of age. Exclusion of the causal food, followed by reintroduction after 4-8 weeks, aids in diagnosis.[22]

Colic

Infantile colic can be considered a functional disease in babies aged 1 to 4 months, which manifests with colicky abdominal pain between 4 and 6 weeks of life and regresses around 12 weeks.[23] It is a self-limiting condition characterized by recurrent and prolonged periods of incessant crying.[24] Crying paroxysms occur especially in the late afternoon and early evening, with no apparent cause. A recent systematic review showed a prevalence rate ranging from 2 to 73%, with a median of 17.7%.[25] Less than 5% of infants with colic and excessive crying have an underlying cause.[26]

The pathophysiology of infantile colic is not completely understood, although many hypotheses have been proposed, such as intestinal immaturity, hypermotility, unstable autonomic control, alterations in the intestinal microbiota, central nervous system, sleep cycle and psychosocial factors (e.g., anxiety in children). parents, which can be exacerbated by inexperience and lack of support).[27]

The presence of infantile colic, in combination with atopic dermatitis, altered stools, colitis with rectal bleeding, or gastroesophageal reflux disease (GERD), may be related to CMPA in exclusively breastfed infants.[28] The association between food allergy and childhood colic is still controversial. However, there is evidence to demonstrate that mucosal allergic responses can alter intestinal motility and nociceptive pathways to cause visceral hyperalgesia.[28,29] The gut microbiota stimulates immune system maturation, tolerance acquisition, and enteric nervous system [RHEE] development and function. Studies suggest that an aberrant intestinal microbiota can affect intestinal motor function, gas production and, thus, generate abdominal pain.[30,31]

In CMPA, the increase in the production of pro-inflammatory cytokines and neurotoxic compounds affects the enteric nervous system and causes peristaltic dysfunction and changes in the perception of physiological stimuli, such as intestinal distention and peristalsis, which are perceived as painful events.[32]

There are no robust clinical trials demonstrating the effectiveness of a food antigen restriction

diet in colicky infants.[33] In the presence of more severe colic, associated with the presence of other gastrointestinal symptoms and a personal history of atopic dermatitis, the therapeutic exclusion diet can be started, according to the type of supply.[11,28] In infants fed formulas based on cow's milk, these can be replaced by Formulas with extensively hydrolyzed cow's milk proteins for two weeks. In case of clinical improvement, the restriction diet should be continued. However, in the absence of benefit after two weeks, dietary restrictions must be lifted.[28] In nursing infants, elimination of LV for two to four weeks from the maternal diet is recommended.[22] In the presence of an evident clinical response, the restriction diet should be continued.[10]

Gastroesophageal reflux

Gastroesophageal reflux (GER) is defined as the retrograde and involuntary passage of gastric contents into the esophagus.[23] In term and preterm newborns, reflux is usually a benign process, self-limiting and without complications. It is considered as part of the physiology and gastrointestinal maturation at this stage of life and, therefore, called physiological reflux. The peak incidence of physiological GER occurs at four months of age, and 95% of infants no longer regurgitate at 12 to 14 months of age.[34] When GER is associated with other clinical symptoms or complications, such as feeding and swallowing difficulties, difficulty in gaining weight or weight loss, growth deficiency, anemia, digestive hemorrhage, respiratory and otorhinolaryngological manifestations, among others, it is called a disease of gastroesophageal reflux (GERD).[34]

The prevalence of GER and GERD varies according to the population, study design (cross-sectional or longitudinal) and diagnostic criteria (signs/symptoms or validated questionnaire). It is estimated that at the peak age of GER, around 2-4 months, prevalence rates vary between 67% and 87%[35-37] and that are 21% between 6 and 7 months of age.[36] A recent systematic review showed that in children up to 18 months, GERD symptoms are present daily in 25% of babies, with a gradual reduction and almost complete disappearance of symptoms at 12 months of age.[38] In Brazil, Costa AJF et al.observed that the prevalence of GERD in 2004 was 11.15% (89/798; 95% CI: 9.10-13.48), being higher in the first two trimesters of life: 14.62% in the first and 13.76% in the second.[39]

Several structures contribute to the antireflux barrier: the lower esophageal sphincter (LES), the angle of His, the phrenoesophageal ligament, the crural diaphragm, and the gastric rosette. The immaturity of the anti-reflux barrier mechanisms typical of the neonatal period contributes to a higher incidence of GER.[40] It is usually associated with transient lower esophageal sphincter (LES) relaxation, being influenced by genetic, environmental, anatomical, hormonal and neurogenic factors.[41] The main mechanism responsible for preventing the development of GERD is the maintenance of adequate function of the anti-reflux barrier located at the esophagogastric junction.[41] Among the mechanisms responsible for esophagogastric junction dysfunction are transient LES relaxations, reduced LES tone and anatomical distortion at the esophagogastric junction.[40]

Symptoms of GER and GERD occur due to both the volume and acid content of the refluxed material, and sometimes it is difficult to distinguish between them.[40,42] In GERD, prolonged contact of gastric acid with the esophageal mucosa intensifies local blood flow and promotes the release of prostaglandin E2, which increases the permeability of the mucosa to acid, perpetuating the inflammatory process and the presence of symptoms and complications, such as apnea, worsening of the pulmonary condition, irritability, sleep disturbance, intolerance/bad acceptance of diet, stridor, inadequate weight gain/development, abnormal posture with posterior arching, nausea, hematemesis, aspiration of gastric contents into the airways.[40]

GERD may be associated with CMPA, however, this association has not yet been established. However, a recent narrative review found an association of CMPA with GERD in 16-56% of suspected GERD cases, with persistence of gastrointestinal symptoms until VL was excluded, regardless of breastfeeding or formula.[43] Infants with CMPA present with regurgitation and vomiting indistinguishable from those associated with physiological GER or GERD, and regurgitation may be the only manifestation.This similarity of symptoms between CMPA and GER/GERD makes it difficult to distinguish the etiology of the condition, especially in the absence of other signs of allergy, such as atopic dermatitis or unexplained rectal bleeding in the first months of life.[40]

The absence of a specific symptom and/or a test considered the gold standard for the diagnosis of GERD and non-IgE-mediated CMPA, in addition to the

overlap with other functional and organic conditions and the spontaneous resolution of symptoms in the first year of life, make the diagnosis and the discrimination between APLV, GER and GERD a challenge.[44] In healthy infants with regurgitation or in those who do not respond to thickened diets and postural therapy, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) suggest that infants using LV protein formula, replacement is made with extensively hydrolyzed formula for 2 to 4 weeks; and for those who are breast-feeding, mothers should be instructed to discontinue LV protein intake for the same period. If symptom improvement occurs after the VL has been eliminated, reintroduction of the allergen is necessary to confirm the allergy.[40]

Constipation

Constipation is often associated with hardened stool consistency, an increase in the interval between bowel movements, and the occurrence of pain during bowel movements.[45] It is classified as functional in the vast majority of cases and only a small proportion of pediatric patients is associated with food allergy.[22]

Children who have a decrease in the frequency of bowel movements in the first weeks of life or after the introduction of VL-based products in the diet should be investigated for this condition.[46] In these cases, constipation is usually associated with the presence of hard stools, in addition to excessive and prolonged straining in the evacuation.[47]

The pathophysiology of the association between food allergy and constipation has not yet been fully clarified.[11] Although the results of the studies are conflicting, food allergy should be considered in the differential diagnosis of children who have persistent constipation and are resistant to conventional treatment.[46]

Diagnosis of food protein-induced constipation in breastfed infants is based on clinical improvement during the maternal elimination diet, followed by recurrence of symptoms after reintroduction of the suspected food.[22]

Food protein-induced proctocolitis - FPIAP

Epidemiology

Among allergic reactions to non-IgE food mediated, to Food protein-induced proctocolitis, better known as allergic proctocolitis, is the most frequent, although its exact prevalence is not well established.[1,6] Usually occurs in the first year of life and resolves in the first few years.[48]

Although it tends to have a benign course, it is usually of great concern to parents and guardians, and therefore deserves special attention.[49] In a prospective study, Martin. V et al. observed a cumulative incidence of 17% over 3 years.[48] Other data showed a variable estimated prevalence, from 0.16% in healthy patients to up to 64% among patients with intestinal bleeding.[50-52] These large variations are due to the different methodologies applied between studies.

In breast-feeding patients, most reactions are related to theLV, egg and soy in the maternal diet; however, wheat, corn, apple, fish, meat and sesame have also been described.[52,53] In formula-fed babies, milk and soy are the main causative agents, but extensively hydrolyzed formulas have been reported to cause proctocolitis in up to 10% of patients.[54]

Despite being a non-IgE-mediated reaction, studies indicate that about 40-50% of patients with Allergic proctocolitis present with atopy, and more than 60% of babies have a positive family history of allergy.[48,52,55]

Pathophysiology

The pathophysiological mechanism of allergic proctocolitis is not fully understood, but it is a non-IgE-mediated reaction.[6,22,56]

It is believed that the main related risk factors may be the immaturity of the innate and adaptive immune system, alteration of intestinal permeability, genetic susceptibility associated with sensitizing foods and dysbiosis.[57,58]

Sensitization to food antigens appears to play a key role in allergic proctocolitis, associated with a failure in the tolerance mechanism. Some studies have demonstrated the participation of several cells in the oral tolerance mechanism.[56,59] Pérez-Machado et al, in a study in children with allergies to multiple foods, demonstrated a failure in the production of TGF-β by regulatory cells in the small intestine.[60] One of the hypotheses for this deficit in the production of TGF-β by Th3 regulatory cells and for the impairment of the oral tolerance mechanism would be an ineffective response of innate immunity to the gut microbiota.[61]

Other studies suggest that a change in the composition of the gut microbiome may influence

immune tolerance by regulatory T cells (T-reg) and its homeostasis. Wang J. et al. demonstrated that these defects can compromise different pathways, including effector Treg cells, defect in the expression of CTLA4 and ICOS, and lower production of IL-10 by intestinal Treg cells.[58]

Another key cytokine in the intestinal inflammatory process would be TNF-α. Studies have already demonstrated its action on the tight-junctions of intestinal epithelial cells, thus altering the intestinal barrier and consequently leading to an increase in permeability.[62,63].

Histologically, biopsies of the rectum and large intestine of patients with proctocolitis showed eosinophilic inflammation in several layers.[48,56] Eosinophils are cells that involve both innate and adaptive immunity, due to their ability to interact with antigen-presenting cells and lymphocytes and to produce various mediators and cytokines.[56] Rycyck A et al. demonstrated an increase in EDN (eosinophil-derived neurotoxin) in feces, which could even represent a biomarker in this pathology.[64]

Despite theproctocolitis is a non-IgE-mediated allergy, some authors have shown sensitization to IgE in a minority group of patients.[65,66]

However, further studies are needed to better understand the pathogenesis and biomarkers of this pathology, which would allow better therapeutic guidance, assessment of prognosis and even of different types of allergic proctocolitis phenotypes.[65,67]

Diagnosis

The diagnosis of allergic proctocolitis, as well as non-IgE-mediated food allergies, is based on characteristic clinical history information. This is a generally eutrophic infant with adequate weight and height development and in excellent general condition, with blood-streaked stools with or without associated mucus.[13] Early diagnosis associated with adequate nutritional intervention will allow the baby to maintain its growth rate.

Symptoms appear, in most patients, gradually and persist until the food involved is removed.[13] If the patient has other gastrointestinal symptoms or changes in growth, an alternative diagnosis should be considered.[13]

Physical examination is usually normal, without lesions such as anal fissure, which often occurs in cases of constipation.

There is no definition in the literature of specific criteria for the diagnosis of allergic proctocolitis, however some data are useful for the elaboration of the clinical suspicion. These are[11](adapted from EAACI – European Academy of Allergy and Clinical Immunology):

– slight bleeding in the stool, hematochezia type, in an apparently healthy infant;
– resolution of symptoms after elimination of the allergen/food involved from the baby's or mother's diet, when exclusively breastfed;
– recurrence of symptoms after reintroduction of the food involved in the diet;
– exclusion of other causes of hematochezia.

Most patients who subsequently reintroduce food do not experience symptoms again, demonstrating the favorable course of proctocolitis with respect to immune tolerance. Some studies show that up to 20% of exclusively breastfed babies have spontaneous resolution of bleeding without changes in maternal diet, and that the long-term prognosis is excellent.[13,54,68] In view of this scenario, and in addition to the observation that episodes of rectal bleeding in childhood are mostly self-limiting, some authors have recently proposed to observe and wait for up to 4 weeks for spontaneous resolution, without an elimination diet, in exclusively breastfed infants, at very low risk of developing anemia.[56]

In the case of a period of more than one month, an elimination diet is suggested, and if the hematochezia resolves, an oral provocation test (OPT) should be performed. The oral provocation test should be performed after a short period of elimination diet, around 72-96 hours, to confirm the diagnosis.[11,56] There is no need, however, for it to be carried out in a supervised manner in a hospital environment. If TPO is positive, it is suggested to resume elimination diet for 3 months.[11,56]

Non-invasive exams

Laboratory tests, such as blood and stool analysis, including analysis of abnormal stool elements (EAF), stool parasitological examination (EPF), fecal alpha 1 antitrypsin assay, occult blood test, or human hemoglobin in stool, should not be used routinely for diagnostic confirmation of allergic proctocolitis.[13]

The blood count is usually normal, and some patients may have iron deficiency anemia.[13] Peripheral eosinophilia may be present in up to 43% of cases.[56]

Other inflammatory markers, such as elevated CRP and thrombocytosis, are usually absent.[56]

Fecal calprotectin levels are usually elevated when compared to healthy controls, indicating inflammation of the intestinal mucosa. However, its use in children under 1 year of age has restrictions due to the lack of validated normal values. This test is also not indicated to be routinely requested for the diagnosis of allergic proctocolitis, as there is no positive correlation between fecal calprotectin levels and positive provocation tests in patients with proctocolitis.[56]

Coproculture and screening for coccidia and viruses can be used to search for underlying infection.[56]

The use of allergy tests, such as prick test, patch test, and total serum IgE measurement have limited validity for diagnosis. Specific serum IgE measurement may be considered in breastfeeding patients who have associated IgE-mediated allergy symptoms, or in those with comorbidities such as atopic dermatitis, as well as before reintroduction of the implicated food after a long period of restriction.[56]

Ultrasound evaluation may reveal increased vascularization and thickening of the intestinal wall, especially the descending and sigmoid colon, suggesting the diagnosis. However, these findings are not specific to allergic proctocolitis, and inflammation in the rectum and sigmoid may not be visualized.

Invasive exams

Occasionally, the etiology of rectal bleeding may be of a different origin, and it is important for the differential diagnosis to exclude other pathologies through invasive tests, such as endoscopy, sigmoidoscopy, or colonoscopy.[56]

Endoscopic evaluation is not necessary for the diagnosis of allergic proctocolitis. Examination may reveal intestinal mucosal congestion, areas with petechiae, focal erythema, loss of vascular pattern, ulceration, diffuse nodularity, or, eventually, appear normal.[56]

Histological changes are characterized by eosinophilic infiltration of the intestinal mucosa and lamina propria, in addition to lymphoid hyperplasia.[56] The mucosal architecture is normally preserved and the eosinophilic infiltrate is typically concentrated in the rectum, especially in the epithelium and muscular layer of the mucosa. Because it is a non-uniformly distributed disease, multiple biopsies may be necessary.

Differential diagnosis of blood in stool

Digestive bleeding can manifest itself in several ways. Upper gastrointestinal bleeding occurs anywhere in the gastrointestinal tract proximal to the ligament of Treitz, which includes the esophagus, stomach, and duodenum. Lower gastrointestinal bleeding occurs in the small intestine (jejunum and ileum) and large intestine.[69]

The same can also be classified according to the characteristics of the stool: hematochezia corresponds to the passage of live blood through the rectum and usually represents lower digestive bleeding, although it can occur in upper digestive bleeding. Melena usually results from upper gastrointestinal bleeding and is characterized by black stools. Occult gastrointestinal bleeding is bleeding that is not visible to the naked eye and can cause symptoms such as iron deficiency anemia, pallor, or fatigue.[69]

The etiology of gastrointestinal bleeding in children varies with age, as can be seen in Table 2.

In addition to the diseases listed in Table 2, there are rarer causes such as malignancies, solitary rectal ulcer syndrome, typhlitis, incarcerated hernia or mesenteric thrombosis.[69]

The evaluation of the patient with bleeding in the stool should start with the anamnesis, highlighting the following points: duration and amount of blood, appearance of the stool and whether the blood appears to be mixed in the stool or just around it. Features such as general condition, abdominal pain, fever, weight loss, history of previous bleeding, use of medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and other medications, in addition to underlying diseases such as liver disease or malignancy, should be investigated. Use of NSAIDs can cause ulcerations throughout the GI tract, including the small intestine and colon.[69] Also, some foods and medications, such as iron supplements, gelatin, and chocolate, can change stool color, mimicking melena or hematochezia.[70]

Acute hematochezia in a toxemic child with abdominal pain suggests intestinal ischemia as a complication of intussusception, volvulus, incarcerated hernia, or mesenteric thrombosis. In children under 2 years of age, intussusception should be the main suspect, and it may be associated with Meckel's diverticulum, polyp, lymphoid nodular hyperplasia, foreign body, lymphoma, among others.[69]

Colitis symptoms such as bloody diarrhea, tenesmus, nocturnal bowel movements, and abdominal

pain may arise in infectious or allergic colitis, in addition to necrotizing enterocolitis and Hirschprung's disease with enterocolitis.[69]

Because most infectious colitis is self-limiting and resolves spontaneously within two weeks, patients with bloody diarrhea for more than two weeks should be investigated for inflammatory bowel disease.[69]

Colitis does not always present with diarrhea. There is often blood mixed with normal stools. In children younger than 6 months, this finding suggests eosinophilic proctocolitis or lymphoid nodular hyperplasia. In infants between 6 months and 2 years it may also suggest juvenile polyp.[69]

When blood is not mixed with stool, there is likely to be perianal disease such as anal fissure or proctitis.[69] Also, when blood is mostly seen on toilet paper or in the toilet bowl after a bowel movement is complete, such a hypothesis is also more likely. If on physical examination there is a fissure and perianal erythema, a diagnosis of beta-hemolytic streptococcal cellulitis should be considered.[69]

Upon physical examination, the patient's hemodynamic status should be initially evaluated and peritonitis, signs of portal hypertension, and abdominal masses should be investigated.

Therapeutic approach

As with most food allergies, treatment of the Allergic proctocolitis consists of elimination of triggering antigens with a diet of exclusion of the suspected food. Cow's milk proteins are the most involved allergens.[71] However, occasionally the elimination of two foods together may be required, followed in this case by the exclusion of soy and egg.

For exclusively breastfed infants, elimination of food from the mother's diet results in resolution of symptoms in most cases, rarely requiring the use of formula to stop intestinal bleeding.[13] The exclusion of food from the maternal diet should always be accompanied by a nutritionist to assess the adequate supply of nutrients for the mother and baby, in addition to verifying the

Table 2
Etiology of gastrointestinal bleeding in children

Newborns	Breastfeeding infants	Preschoolers	School children and teenagers
Anorectal fissures	Anorectal fissures	Anorectal fissures	Anorectal fissures
Allergic colitis	Allergic colitis	Infectious colitis	Infectious colitis
Swallowed maternal blood	Infectious colitis	Intussusception	Henoch-Schonlein purple
Necrotizing enterocolitis	Intussusception	Meckel's Diverticulum	Meckel's Diverticulum
Volvo	Meckel's Diverticulum	Hemolytic uremic syndrome	Hemorrhoid
Hirschprung's Disease (toxic megacolon)	Hirschprung's Disease (toxic megacolon)	Henoch-Schonlein purple	Inflammatory bowel disease
Coagulopathies	Lymph node hyperplasia	Juvenile polyps	Juvenile polyps
Vascular malformations	Gastrointestinal duplication cyst		
Gastric and duodenal ulcer	Coagulopathies		
Neonatal transient eosinophilic colitis	Early-onset inflammatory bowel disease		
Gastrointestinal duplication cyst			

need for supplementation.[11] Breastfeeding should always be encouraged, and there is no indication to suspend breast milk supply.[56]

For babies who develop symptoms when fed infant formula, 80% respond to substitution with extensively hydrolyzed formula (FEH) and few cases require formula amino acid (FAA).[11,13,16] Soy protein-based formulas are generally not recommended as co-reactivity between cow's milk and soy proteins occurs in 10% to 30% of patients with proctocolitis.[1]

Removal of foods that cause Allergic proctocolitis, by exclusion in the maternal diet or in the formula-fed infant, results in rapid improvement of symptoms. In most cases, within 72 hours of dietary changes, resolution of hematochezia is observed, although stool bleeding may persist for up to 1 to 2 weeks for the most symptomatic patients.[11,16]

If, after 2 weeks of starting the exclusion diet, the infant is still symptomatic, it is important to check and adjust the exclusion of the antigen in the maternal diet and then check for other possible foods to be eliminated from the diet, suggesting the exclusion of soy, and later from the egg.[56,71] If more than one food protein is restricted from the diet of the breastfeeding mother, the importance of supervision by a nutritionist is again highlighted to ensure nutritional support and to avoid excessive maternal weight loss.[1,56]

The use of probiotics for the treatment of allergic proctocolitis still lacks more elaborate studies for its indication. A randomized clinical trial showed no benefit from using a probiotic, in addition to the maternal diet, in patients with proctocolitis.[16] Another study with very limited evidence suggests that the probiotic with Lactobacillus Rhamnosus GG may promote recovery or tolerance acquisition.[56]

Early and accurate diagnosis of allergic proctocolitis is important in order to avoid unnecessary exclusion diets that can have harmful health effects. Nutritional support is essential to avoid nutritional deficiency in the mother or in babies with allergic proctocolitis. Diet assessment by a nutritionist aims to provide food replacements that ensure adequate intake of vitamins and minerals, including mainly calcium, vitamin D, zinc and selenium. Supplementation of these nutrients is not always mandatory if there is an adequate diet.[1]

Prognosis and food reintroduction

The natural history of allergic proctocolitis is benign and most affected children outgrow this condition within the first year of life. Allergic proctocolitis rarely persists between the 1st and 2nd year of life.[22]

A prospective cohort, following 185 children with proctocolitis to assess possible factors associated with the development of tolerance, showed that 99.4% of patients acquired tolerance at a median age of 11 months (10 to 13 months). However, in a group of 57 children, 33% were only able to ingest the offending food between 12 and 19 months. The main factors related to this acquisition of "delayed tolerance" were: delay in the introduction of complementary foods, concomitant atopic dermatitis, familial atopy, and ingestion of infant formula milk (at least once).[67]

In the study by Martin VM et al., following 153 patients diagnosed with allergic proctocolitis, it was observed that the average age for successful reintroduction of the causative food was around 11 months. In this study, 15% of the patients did not have any dietary restrictions and, despite continued exposure to the food, developed tolerance to the foods involved throughout childhood, however, some of these at a later age.[48]

Despite its benign character and complete resolution, one study suggests that proctocolitis could be a risk factor for the development of functional gastrointestinal disorders (FGID) in later childhood. FGID is characterized by intestinal motility disorder and visceral hypersensitivity (irritable bowel syndrome). The longer duration of hematochezia would be the main factor associated with the presence of these symptoms at four years of age.[72]

Although classically non-IgE-mediated, some cases of proctocolitis may present with IgE specific to the causal food, or develop IgE-mediated symptoms later in life, especially in children who have concomitant atopic dermatitis. For this reason, although it is not recommended to measure food-specific IgE in most cases of proctocolitis, the EAACI (European Academy of Allergy and Clinical Immunology) recommends that specific IgE should be measured in children with associated atopic dermatitis. before reintroduction of the causal food, after long periods of exclusion.[22]

Based on this aspect, a recent study by Cetinkayan et al. suggests that there could be three phenotypes of proctocolitis, according to the presence or development of IgE specific to the suspected food. There is a phenotype without IgE sensitization for the food in question, a second phenotype with IgE sensitization, but without the presence of IgE-mediated symptoms,

another with positive specific IgE and evolution to the IgE-mediated clinical form. The authors observed that individuals with the "transition to IgE-mediated form" phenotype would reach tolerance later than the other two forms. These findings, however, need to be confirmed by further studies.[65]

As it is benign and self-limiting, the food reintroduction of the suspected food can be conducted at home, gradually, under the guidance of the doctor, when he considers that the child has probably already reached tolerance, which usually occurs up to 11-12 months of age for most patients.[1,22,48]

If the diagnosis was not so accurate and the presence of blood in the stool was mild, reintroduction of food can be attempted earlier, given the transient nature of the disease.[1] Some authors also suggest that the early introduction of other foods, starting at 4 and a half months, could accelerate the development of milk tolerance in children with allergic proctocolitis.[48]

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Tuberculosis immunology: a narrative literature review

Imunologia da tuberculose: uma revisão narrativa da literatura

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ABSTRACT

The immune response developed by the host against *Mycobacterium tuberculosis* is considered a complex and multifaceted nature. This host-bacillus interaction, which in most cases results in an asymptomatic latent infection that may or may not evolve to the development of active pulmonary tuberculosis (TB). The present study aimed to update and summarize the current scientific knowledge regarding the immunological mechanisms associated with infection and the development of active disease. This is a narrative review, based on scientific articles indexed in the PubMed/MEDLINE and SciELO databases over the last 20 years. In recent decades, the characterization of Tγδ lymphocytes, MAIT, iNKT and CD1-restricted T cells has provided a better understanding of the role of innate immunity in bacilli infection. The migration of T CD4+ lymphocytes that produce IFN-γ, TNF-α and other soluble molecules, promotes the recruitment and formation of the granuloma, a structure that benefits both the host and the bacillus. Eventually, an imbalance in this complex interaction network results in an exacerbated inflammatory response that contributes to the development of a necrotic granuloma. Finally, exhaustion of the local immune response due to continuous exposure to the bacillus, associated with the anti-inflammatory profile of Th2 lymphocytes and Treg lymphocytes, favor functional inactivation and, consequently, the development of active disease. The immune response is crucial for the development of *M. tuberculosis* infection. Therefore, studies that enable a greater understanding of the host-bacillus interaction may enable the development of new diagnostic methods, therapeutic strategies and, above all, advances in the development of immunobiologicals.

Keywords: Tuberculosis, *Mycobacterium tuberculosis*, immunity, granuloma.

RESUMO

A resposta imune desenvolvida pelo hospedeiro contra o *Mycobacterium tuberculosis* é considerada de natureza complexa e multifacetada. Esta interação bacilo-hospedeiro resulta, na maioria das vezes, em uma infecção latente assintomática, podendo ou não evoluir para a forma ativa da tuberculose (TB). O presente estudo objetivou atualizar e sumarizar o conhecimento científico acerca dos mecanismos imunológicos associados à infecção e sua progressão para a TB ativa. Trata-se de uma revisão narrativa, realizada a partir do levantamento bibliográfico de artigos científicos indexados nas bases de dados PubMed/MEDLINE e SciELO, nos últimos 20 anos. Nas últimas décadas, a caracterização de linfócitos Tγδ, MAIT, iNKT e outra células T CD1 restritas proporcionaram um maior entendimento do papel da imunidade inata na infecção pelo bacilo. A migração de linfócitos T CD4+ produtores de IFN-γ, TNF-α e de outras moléculas solúveis, promove o recrutamento e formação do granuloma, estrutura que beneficia tanto o hospedeiro quanto o bacilo. Eventualmente, um desequilíbrio nesta complexa rede de interação, resulta em uma resposta inflamatória exacerbada que contribui para o desenvolvimento de um granuloma necrótico. Por fim, a exaustão da resposta imune local frente à contínua exposição ao bacilo, associada ao perfil anti-inflamatório dos linfócitos Th2 e linfócitos Treg, favorecem a inativação funcional e, consequentemente, o desenvolvimento da doença ativa. A resposta imunológica é crucial para o desenvolvimento da infecção por *M. tuberculosis*. Portanto, estudos que possibilitem uma maior compreensão sobre a interação bacilo-hospedeiro podem viabilizar o desenvolvimento de novos métodos diagnósticos, estratégias terapêuticas e, sobretudo, avanços no desenvolvimento de imunobiológicos.

Descritores: Tuberculose, *Mycobacterium tuberculosis*, imunidade, granuloma.

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Introduction

Tuberculosis (TB) is a chronic infectious disease caused by the bacillus *Mycobacterium tuberculosis* that preferentially affects the lung. Known sequences of the mycobacterial genome have already been identified in Egyptian mummies, proving the existence of the disease in ancient civilizations.[1] Although TB represents an ancient disease, at the present time, it continues to be a serious public health problem in Brazil and in the world, especially after the reallocation of human and financial resources for TB control to face the health crisis caused by the coronavirus disease 2019 (COVID-19).[2]

In 2020, tuberculosis attacked around 9.9 million individuals worldwide and was responsible for just over 1.5 million deaths, What represents a variation of 7,5% more compared to deaths recorded in 2019, previous year to the pandemic from COVID-19.[2,3] Still in the year 2020, Brazil registered approximately 67.2 thousand TB cases and 4.5 thousand deaths,[4] being considered the country with the highest number of absolute cases in the Americas and one of the 30 countries with the highest disease burden.[3] Such data reinforce the necessity to restructure public policies in order to allow more effective strategic planning in the fight against TB in the midst of the COVID-19 pandemic.

The natural history of the disease is closely related to biopsychosocial determinants, host immunogenetics and bacillus virulence.[5,6] Factors that promote an intense and complex bacillus-host relationship and that can culminate in the development of three clinical outcomes: (1) clearance and control of infection at the point of entry through an effective innate immune response, even before the adaptive immune response is initiated; (2) establishment of a latent *M. tuberculosis* infection (LTBI), or (3) development of active disease. In LTBI, *M. tuberculosis* is in a latent state (dormancy), in the lung lobes, within a tissue structure called granuloma. In these cases, the host controls but does not eliminate the bacillus, remaining asymptomatic and representing potential reservoirs of *M. tuberculosis*.[1,3] According to estimates by the World Health Organization, a quarter of the world's population is infected and at risk of developing active disease through the reactivation of these dormant bacilli.[3]

Given this perspective, several questions emerge from this discussion in order to clarify the phenomena involved in TB immunology. What initial events allow infection control? Why are some people infected and others not, even when they are equally exposed to the bacillus? Is the bacillus capable of modulating the host response? What factors contribute to the establishment of LTBI and progression to active disease? Thus, considering the need to promote the continuing education of health professionals with strategies for early detection of the disease and, for the improvement of public policies related to prevention and treatment, the aim of the study was to summarize current scientific knowledge in light of the immunological mechanisms already described in relation to the infection and development of active TB, emphasizing the bacillus-host interaction.

Methodology

A descriptive narrative review was carried out with a qualitative approach, with the objective of knowing the "state of the art" of the immunological aspects of TB, but without the need to establish a replicable methodology at the level of data reproduction. Although this type of review does not use explicit and systematic methods, it plays a fundamental role in continuing education and updating knowledge on the proposed theme.[7]

Scientific articles indexed in the databases at the National Library of Medicine/ Medical Literature Analysis and Retrieval System Online (PubMed/ MEDLINE) and Scientific Electronic Library Online (SciELO) were retrieved during October and November 2021 using the following health science descriptors (DeCS): "tuberculosis", "*Mycobacterium tuberculosis* infection", "immunity", "immune response" and "granuloma" combined using the Boolean operator AND. Subsequently, upon need for theoretical complementation, gray literature sources and the manual search in reference lists of the selected articles were also consulted.

As an inclusion criterion, articles published in English or Portuguese were used, available in full, that addressed the proposed theme in the format of original articles and/or reviews, having the last 20 years as a reference period. The exclusion criteria adopted were: theses, monographs, dissertations and/or letters to the editor. Finally, the articles were critically reviewed and selected according to their degree of relevance in relation to the object of study of this review. Then the data were systematized into the following categories: "From exposure to infection", "Contributions of innate immunity: new and old paradigms", "Modulation of

acquired immunity and granuloma formation – a host defense?", "What to expect of humoral immunity?", and finally, "Development of active disease: regulatory mechanisms and tissue damage".

Results and discussion

From exposure to infection

The transmission of *M. tuberculosis* occurs from person to person mainly through contaminated droplets, known as "Flügge droplets", which are eliminated through the nose or mouth when a bacilliferous patient talks, sneezes or coughs. These droplets quickly dry up and turn into particles minors, what remain suspended in the environment for hours and can be easily inhaled by a host susceptible. In turn, these microparticles, also known as "core Wells", contain one to two bacilli that are able to reach distant segments of the bronchial tree, mainly the lower lobes of the lungs, where they multiply and cause the so-called primary TB or primary infection.[8-10]

Although transmission of the bacillus is classically associated with the production of infectious aerosols after coughing, a recent study showed that "tidal breathing" eliminates more bacilli per particle than coughing itself.[11] Similarly, it was possible to identify the presence of *M. tuberculosis* using the polymerase chain reaction technique in aerosols released by patients who did not report cough.[12] Taken together, the results suggest that transmission without coughing is possible in pulmonary TB and that, therefore, other signs and symptoms should be considered in the individualized diagnostic investigation.

Once exposed to the bacillus, the course of infection is variable and directly associated with environmental conditions (ventilation and lighting), host immunogenetics, coexisting illnesses, nutritional status, virulence of the infecting strain, among others.[5,13] In this context, it is plausible to consider that not all microparticles that reach the pulmonary alveoli result in a sustained infection. The multiple strategies of the innate immune response could act in the clearance of an incipient *M. tuberculosis* infection. Furthermore, there is evidence that such mechanisms can be enhanced through repeated exposure or an unrelated stimulus (cross-protection),[14-15] a phenomenon known as "trained immunity" that could explain the initial clearance and the absence of infection even after exposure to the bacillus.

The first line of defense of the host understands the lymphoid tissues associated with the mucosal surface of the respiratory tract. Mucosal epithelial cells play a crucial role in protecting against *M. tuberculosis*, as they produce many types of antimicrobial substances and act as physical barriers that limit the entry of the bacillus in the alveolar space. Eventually, in a second moment, alveolar macrophages play an important role in the recognition, phagocytosis and release of pro-inflammatory cytokines that result in the elimination of *M. tuberculosis*.[14,16,17]

Although there is not enough scientific evidence, the effectiveness of these mechanisms could be associated with the reason why some individuals are exposed to the bacillus, but do not show any evidence of immunological sensitization by the tuberculin skin test (TST) and/or by the interferon-gamma release assays (IGRAs)[15] (Figure 1A). Although further studies are needed to better characterize the host peculiarities associated with the resistance to *M. tuberculosis*, there are no study models capable of discerning initial clearance from non-exposure, since a negative TST or IGRA result may reflect either situation.

Contributions of innate immunity: new and old paradigms

In 10 to 30% of cases, immunity against *M. tuberculosis* is insufficient in completely sterilizing the bacillus and therefore requires the host to develop a chronic granulomatous inflammatory response (Figure 1B). Thus, in the early stage of infection, alveolar macrophages, of the M1 type, in reference to the classical activation pathway, phagocytize the bacillus by means of pattern recognition receptors (PRR) that bind to evolutionarily conserved structures called pathogen-associated molecular patterns (PAMP)[16,18].

The most studied PRRs in *M. tuberculosis* infection correspond to Toll-like receptors (TLR). The bacillusis initially recognized by TLR4, TLR9 and the heterodimers TLR2/1 and TLR2/6, which interact with the adapter protein myeloid differentiation factor 88 (MyD88) it's the domain of the toll-interleukin 1 receptor (TIR) containing the adapter protein (TIRAP), capable of activating macrophages and dendritic cells (DC). Furthermore, TLRs play an integral role in activating pro-inflammatory cytokine signaling pathways and other inflammatory mediators, leads gone by activation of transcription factors such as nuclear factor kappa B (NF-κB).[10,16,19,20] The observation of polymorphism of TLR genes has been associated with susceptibility to

TB,[21] demonstrating that these receptors play a role in regulating the expression of inflammatory cytokines produced by these phagocytic cells.

Although TLRs represent the main receptors in the initial recognition of *M. tuberculosis*, other type-domain of ligand oligomerization nucleotide (NLR), C-type lectins, receptors scavenger, among others, are involved in the recognition of different mycobacterial ligands. Furthermore, in addition to phagocytosis, the receptors are responsible for activating other cellular mechanisms, such as autophagy, apoptosis and pyroptosis/inflammasome assembly, contributing to the modulation of the innate immune response during *M. tuberculosis* infection.[14,20,22,23]

These early mechanisms of phagocytosis allow the elimination of the bacillus, through the action of lysosomal enzymes and formation of free radicals within the phagolysosomes. However, virulent strains of *M. tuberculosis* are sometimes able to evade host defense and remain viable within the lysosomes of macrophages and/or DCs. This is due to escape mechanisms that, although poorly understood, are related to: (1) inhibition of the production of cytokines such as IL-12 and IFN-γ by the 6kDa primarily secreted antigenic target, from the English *early secreted antigenic target-6kDa* (ESAT-6); (2) inhibition of phagosome fusion-lysosome and eventually escape of *M. tuberculosis* from the phagosomes of macrophages and/or DC into the cytoplasm; (3) inhibition of apoptosis of infected macrophages through increased production of IL-10 and reduced secretion of TNF-α.[16,24,25]

The study of the so-called inborn errors of immunity (IEI) reinforces what is known about the importance of the cytokines described above. Patients with the Mendelian susceptibility to mycobacterial disease (MSMD) have defects in the regulatory pathways of the IL-12/IFN-γ axis and their receptors, culminating in an infectious predisposition to intracellular pathogens. The most common defect is IL-12Rb1, which affects an average of 60% of patients diagnosed with MSMD.[26]

The bacilli that survive the host's primary phagocytic defenses are able to multiply exponentially within these macrophages and/or DC, inducing the production of a variety of chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL10) and cytokines (IL- 1β, IL-6, TNF-α, IL-12, IL-23, IL-17, IFN-γ) capable of recruiting and activating different populations of leukocytes to the infectious site.[27]

CXCL8 (IL-8) is anti-apoptotic and pro-angiogenic, and in tissues infected with *M. tuberculosis*, he can have additional immunological effects on chemotaxis. This is, is associated with the formation of tuberculous granuloma, since this chemokine acts through chemotaxis in the recruitment of neutrophils and death of the bacillus by macrophages.[28] Similarly, CCL2 or monocyte chemotactic protein-1 (MCP-1), CCL3 or macrophage inflammatory protein 1 alpha (MIP-1a), CCL5 or normally expressed and secreted T cells (RANTES), and CXCL10 or protein 10 induced by interferon-gamma (IP-10), are also chemokines that play an important role in chemotaxis, activation of monocytes and T lymphocytes and, consequently, granuloma formation.[10,14,16,29] Gene expression studies have shown that after infection by the bacillus, monocytes up regulate the transcription of these chemokines,[29] suggesting a potential role in prospecting biomarkers for infection.

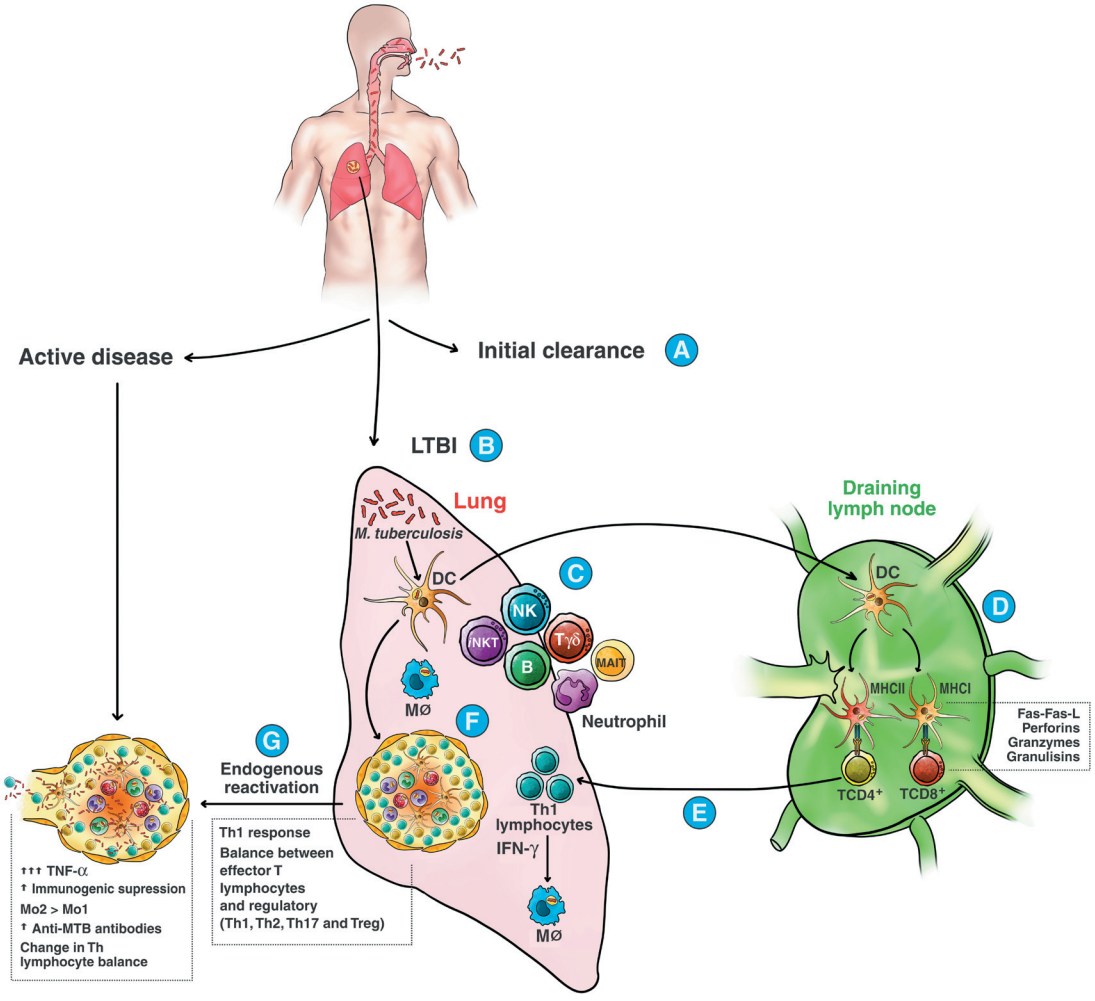
The IL-1β, together with TNF-α, are cytokines that during the inflammatory process increase the expression of endothelial adhesion molecules, promoting the aggregation of other inflammatory cells to the activated endothelium. Furthermore, they activate macrophages and/or DC, helping them to control mycobacterial replication and directly inhibit the intracellular growth of *M. tuberculosis*.[10,14,30] The IL-12p80 subunit increases the IFN-γ induction-in natural killer (NK) cells and the expansion of T lymphocytes $CD4^+$ helper 1 (Th1) antigen-specific, in addition to maintaining the activation and proliferation of lymphocytes, which induces a predominantly pro-inflammatory cellular response.[10,25] IL-6 is also a pro-inflammatory cytokine that acts by negatively regulating the p38 and JNK pathways involved in the autophagy process and contributes to the generation of T lymphocytes. $CD4^+$ helper 17 (Th17) in inflammatory conditions, regulating and promoting the balance between Th17 and $CD4^+CD25^+FoxP3^+$ regulatory T lymphocytes (Treg).[10,14,31]

There are interesting speculations about patients with autoinflammatory syndromes such as Familial Mediterranean Fever (FMF) that corroborate the importance of inflammatory cytokines in the pathogenesis of TB. Studies carried out by some groups in Turkey hypothesize that an evolutionary advantage in these patients would make them less susceptible to the development of infection by the bacillus. This would be explained, at least in part, by the exaggerated chronic inflammatory process with the release of pro-inflammatory cytokines such

as IL-1ß, which would probably be responsible for destroying intracellular pathogens by a process known as pyroptosis by activating inflammasome pathways.[32]

In addition to these cytokines and chemokines, NK cells also stand out through their cytolytic capacity. Although the NKs belong the innate immunity, its mechanisms are similar to those used by $CD8^+$ T lymphocytes, also called cytotoxic T lymphocytes (CTL). However, unlike $CD8^+$ T lymphocytes, they do not have the T lymphocyte receptor (TCRαβ) conventional method for recognizing major histocompatibility molecule (MHC) class I-associated antigens, therefore, they are not MHC-restricted.[16,20] Additionally, NK cells have been linked to an important source of IFN-γ and may also promote the proliferation of Tγδ lymphocytes, producing TNF-α, GM-CSF and IL-12.[20,33]

New lines of evidence suggest that unconventional T lymphocytes, such as those associated with mucosal invariant T cells (MAIT), Tγδ lymphocytes, invariant natural killer T cells (iNKT) and other CD1-restricted T cells are also involved in host defense against the bacillus[14,20,30] (Figure 1C). Unlike NK



B = B lymphocytes, DC = dendritic cells, LTBI = latent tuberculosis infection, iNKT = invariant natural killer T cells (iNKT), MAIT = mucosal invariant T cells (MAIT), MHCI = major histocompatibility complex class I, MHCII = major class II histocompatibility complex, MØ = macrophages, NK = natural killer, Tγδ = gamma delta T cells.

Figure 1
Schematic representation of immunological aspects associated with *Mycobacterium tuberculosis* infection and its outcomes

cells, the effector mechanism of iNKT and other CD1-restricted T cells is dependent on the lipid antigen recognition pathway, and glycolipids presented by the CD1d and CD1a/CD1b/ or CD1c molecule, respectively. Thus, *M. tuberculosis* can be recognized by both iNKT and CD1-restricted T cells.[34] Since the bacillus cell wall is rich and has a wide variety of lipids, it is possible to hypothesize that these cells are essential in the control of the bacillus, because they respond quickly to mycobacteria in the initial stage of infection.

MAIT cells predominantly express the CD8 coreceptor ($CD8^+$) and also respond quickly and effectively to *M. tuberculosis*, even before the classic T lymphocyte response is established.[14] Another subgroup of lymphocytes that also have a TCR distinct from the classic receptors present on T lymphocytes are Tγδ lymphocytes, able to recognize small organic phosphate antigens and alkylamides. Furthermore, they are the main source of IL-17 in the lung during *M. tuberculosis* infection.[30] Altogether, although studies indicate that these unconventional T cells (MAIT, Tγδ lymphocytes, iNKT and other restricted CD1 T cells), may have a promising role in the pathogenesis of TB, the exact function and/or mechanisms of activation of these by the host during the infectious process have not yet been fully clarified and require more detailed studies. On the other hand, these cells have a possible therapeutic potential to be explored, according to their role in the immunomodulation of TB.

Another strategy of innate immunity evidenced in TB refers to the ability of neutrophils activated by *M. tuberculosis* to form complex extracellular networks composed of DNA and several other biologically active cytosolic and granular proteins. This mechanism, which stands for neutrophil extracellular traps (NETs), assists the host in the innate defense against the bacillus and plays an important role in the interaction between neutrophils and macrophages in the initial phase of *M. tuberculosis* infection. However, its formation is dependent on factors such as phagocytosis, production of reactive oxygen species and significant secretion of cytokines such as TNF-α, IL-6, IL-1ß and IL-10.[35] Together, the identification and discoveries of these "new" subsets of cells and/or of the host's effector mechanisms have raised interest and new perspectives in the study of innate immunity in the last 10 years, until then less explored than acquired immunity.

Modulation of acquired immunity and granuloma formation – a host defense?

Since the innate immune response is not capable enough to destroy *M. tuberculosis*, other cells such as monocytes and lymphocytes, are targeted to the site of infection for the development of a more effective response and granuloma formation. Peptides from the proteolysis of *M. tuberculosis*, present in the apoptotic vesicles of M1 and DC macrophages, called professional antigen-presenting cells (APC), bind to the class II MHC molecule, forming the peptide-MHC II complex on the surface of the APC and migrate towards the draining regional lymph node where they present to naïve T lymphocytes, also known as T helper type 0 (Th0) lymphocytes (Figure 1D).[19]

Recognition of the peptide-MHC II complex associated with costimulatory signals given by APC induces the expression of transcription factors, such as T-bet and RORgt, which promote clonal expansion and differentiation into Th1 and Th17 effector lymphocytes, respectively. Thus, $CD4^+$ T lymphocytes, especially the Th1 and Th17 subpopulations, represent the main effector populations that migrate to the primary site of infection, amplifying the immune response and mediating protection during *M. tuberculosis* infection.[14,16,31]

The immune response mediated by *M. tuberculosis*-specific Th1 lymphocytes is associated with the production of pro-inflammatory cytokines, such as IL-1ß, IL-2, IL-12, TNF-α and especially IFN-γ (Figure 1E). In turn, Th17 lymphocytes produce IL-17 which has an initial role in the secretion of IFN-γ, which stimulates the recruitment of Th1 lymphocytes.[14,16,31] Furthermore, in an animal model, Th17 lymphocyte responses precede a strong Th1 response in the lungs, suggesting that these cells are important in the recruitment of Th1 lymphocytes to the infectious site and subsequent granuloma formation.[27]

The IFN-γ is classically described in the literature as the key cytokine in infection control. However, studies in animal and human models indicate that the production of this cytokine alone is not sufficient to provide protection to the host.[10,19,30,36] Cytokine is well known for its ability to activate macrophages, stimulate phagocytosis, phagosome maturation, production of reactive oxygen and nitrogen intermediates, and antigen presentation, seeking to eliminate or restrict intracellular mycobacterial multiplication.[31] Not only $CD4^+$ T lymphocytes of the Th1 profile, but also $CD8^+$ T

lymphocytes and NK cells produce IFN-γ in response to IL-12 produced by APC.[14]

The $CD8^+$ T lymphocyte-mediated response is normally of lower magnitude than those of $CD4^+$ T lymphocytes. Activation of CTL occurs via peptide-MHC I through the mechanism of cross-presentation by DC after absorption of apoptotic vesicles, originating from infected macrophages and neutrophils and containing bacillus antigens. The action of these cells can occur in three different ways: (1) exocytosis of cytotoxic granules containing perforins, granulysin and granzymes that cause the lysis and apoptosis of macrophages and infected DCs; (2) interaction of surface proteins FasL and Fas that result in the death of the target cell infected with *M. tuberculosis*, and (3) production of IFN-γ and TNF-α by these cells, amplifying the microbicidal effects.[8,16,30,36]

In tissue, cell-cell interaction helps contain/isolate the infection through the formation of barrier physical and immune system known as granuloma, resulting from chronic stimulation of cells/cytokines (delayed hypersensitivity) and the inability of the immune system to destroy the bacillus. The architecture of the granuloma is characterized by masses of tissue of the chronically inflamed, formed by bacilli alive or dead, surrounded by macrophages and epithelioid cells that become giant and multinucleated, surrounded by a halo of $CD4^+$ and $CD8^+$ T lymphocytes, plasma cells and fibroblasts (Figure 1F).[37] Furthermore, the role of pro-inflammatory cytokines and chemokines in granuloma formation and stability is highlighted, especially TNF-α.

It is already known that TNF-α plays a critical role in the host response to infection, as it influences the migration of leukocytes to until the infectious focus, promoting the formation of the granuloma capable of containing the multiplication and preventing the dissemination of the bacillus. Although other cytokines and chemokines influence leukocyte recruitment, TNF-α seems to have a major role in maintaining the structural integrity of the granuloma. These findings were later validated by the observation of endogenous reactivation in LTBI patients who used TNF-α inhibitors in the treatment of immune-mediated diseases such as rheumatoid arthritis, Crohn's disease, and immune dysregulated IEI such as adenosine deaminase deficiency type 2 (DADA2).[38-40]

Similarly, people living with HIV (PLHIV) with a $CD4^+$ T lymphocyte count of less than 350 cells/mm^3 are of equal importance, as the risk of TB reactivation among those with LTBI is considerably high. HIV has a tropism for $CD4^+$ T lymphocytes, therefore, the intense viral replication compromises cellular immunity and the organizational structure of the granuloma in the host. This scenario of TB/HIV co-infection not only impacts the reactivation and development of active disease among those with LTBI, but also increases the mortality and lethality rate of TB, characteristics that encourage timely HIV testing in TB patients and vice versa.[8,14,30] In addition, it is worth mentioning that polymorphisms in the CARD8 gene – responsible for controlling inflammation and apoptotic pathways – in PLHIV exponentially increase the chance of active infection due to uncontrolled inflammasome and exaggerated cell death.[41] Therefore, the ability of the host's immune system to contain the bacillus involves a complex network of genes and different subpopulations of lymphocytes, cytokines, among other inflammatory mediators, responsible for the formation and maintenance of the granuloma, especially $CD4^+$ T lymphocytes and TNF-α.

Although granuloma formation is traditionally considered necessary to limit infection, the mechanisms that regulate cell dynamics, behavior and maintenance have only been understood with the latest advances in the use of microscopy intravital, which has allowed a more accurate and detailed analysis of granuloma formation. New findings suggest that mycobacteria benefit from tissue structure formation. Using the experimental model zebrafish, Davis and Ramakrishnan[42] demonstrated that in infection with *M. marinum* (and presumably, *M. tuberculosis*), macrophages are highly mobile and that the initial granuloma benefits the bacillus as it allows the recruitment of uninfected macrophages to the site of infection, providing an environment constant of renewable cells susceptible to the entry of the bacillus. More recently, advances in the creation of in vitro granuloma models have also provided the use of this technique in the study of granuloma biology.[43] Although incipient, the experimental model for study is feasible and should be used from the perspective of a translational approach correlating in vivo experimentation with clinical studies.

Over the years, this complex becomes stable, with areas of fibrosis or even calcification (healing) and, although the infection is controlled, the bacilli can remain viable inside these lesions for many years (primary tuberculosis). In these cases, the production of transforming growth factor beta (TGF-β), which actively participates in the induction of fibrosis.[37] The formation of the granuloma is therefore known as a

primary nodule or Ghon's nodule, usually located in the middle and lower lobes of the lungs, occurring most often in children. In turn, its association with a lymph node is commonly visualized through chest radiography and is called Ghon's complex, these characteristics result in the LTBI condition that represents a "successful" balance in the bacillus-host interaction, with blockage bacillary multiplication and lesion expansion.[8,37,44]

That said, LTBI is defined solely through evidence of immunological sensitization. In TST, effector and memory cells, previously sensitized, migrate to the inoculation site of the purified protein derivative (PPD) and develop a strong late hypersensitivity response, with skin induration equal to or greater than 5 mm. However, the skin reaction is only visible after 48 to 72 hours of intradermal application of PPD. In turn, in the most recent versions of IGRA, the whole blood of the host and, consequently, the cells previously exposed to *M. tuberculosis*, are cultured with a pool of antigens (ESAT.6, CPF-10 and TB7.7) for a period of 24 hours. Consequently, they induce the production of IFN-γ, a cytokine that is measured by an enzyme-linked immunosorbent assay and that is present at levels equal to or greater than 0.35 IU/mL. In both cases, immunological sensitization is observed approximately two to three weeks after exposure to a bacilliferous source, at which point the test results will be positive.[45] Although the tests have high sensitivity and specificity for identifying exposure to *M. tuberculosis*, none of them distinguishes latent from active infection.

What to expect from humoral immunity?

Although immunity against TB is primarily mediated by a cellular response, the role of the humoral response through the participation of antibody-producing B lymphocytes anti-*M. tuberculosis* is still unclear.[16,19,36] Numerous studies have demonstrated high serum levels of antibodies in response to structures present in *M. tuberculosis* in individuals with the latent form and, more often, in patients with active disease, so that higher antibody titers correlate with active disease and/or severity of illness.[46,47] However, patients with active disease and with high levels of anti-*M. tuberculosis* show absence of specific cellular immune response (anergy) to PPD,[48,49] as well as in the more advanced clinical forms of leprosy.

It is known that antibodies, when coating the *M. tuberculosis*, can promote (1) the opsonization process through phagocytic cells that have receptors for the Fc portions of antibodies, (2) antibody-dependent cellular cytotoxicity (ADCC) through NK cells that also recognize the Fc portion of antibodies, (3) activation of the complement system, (4) immune regulation in inflammation, and (5) elimination and neutralization of bacilli in the extracellular environment.[50] However, as is the case with many intracellular bacteria, *M. tuberculosis* is able to evade antibody-mediated antimycobacterial effects as they are able to survive within alveolar macrophages and/or DC.

Although little is said about the role of B lymphocytes in TB, some studies have evaluated the subpopulations of these cells revealing interesting results. The presence of atypical B lymphocytes ($CD21^-CD27^-$ or $CD27^-IgD^-$), in addition to activated lymphocytes ($CD27^+IgD^-$) were increased compared to healthy controls. However, they showed reduced proliferation associated with deficient production of cytokines and antibodies. These functions normalized after adequate treatment with anti tuberculostatic drugs. Other studies corroborated the above finding showing that mycobacteria suppress or deplete the effector functions of B lymphocytes. In turn, memory lymphocytes ($CD19^+IgM^{+/-}CD27^{++}$), plasmablasts ($CD19^+IgM^{+/-}CD138^+CD27^+$), memory plasmablasts ($CD19^+IgM^{+/-}CD138^+CD27^{++}$), as well as circulating marginal zone lymphocytes ($CD19^+CD27^-CD23^-$) were significantly increased in patients diagnosed with TB compared to those already treated, presenting as a potential biomarker of response to treatment.[51]

Another important subtype, recently described in the literature of B lymphocytes, refers to regulatory B lymphocytes ($CD19^+CD1d^+CD5^+$), which would be increased in active TB with cavitation and in more severe forms of the disease. Interestingly, another cellular phenotype of regulatory B lymphocytes, also known as killer B lymphocytes ($CD19^+CD5^+IgM^+FasL^+$) is increased in patients with active disease, but with much higher levels in LTBI with normalization after treatment and re-elevation after stimulation in vitro with BCG,[51] results that suggest a potential protective role in infection against mycobacteria, requiring further confirmatory studies.

However, a study published by Lu et al.[50] showed that individuals with the latent and active form of the disease have different anti-*M. tuberculosis*. Thus, individuals with LTBI exhibit a unique functional profile, selective binding to the FcγRIII isoform, and a distinct glycosylation pattern, features that appear to contribute to infection control. In light of these findings, it is possible to consider (1) high amounts

of anti-*M. tuberculosis* are not necessarily able to provide a satisfactory response, and (2) immunity against the bacillus in individuals with LTBI appears to be associated with a profile of functional antibodies, regardless of their quantity, and with the generation of regulatory B lymphocytes in these individuals.

Although the importance of antibodies is currently uncertain and may differ from host to host, the fact that antibodies have the ability to modulate and potentiate host immunity (opsonization, complement activation, inflammation, etc.) suggests that this arm of the adaptive immune system may contribute to the outcome of *M. tuberculosis* infection and therefore should not be ignored.

Development of active disease: regulatory mechanisms and tissue damage

Eventually, about 5-10% of infected individuals, that is, with LTBI, develop active disease within the first two years.[3,18] This endogenous reactivation occurs mainly in patients with some degree of immunosuppression – a condition that can lead to granuloma rupture and dissemination of viable bacilli (Figure 1G). The main risk factors and vulnerable populations established in the literature are smoking, alcoholism, illicit drug use, diabetes mellitus, malnourished children, the elderly, PLHIV, other chronic diseases and exposure to environmental mycobacteria.[3,52] In these cases, in addition to the development of active lung disease, patients are more likely to progress to severe and disseminated forms, the latter being a result of the dissemination of the bacillus, via the hematogenous, lymphohematogenous, contiguity or intracanalicular route, to other organs and tissues, such as the kidneys, skin, genitourinary system, central nervous system, bones, among others.[14,53]

Considering the multifactorial influence on the outcome of *M. tuberculosis* infection, the generalizations in the immunopathology of active TB presented here may be limited. In immunocompromised individuals and children, the absence of an effective cellular immune response facilitates the multiplication of the bacillus and promotes the development of the disease. In immunocompetent adults, the exacerbation of cellular immunity is responsible for tissue damage and dissemination of the bacillus, as can be seen in PLHIV when they present the so-called Immune Reconstitution Inflammatory Syndrome. Since the mechanisms of disease development are heterogeneous, this work aimed to focus on cases of development of active pulmonary TB in immunocompetent individuals.

That said, most of the time, reactivation occurs in the adult phase and results in an imbalance of the complex network of bacillus-host interaction, which causes a necrotic process in the central area of the granuloma, known as caseous necrosis. Necrotic lesions are similar to cheese, as they have a homogeneous, white appearance, rich in proteins and fats due to bacillary metabolism,[37] and, when they reach the blood vessels, they lead to the occurrence of sputum with hemoptoics, findings that characterize the bronchial cavitations (caves) of secondary (post-primary) TB and that symbolize the classic symptom of pulmonary TB: productive cough accompanied by hemoptoic sputum. In these cases, the formation of cavities can range from a few centimeters, especially in the posterior apical lung segments, to extensive areas. The so-called secondary TB is, therefore, a consequence of the reactivation of a primary focus or, in most cases, through a new contact with bacilliferous patients (exogenous reinfection).[44]

Although the inflammatory response mediated by Th1 lymphocytes is primarily responsible for protecting against infection with *M. tuberculosis*, it is also capable of provoking the exacerbation of a harmful inflammatory response to the host, which results in the development of active disease and the formation process of cavities. In this context, host-derived factors, such as excess TNF-α, the degranulation of phagocytic cells with the release of proteinases, nucleases and lipases, favor the liquefaction of the caseum with the formation of cavities in the centers of the granulomas and, therefore, the loss of the architecture of the lung tissue.[27] In addition, TB patients have an excessive production of cytokines such as IL-1, IL-2 and IFN-γ, associated with an increase in hepatic synthesis and in serum levels of acute phase proteins, such as C-reactive protein, erythrocyte sedimentation rate and serum amyloid A protein, characterizing a classic hyperinflammatory state.[54] Differing from these results, hospitalized TB patients show a decrease in the Th1 response, most likely due to the exhaustion of the local and/or systemic immune response. Thus, antigen-specific T lymphocytes reduce the ability to proliferate and produce inflammatory mediators. Some studies have even shown that IFN-γ levels are lower in TB patients when compared to individuals with LTBI.[55] In turn, Bertholet et al.[56] and Peresi et al.[54] also showed that throughout treatment there is an increase in IFN-γ levels, suggesting a possible restoration of

the specific immune response. These observations are supported by cases of pulmonary TB in which immunocompromised patients with advanced disease are shown to be TST-anergic.[48] Given the results, it is plausible to consider that these are not divergent data, but different stages of the disease in which the exacerbated inflammatory response, most likely, precedes the exhaustion of the immune system.

Interestingly, a study carried out by Berry et al.[57] showed that transcripts of genes induced by IFN type I, most frequently associated with viral infections, are able to discriminate active pulmonary TB from healthy individuals, patients with other chronic respiratory diseases and most individuals with LTBI. Since then, numerous studies have shown that high levels of IFN type I result in increased bacillary burden and disease exacerbation in experimental models of TB.[53,58-60]

On the other hand, cellular hypersensitivity stimulates important mechanisms in the host capable of regulating and preventing the harmful effects of inflammation, which can invariably reduce protective immunity and contribute to cellular suppression. $CD4^+$ helper 2 T lymphocytes (Th2) and/or Treg lymphocytes secrete anti-inflammatory cytokines such as IL-4, IL-10 and TGF-β, and interact directly with other cells through inhibitory molecules such as CTLA-4 and PD-1, which are present on the cell surface.[30]

More recently, studies have shown that, during the development of active disease, differentiation and polarization of M1 macrophages to the M2 profile is observed, which is directly related to the evasion of *M. tuberculosis*.[14] Normally, M1 macrophages are the main effectors of the host response against mycobacteria and produce immunostimulatory cytokines. In contrast, alternatively activated M2 phenotype macrophages have a low ability to promote antigen presentation and are induced by IL-4, IL-13, IL-10 and TGF-β, cytokines that suppress the Th1 lymphocyte response.[20] Therefore, it can be concluded that the M1 phenotype is pro-inflammatory and acts in the initial control of *M. tuberculosis* infection, while M2 can be induced through the anti-inflammatory microenvironment promoted by Th2 lymphocytes and by Treg in active disease. Finally, the quality of the immune response associated with early diagnosis and appropriate treatment can promote lesion regression with scarring and fibrosis. Otherwise, the greater the delay in therapeutic management, the greater the destructive process, making tissue repair in the affected parenchyma unfeasible.[44]

Conclusion

The immune response developed by the host directly affects the course of infection by *M. tuberculosis*. Despite considerable advances in the area, the understanding of natural resistance to the bacillus is still uncertain. Similarly, the contribution of different B-lymphocyte subpopulations and antibodies remains to be elucidated. On the other hand, latent asymptomatic infection is a model associated with the development of an innate and acquired immune response in which numerous soluble mediators (cytokines and chemokines), cells (macrophages, neutrophils, NK) and several subpopulations of conventional lymphocytes (T $CD4^+$ Th1 profile, Th17 lymphocytes, $CD8^+$ T lymphocytes) and unconventional (Tγδ lymphocytes, MAIT, iNKT and other restricted CD1 T cells) participate.

This complex bacillus-host interaction allows the formation of granuloma, a tissue structure capable of containing the multiplication and dissemination of the bacillus, often leading to scarring. Sometimes, unfavorable immunological conditions, which promote an environment of exacerbated inflammation and/or suppression of cells and soluble mediators that orchestrate the granuloma, contribute for the development of immunopathology. However, in an attempt to prevent tissue damage, $CD4^+$ T lymphocytes, Th2 profile, Treg lymphocytes and M2-type macrophages, also favor the progression of pulmonary TB, through the production of cytokines that suppress the inflammatory immune response necessary for the formation and maintenance of the granuloma.

Although different soluble mediators and cells play a key role for the host in the defense and containment of *M. tuberculosis* infection, it is still unclear which ones are more effective in preventing TB, as there are different pathways involved in triggering an immune response successful protector. Thus, further studies are necessary, since knowledge about the immunology of TB is of great importance for the development of new correlates of infection and/or disease, which can be used to build new diagnostic methods and therapeutic strategies, especially in the current era of immunobiologicals.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Vaccination and exercise: immunology in action in pandemic times

Vacinação e exercício: imunologia em ação em tempos de pandemia

Sérgio Duarte Dortas-Junior[1], Guilherme Gomes Azizi[1], Solange Oliveira Rodrigues Valle[1]

ABSTRACT

COVID-19 is a disease caused by SARS-CoV-2, which was first described in Wuhan in 2019. Since then, it has caused the death of millions of people. COVID-19 is characterized by flu-like and gastrointestinal symptoms and may become severe. The importance of understanding how to improve vaccination effectiveness has led to the investigation of factors that may influence immune response. Exercise has been associated with improved immune function and, therefore, may be a potential adjuvant to vaccine-induced immune responses. Chronic training (high levels of physical activity over a prolonged period [months/years]) or acute exercise alone (engaging in a single exercise session [minutes/hours)] are two segments related to the immune response to physical exercise. Acute exercise is known to have short-term effects on the immune system, but there seems to be contrasting effects between moderate exercise sessions and prolonged exercise. In the absence of prophylactic medication or effective treatment, vaccination plus exercise, particularly in populations at risk for immune dysfunction such as older adults, should be encouraged. Thus, in this review, we aimed to discuss and hypothesize the effects of exercise on vaccination responses. Exercise is presented as an adjuvant to improve the immunological effects of vaccination; however, as the COVID-19 vaccination advances worldwide, studies with regular monitoring will be necessary to evaluate the correlation between physical activity and the immune response to these vaccines.

Keywords: Immunology, exercise, vaccination.

RESUMO

A COVID-19 é a enfermidade causada pelo SARS-CoV-2, descrita em 2019, em Wuhan. Desde então, causou a morte de milhões de pessoas. A doença caracteriza-se entre sintomas gripais e gastrointestinais, podendo evoluir com gravidade. A importância de compreender como melhorar a eficácia da vacinação levou à investigação de fatores que podem influenciar a resposta imune. A prática de exercícios foi identificada como um fator que pode melhorar a função imunológica e, portanto, ser um potencial adjuvante para respostas imunes. O treinamento crônico, ou altos níveis de atividade física durante um período prolongado (mês/anos) e, separadamente, o exercício agudo – a realização de uma única sessão de exercício (minutos/horas), são dois segmentos relacionados à resposta imunológica ao exercício físico. O exercício agudo é conhecido por gerar efeitos de curto prazo sobre o sistema imune, mas parecem existir efeitos contrastantes entre sessões de exercícios moderados e exercícios prolongados. Na ausência de uma medicação profilática ou tratamento efetivo, a existência de vacinas e associação com a prática de exercícios, particularmente em populações em risco de disfunção imunológica, como idosos, deve ser estimulada. Assim, nesta revisão os autores buscam dissertar e hipotetizar sobre os efeitos do exercício nas respostas à vacinação. Enfim, a prática de exercícios se apresenta como adjuvante dos efeitos imunológicos sobre a vacinação, todavia, com o andamento da vacinação global para SARS-CoV-2, serão necessários estudos com acompanhamento regular para que possamos avaliar a correlação entre a atividade física e a resposta imunológica a estes imunizantes.

Descritores: Imunologia, exercício físico, vacinação.

COVID-19, a disease caused by the SARS-CoV-2 coronavirus, was initially described in late 2019 in Wuhan (China). Since then, the virus has spread throughout the world, causing the infection and death of millions of people.[1-3] The disease presents with flu-like symptoms (fever, chills, cough; 83% of patients),

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pneumonia (31% of patients), severe acute respiratory syndrome (17% of patients), nausea/vomiting (1% of patients), and diarrhea (approximately 2% of patients).[4-6]

A number of drugs are being explored to treat the disease, however the best scientific evidence concludes that no medication is effective in preventing or "early treatment" for COVID-19 to date.[7] In this way, the scientific community and the biotechnology industry have been working tirelessly to develop vaccines to prevent SARS-CoV-2 infections. An ideal vaccine for SARS-CoV-2, to fight the pandemic, should have the following features: (1) promote long-lasting protective immune responses; (2) possibility of administration to all, regardless of comorbidity or age, immunological status, pregnancy/breastfeeding status; (3) unable to potentiate antibody-dependent facilitation (ADE) or immunopathology/lung inflammation; (4) be thermostable, to allow transport and storage in developing countries with unsatisfactory refrigeration facilities; (5) be highly immunogenic in the general population, including the population with antibodies resulting from previous infection.[8]

In recent times, the importance of understanding how to improve vaccination effectiveness has led to the investigation of factors that can influence the immune response. There are several well-established demographic and behavioral characteristics that are known to be associated with reduced responses to vaccination. The first one is the age group, which leads to immunosenescence; followed by other clinical conditions such as malnutrition, type 2 diabetes mellitus, cardiovascular diseases, rheumatological diseases, certain oncologic diseases and osteoporosis.[9-12] In addition, other behavioral factors, such as chronic stress, depression, excessive alcohol consumption, dietary restriction or excessive weight loss, and smoking are known to decrease the effectiveness of the immune response to vaccinations and/or change susceptibility to infections.[13]

Exercise practice has been identified as a factor that can improve immune function in some situations and, therefore, serve as a potential adjuvant for immune responses.[14] In fact, interest in exercise-induced changes in immune function can be seen in two segments: exercise or chronic training, or high levels of physical activity over a prolonged period (months/years), and separately acute exercise: the performance of a single exercise session (minutes/hours).[14]

Acute exercise is known to have many short-term effects on the immune system, but there seem to be contrasting effects between moderate exercise sessions and prolonged/intense exercise sessions.[14,15] A single bout of exercise is referred to here as "acute exercise," but the intensity and duration can have different effects on the immune system. Prolonged intense exercise, such as completing a marathon, appears to result in temporary suppression of the immune system, described as the "open window hypothesis", related to a higher rate of self-reported symptoms of upper airway infection when compared to those who perform physical activity of lower intensity and duration[14-16] After intense and prolonged exercise, the phagocytic function of neutrophils, the number of natural killer (NK) cells and the total lymphocyte count are reduced during the following 2-24 hours.[17] On the other hand, moderate exercise stimulates the immune system, exemplified by the sudden influx of both NK cells and $CD8^+$ lymphocytes (increasing to 10-fold and 2.5-fold, respectively), which favors an effector memory immune response. This effect is driven by the stimulation of beta-2-adrenergic receptors on the surface of lymphocytes (due to adrenaline released during exercise), leading to endothelial detachment and lymphocyte recirculation, which also induces the expression of $CD4^+$ B cells and regulatory T cells. In addition, exercise helps maintain immune homeostasis by homing in the bone marrow and increasing apoptosis of worn-out/senescent T cells, thereby stimulating the production and release of new progenitor cells (IFN-producing $CD8^+$ T cells).[16]

The ability of exercise to induce a pro-inflammatory environment in the muscles may result in an increase in lymphocytes directed to the vaccine administration site, and/or an increase in antigen uptake and processing, making the initial phase of the immune response more efficient. In fact, exercise seems to mobilize leukocytes with tissue-directed return potential, which could contribute to the development of a proinflammatory environment.[18] Another mechanism is the well-known leukocytosis in response to exercise, which is driven by neuroendocrine mechanisms, and is associated with an increase in the number of circulating monocytes and dendritic cells from antigen-presenting cells (CAA), increasing the possibility of migration of these cells to the site of antigen exposure. Finally, lymphatic drainage is also known to be elevated during muscle contractions, and therefore exercise may enhance

the immune response by transporting cells from the site of antigen administration (vaccination site) to the draining lymph nodes.[19]

Given the importance of vaccination in preventing morbidity and mortality due to infectious diseases, including viral infections, and the variability of the vaccine response, particularly in vulnerable populations, the role of exercise as an important moderator in the effectiveness of vaccines is determined. In addition, it is possible that the elderly obtain great benefits for their immune health induced by exercise.[14]

In this narrative review, the authors seek to discuss and hypothesize about the effects of exercise on responses to vaccination, through some clinical studies on the effects of exercise on responses to vaccination.

Edward et al. carried out two studies where they identified that a moderate cycling session or an activity of the same duration (45 min) are able to significantly increase antibody responses to vaccinations for influenza and meningococcal meningitis. However, the improvements were not uniform, with only women showing a significant increase for the influenza vaccine, and only men showing a significant increase for the meningococcal vaccine.[20,21]

We selected 133 participants without comorbidities, randomized to one of four groups that received the anti-pneumococcal (anti-Pn) vaccine. Specific or control physical exercise, receiving a full or half dose of anti-Pn vaccine. Before vaccination, the groups selected for exercise performed arm and shoulder exercises for 15 minutes, the control groups rested in silence. Antibody levels to the 11 pneumococcal strains of this vaccine were assessed at baseline and at one month. The exercise groups showed a significantly greater increase in antibody levels than the control groups. When doses were compared, it was found that those who exercised had significantly greater responses than those who rested in the half-dose group, but in the full-dose groups the responses were similar.[22]

Three cross-sectional studies with adult subjects who exercise regularly found statistically significant positive effects of higher levels on the response to vaccination. Using the anti-influenza vaccine, Kohut et al. reported higher concentrations of IgG and IgM in individuals who exercised vigorously, suggesting that the practice of regular exercise for at least one year may contribute to a greater increase in the immune response to immunization against influenza in the elderly.[23-25]

Four randomized clinical trials evaluated the elderly. Three studies employed similar interventions for 10 months with groups of moderate-intensity aerobic exercise, three times a week, for 25-60 min per session, and control groups participating in flexibility training for similar periods. All three studies found beneficial effects on vaccine responses in exercise groups.[26-28] The latest randomized clinical trial evaluated influenza vaccine response in older adults randomized to participate in three 60 min classes of Taiji and Qigong (a fusion of martial arts and meditation) per week for 20 weeks or to maintain usual activities. In this study, vaccination was administered in the first week of intervention, and at weeks 3 and 20 the exercise group had significantly higher antibody titers than at baseline, while the control group had no increase.[29]

Kapasi et al. tested secondary antibody production in older versus younger mice after bouts of physical exercise. The secondary antibody response appeared to be exercise-dependent, because older mice that received a bout of intense exercise demonstrated increased levels of antibodies compared to elderly mice that did not exercise. In addition, old mice that received booster doses of immunizers after single physical activity and intense exercise achieved antibody levels comparable to those seen in young mice.[30]

Recently, it was investigated whether regular physical training could improve the response of specific antibodies to the influenza virus in elderly seropositive for cytomegalovirus (CMV). Eighty elderly were divided into two groups: non-practitioners of physical activity (n = 31; age = 74.06 ± 6.4 years) and practitioners of regular combined physical training for at least 12 months (n = 49; age = 71.7 ± 5.8 years). Volunteer groups underwent influenza vaccination and blood samples were collected before and 30 days after vaccination. Regarding the influenza-specific antibody response, higher levels of specific immunoglobulin M (IgM) were observed in both groups post-vaccination compared to pre-vaccination values. Serum levels of anti-influenza and anti-CMV IgG, as well as interleukin 6 (IL-6) and IL-10, were similar between the evaluated times. However, the post-vaccination IL-10/IL-6 ratio was higher in the physical activity group than before vaccination.[31]

In addition, negative correlations between IL-10 and CMV-specific IgG were found in all pre- and post-vaccination groups of volunteers, while a positive correlation between IL-10 and influenza-specific IgG pre- and post-vaccination was observed in the group. physical activity practitioner, as well as showed significant reductions in the proportion of $CD8^+$ effector T cells to naive and increased levels of IL-10 post-vaccination. Thus, this study demonstrated that the improvement in the response to vaccination in elderly seropositive for CMV was related to an anti-inflammatory state and an increase in naive $CD8^+$ T cells, associated with the regular practice of physical activity.[31]

A case of a male individual with no history of comorbidities, who was followed up with graded bicycle exercise before and after SARS-CoV-2 infection, and again after receiving adenovirus vector-based COVID-19 vaccine, has recently been reported. Using whole blood SARS-CoV-2 peptide stimulation, IFN-γ ELISPOT assays, flow cytometry, virus-specific T cell expansion assays, exercise was shown to robustly mobilize SARS-specific T cells. CoV-2 (T $CD3^+/CD8^+$ and T $CD3^+$ double negative [$CD4^+/CD8^+$]) into the bloodstream and capable of recognizing the spike protein, membrane protein, and nucleocapsid antigen. Neutralizing antibodies to SARS-CoV-2 were transiently elevated during exercise after infection and vaccination. However, data are presented in only one individual and within controlled parameters.[32]

In view of all these findings and in the absence of prophylactic medication or effective treatment, the existence of vaccines and their association with exercise, particularly in populations at risk of immune dysfunction, such as the elderly, should be encouraged.

Finally, when the COVID-19 pandemic promoted changes in life habits due to quarantine, reducing the practice of outdoor activities, anti-SARS-CoV-2 vaccines emerge as a tool of hope for the gradual return to activities. The practice of exercises is presented as an important adjuvant of the immunological effects on vaccination, however, with the progress of global vaccination for SARS-CoV-2, studies with regular follow-up will be necessary so that we can evaluate the correlation between physical activity and the immune response to these immunizers.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

The COVID-19 pandemic and its impact on planetary health

A pandemia de COVID-19 e o seu impacto à saúde planetária

Raphael Coelho Figueredo[1], Marilyn Urrutia-Pereira[2], Dirceu Solé[3]

ABSTRACT

The COVID-19 pandemic has painted a clear picture of what a multidimensional planetary crisis is, revealing the central role played by the health sector and the deep inequalities in access to health care that exist between and within each country. Decreasing the environmental effects of the health sector and reducing greenhouse gas emission may not only improve people's health, but also reduce health care costs. The health care sectors around the world directly and indirectly release greenhouse gases by providing their services and purchasing products, services, and technologies within a carbon-intensive supply chain. Further educating health care professionals about the effects of climate change may lead to more sustainable clinical practices, improving patient outcomes and providing substantial impetus to increased efforts to reduce carbon emission. The health sector must take responsibility for its climate footprint by responding to the growing climate emergency not only by assisting the sick, injured, or dying from the climate crisis, but also by doing primary prevention and drastically reducing its own carbon emission.

Keywords: Pandemic, carbon emission, planetary health.

RESUMO

A pandemia de COVID-19 deu ao mundo uma imagem clara do que é uma crise multidimensional em escala planetária, revelando o papel central que ocupa o setor de saúde e as profundas desigualdades no acesso aos cuidados em saúde que existem entre os diferentes países, e dentro de cada um deles. Melhorar os efeitos ambientais do setor e reduzir as emissões de gases de efeito estufa pode não apenas melhorar a saúde de todos, mas também reduzir os custos com os cuidados em saúde. O setor de saúde de cada país libera direta e indiretamente gases de efeito estufa ao fornecer seus serviços e ao comprar produtos, serviços e tecnologias em uma cadeia de fornecimento de carbono intensivo. Educar os profissionais de saúde mais profundamente sobre os efeitos das mudanças climáticas pode levar a práticas clínicas mais sustentáveis, melhorando os resultados para os pacientes e fornecendo um impulso substancial para aumentar os esforços para reduzir as emissões de carbono. O setor da saúde deve assumir a responsabilidade por sua pegada climática respondendo à crescente emergência climática, não apenas prestando assistência aos doentes, feridos ou moribundos como resultado da crise climática e suas causas, mas também fazendo a prevenção primária e reduzindo drasticamente suas próprias emissões.

Descritores: Pandemia, emissões de carbono, saúde planetária.

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Introduction

Effects of climate change are manifested in human health as a result of the impacts of air pollution, severe weather, forest fires, extreme temperatures, changes in vector ecology, problems with food supply, among other stressors.[1]

These health threats are not experienced uniformly across geographic regions or populations, as they disproportionately affect the most vulnerable and disadvantaged groups, such as people of lower socioeconomic status, the sick, women and children.[2]

Much attention has been paid to the role that health systems play in combating climate change.[3] They are necessary to sustain and enhance human well-being, but they have an environmental footprint that contributes to environment-related threats to human health.[4]

Improving the sector's environmental effects and reducing greenhouse gas emissions can not only improve everyone's health, but also reduce healthcare costs.[1]

The World Health Organization (WHO) estimates that the costs generated by the direct damages of climate change to health (not including the costs of damage mediated by the effects on agriculture, water and sanitation) will reach between US$ 2 billion and US$ 4 billion per year by 2030,[5] to meet the Development Goal Targets for universal health coverage.[6]

In this way, achieving these health goals could result in the generation of an additional 382 million tonnes of CO_2 equivalent (tCO_2e) in one year. This would increase the global healthcare carbon footprint by around 16% or 2.4 billion tonnes, accentuating the environmental impact of healthcare, thus running counter to its core mission.[4]

Differences in health challenges between high- and low-income countries, and how these challenges relate to environmental impact, are important considerations. In many low-income countries, the provision of health care is insufficient and the health of the population is often compromised. Unlike what happens in high-income countries, which have high health expenditures, accompanied by significant wasteful practices.[4,7]

Health services participate in this cycle by producing waste and not segregating and disposing of it correctly, by consuming a lot of water or energy in a non-rational way, by not carrying out adequate selective collection, discarding packaging or other materials that could be recyclable in white waste, or continue using disposable cups for their team. There is also environmental damage by continuing to build unsustainable buildings, with poor lighting and without natural ventilation, without thinking about more sustainable energies such as photovoltaics, and not building cisterns to collect rainwater or reuse water, among others; that is, by continuing with these unsustainable actions, they are increasing their carbon footprint,[8] generating more greenhouse gases and contributing to global warming, that will harm the health of people, who will return to services more often and sick. It is necessary to break this cycle.[9]

The objective of this study was to assess and relate environmental health footprints not only to health expenditures, but also to the quality of health service delivery, health outcomes and inequality.[10]

Data source

Non-systematic literature review, searching for articles in PubMed, Google Scholar, SciELO and Embase published between 2017 and 2022, in English, French or Spanish, using the search words “footprint” or “COVID-19” or “ decarbonization” AND “planetary health” or “health care”. The bibliographic survey was carried out in January 2022.

Sources of the health care's climate footprint[9]

While there are significant differences in scale, each country's healthcare sector directly and indirectly releases greenhouse gases when providing its services and when purchasing products, services and technologies in a carbon intensive supply chain.

The healthcare sector contributes to greenhouse gas emissions by consuming energy, transporting and manufacturing, using and disposing of products. The following are several observations:[9]

– emissions directly from healthcare facilities constitute 17% of the sector's global footprint, and indirect emissions from purchased energy sources (electricity, steam, cooling and heating) represent another 12%;
– the largest share of emissions (71%) comes primarily from the healthcare supply chain for the production, transport and disposal of goods and services (pharmaceuticals and other chemicals, food and agricultural products, medical devices, hospital equipment and instruments);

– three-quarters of total healthcare emissions, including those from the supply chain, are generated at the national level. This means that about a quarter of the sector's total emissions are generated outside the country where the product will be used;
– the use of fossil fuels is a central factor in terms of emissions in the sector. Energy consumption, primarily the burning of fossil fuels, accounts for more than half of the healthcare sector's climate footprint.

Impact of the COVID pandemic

The COVID-19 pandemic has given the world a clear but shocking picture of what a multidimensional crisis on a planetary scale is, revealing the central role that the health sector occupies and the profound inequalities in access to health care that exist between and within different countries.[11]

Healthcare delivery is the second biggest area of opportunity for decarbonisation.[1] The pandemic highlighted the need to strengthen and transform health systems in order to prepare them for future pandemics and the other major health challenges of the 21st century, climate change.

Educating healthcare professionals more deeply about the effects of climate change can lead to more sustainable clinical practices, improving patient outcomes and providing substantial impetus to increased efforts to reduce carbon emissions.[12]

It is necessary to enable health professionals to understand their own footprints, which will help drive change in practice, as well as result in partnerships with professional networks, policymakers, communities, for the development and implementation of joint plans.[13]

The WHO, in a recent report, urges the need for urgent improvements in waste management systems, given the thousands of tons of extra medical waste produced in response to the COVID-19 pandemic. The report warns that COVID-19-related health waste has put enormous strain on waste management systems around the world, threatening human and environmental health.[14]

The report estimates that one and a half billion units of personal protective equipment (PPE) that generated 87,000 tons were purchased between March 2020 and November 2021, and shipped to countries around the world through a joint emergency initiative of the Organization of United Nations (UN). However, this represents only a small fraction of the total global waste problem, as it does not include PPE purchased outside the initiative or from publicly generated waste such as disposable face masks.[14]

Globally, three out of 10 healthcare facilities do not have waste segregation systems that they normally consume, much less they would have to manage the increase in waste volumes caused by the pandemic.

The report also warns that poor waste management has the potential to affect the health of workers through puncture wounds, burns and exposure to pathogenic microorganisms, and can also affect communities living in the vicinity of landfills and waste disposal sites, inhaling contaminated air, poor water quality or disease-carrying pests.[14]

Plastic production has more than doubled, raising concerns about short-term impacts on water, oceans and air quality (from fires) in addition to the long-term impacts of nanoplastic particles.[15]

One hundred and forty million COVID-19 test kits have been made available globally. This generated 2,600 tonnes of non-infectious waste and 731,000 liters of chemical waste, according to the report.[12] In addition, more than eight billion doses of vaccine were administered, producing 144,000 tons of additional waste in the form of syringes, needles and safety boxes.[14]

Plastic waste generated by testing and vaccines is incinerated and puts an additional burden on already strained waste management systems and increases pollution where incineration is not well controlled.[16]

Excessive use of gloves has been a long-standing problem even before the COVID-19 pandemic, resulting in unnecessary financial costs and adverse environmental impacts. It is necessary to ensure that adequate amounts of supplies (including water and soap or hand sanitizer) are provided in the right places and there is training and monitoring regarding targeted use.[17]

The report fundamentally recommends: (a) reducing unnecessary consumption of PPE by promoting its safe and rational use, (b) using smaller and more sustainable packaging, (c) developing reusable and easy-to-disinfect PPE, (d) manufacturing PPE with a higher proportion of renewable or recyclable materials, (e) use of technologies such as autoclaves as an alternative to burning, (f) investment in local production of PPE.[14]

In addition, strengthening health waste collection systems, with the implementation of more sustainable improvements, standards and regulations, regular monitoring and reporting, and increased investments in safe waste management, along with water, sanitation, hygiene infrastructure , energy, in addition to a well-trained and skilled workforce, capable of safely managing waste and using the necessary PPE.[14]

Taking all of the above into consideration, what can we do to encourage decarbonization in primary care? How can we change our practices to build adaptation and resilience to these changes?

They can be achieved by high-impact actions,[11] such as:

– supply the healthcare sector with 100% clean and renewable electricity;
– investments in zero-emission infrastructure and buildings;
– initiate a transition to sustainable, zero-emission modes of transport;
– provide healthy, sustainably grown food;
– encouraged the manufacture of low-carbon pharmaceutical products;
– implement circular health care and sustainable health waste management;
– and establish more efficient health systems. Reducing emissions by increasing the efficiency of the system, removing unnecessary and inefficient practices, linking emissions reduction with the quality of care and building resilience.[18]

How can we collaborate individually

Even private health clinics can consciously collaborate with the reduction of the carbon footprint (Table 1). Below we describe the adaptations made to achieve these decarbonization targets. Allergy and Immunology Clinic with an area of 102 m^2 and consisting of three offices (immunology, infectology and dermatology), an exam room and a vaccine room, with an average daily flow of care of 100 people. Because it has large glass windows in all

Table 1
Measures adopted to reduce the environmental impact in the clinic in the care of patients

Measure	Main impact
Solar energy	Clean energy
Collection of contaminated material	Prevents soil and groundwater damage
Selective garbage collection	Generates income and prevents environmental damage
Steam hand dryer	Decrease the use of paper towels
Natural lighting and ventilation	Decreases energy consumption
Biodegradable cups	Avoid using plastic
Electronic medical record	Avoid using paper
Telemedicine	Avoid traveling by vehicles
Digital prescription	Avoid using printed paper
Electric locomotion vehicle	Does not use fossil fuels

environments, natural lighting is the main source of light. In addition, the installation of solar panels on the roof of the building has been sufficient to meet the energy demand of the clinic. Another point to note concerns the generation of waste. The change from disposable cups to biodegradable ones (they are reusable and decompose in 18 months) and the replacement of paper towels with steam dryers helped in this control.

The pandemic brought the legal opportunity of telemedicine, facilitating the care of patients at any distance in the national territory, thus reducing the emission of gases and pollutants because there is no displacement of vehicles. By using electronic medical records and digital prescriptions, waste of graphic materials and consumption of paper, trees and forests are avoided.

In addition to everything mentioned above, depending on the location where we operate, to further reduce the generation of pollution, we as health professionals can replace our commuting with less polluting vehicles, such as electric vehicles or bicycles.

All these measures generate less costs in the short, medium and long term, in addition to positive impacts on global health (Table 1). Therefore, practical changes in our routine in our clinics can bring great benefits from an economic, environmental and, why not, mental point of view.

Conclusion

The health sector must take responsibility for its climate footprint by responding to the growing climate emergency, not only providing assistance to the sick, injured or dying as a result of the climate crisis and its causes, but also doing primary prevention and drastically reducing its own emissions.

The sector must take this initiative forward and, at the same time, reach global health goals, such as universal health coverage and work towards achieving the Sustainable Development Goals, by educating its professionals more thoroughly about the effects that climate change can lead to more sustainable clinical practices.

Climate change, in all its dimensions, will become a growing priority for consumers and decision-makers in all societies around the world, and the health sector must take the lead in tackling this serious problem.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Telemedicine knowledge and practices among Brazilian allergists and immunologists

Conhecimentos e práticas sobre telemedicina entre alergistas e imunologistas brasileiros

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ABSTRACT

Introduction: The aim of this study was to evaluate the characteristics of telemedicine (TM) practices among Brazilian allergists/immunologists (A/I) and to assess their knowledge of regulatory recommendations. **Methods:** A self-report electronic survey was sent by email once a week between August and October 2021 to 2,600 Brazilian A/I physicians. **Results:** A total of 205 (7.9%) participants completed the survey. TM was used in clinical practice by 143 (70.2%) physicians, and 184 (89.9%) had never used it before the COVID-19 pandemic. Among participants, 192 (93.8%) used TM for follow-up consultations, 186 (91%) for checking complementary exams, and 136 (66.7%) for first consultations. The number of A/I physicians (70.2%) that felt confident in their diagnosis using TM was 143, and 7 (3.5%) reported that they could not reach the correct diagnosis using TM. Participants reported that the main benefits of TM were greater accessibility, especially in more distant areas (159, 77.6%), reduced travel costs (158, 77.1%), and safety regarding the transmission of COVID-19 (145, 71.2%). Conversely, the lack of physical examination (183, 89.7%), poor doctor-patient relationship (59, 28.8%), and internet connection problems (45, 22%) were mentioned as disadvantages. Regarding legal/ethical aspects, 105 (51.4%) physicians reported applying a consent form and 34 (16.7%) reported making a record of the teleconsultation, both of which are required for TM consultations, according to

RESUMO

Introdução: O objetivo deste estudo foi avaliar as características das práticas de telemedicina (TM) entre médicos alergistas/imunologistas (A/I) brasileiros e avaliar seu conhecimento sobre as recomendações regulatórias. **Métodos:** Uma pesquisa eletrônica autorreferida foi enviada por e-mail uma vez por semana entre agosto e outubro/2021 a 2.600 médicos A/I brasileiros. **Resultados:** 205 (7,9%) participantes preencheram os formulários. 143 (70,2%) médicos usaram TM em sua prática clínica, e 184 (89,9%) nunca o usaram antes da pandemia de COVID-19. Dentre os médicos, 192 (93,8%) utilizaram a TM para consultas de acompanhamento, 186 (91%) para verificação de exames complementares e 136 (66,7%) nas primeiras consultas. Cento e quarenta e três médicos A/I (70,2%) sentiram-se seguros em seu diagnóstico por meio da TM, e 7 (3,5%) responderam que não conseguiram encontrar um diagnóstico correto usando a TM. Os principais benefícios da TM relatados foram: maior acessibilidade, principalmente em áreas mais distantes 159 (77,6%), redução dos custos de deslocamento 158 (77,1%) e segurança quanto à transmissão do COVID-19 145 (71,2%). Por outro lado, algumas desvantagens da TM foram listadas pelos participantes: ausência de exame físico 183 (89,7%), relação médico-paciente fragilizada 59 (28,8%) e problemas de Internet 45 (22%). Em relação ao campo jurídico/ético, 105 (51,4%) dos especialistas aplicaram o termo de consentimento e 34 (16,7%) registraram a teleconsulta,

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local regulatory recommendations. The use of inappropriate online platforms for TM, such as social media applications and nonspecific online meeting programs, was reported by 131 (64.1%) participants. Eighty (40%) participants did not read the official statements and recommendations that regulate the practice of TM in Brazil. **Conclusions:** An increasing use of TM was observed in Brazil, mainly influenced by the COVID-19 pandemic. Despite being a useful tool in the pandemic, with advantages and disadvantages, physicians should have knowledge of regulatory recommendations.

Keywords: Telemedicine, remote consultation, allergy and immunology.

ambas as etapas exigidas em uma consulta de TM, conforme recomendações regulatórias locais. Além disso, plataformas *online* inadequadas para TM, como aplicativos de mídia social e programas de reuniões online não específicos, foram relatadas como sendo usadas por 131 (64,1%) dos participantes. Oitenta (40%) não leram as declarações e recomendações oficiais que regulamentam a prática da TM no Brasil. **Conclusões:** Observou-se um uso crescente de TM no Brasil, influenciado principalmente pela pandemia de COVID-19. Apesar de ser ferramenta útil na pandemia, com vantagens e desvantagens, há necessidade de conhecer as recomendações regulatórias.

Descritores: Telemedicina, consulta remota, alergia e imunologia.

Introduction

Medicine has always been, within the fields of science and human knowledge, one of the most present areas at the forefront of research and innovation. The history of telemedicine (TM) in the world is a good example, with reports of consultations carried out remotely since the 1950s.[1] In Brazil, in 2022, we completed 20 years of the first resolution of the Conselho Federal de Medicina (CFM) who dealt with the subject,[2] defining TM as "(...) the exercise of Medicine through the use of interactive methodologies of audiovisual and data communication, with the objective of assistance, education and research in Health".

According to the Office of the National Coordinator for Health Information Technology, TM can be defined as "the use of electronic information and telecommunications technologies to support and promote clinical health care, patient and professional health-related education, public health and health administration".[3]

However, despite its two decades of history, TM in Brazil has continued to make punctual advances only in some specific areas, such as cardiology, intensive care medicine and radiology. The lack of broad discussions, associated with the difficulty of reaching a consensus among the entities, led to the publication and revocation of several resolutions by the CFM.

Even before the COVID-19 pandemic, there were already several studies, protocols and consensus demonstrating the use of telehealth services in allergy and immunology in a complementary or even substitutive way to traditional face-to-face monitoring. We can cite, as examples, the use of TM tools for daily control and assessment of allergic rhinitis activity[4] and the use of applications to control asthma and dermatitis performed by the patient.[5,6] Therefore, the potential viability of telemedicine as a viable alternative to traditional in-person medical care for the treatment and management of allergic and immunological diseases was already known.

The advent of COVID-19 in early 2020 brought with it the need for social distancing and a high demand for health services in this period. In a few months, this situation led to changes in legislation and in the understanding of the need to implement the TM practice. Physicians of all specialties saw their practices being quickly converted to telemedicine in a few days, without preparation or advance planning by professional bodies.[7] The practice of TM performed in an unregulated way can lead to several implications, not only regarding the patient's health, but also in the ethical-legal scope.[8]

The Ministry of Health published, on March 20, 2020, Ordinance No. 467, authorizing and regulating the practice more comprehensively.[9] The National Congress, in turn, drafted law No. 13,989 on April 15, 2020, which authorizes the practice of TM while the pandemic lasts.[10] These changes, in such a short time, were not accompanied by a deeper understanding of how TM could be performed in practice by health professionals in a safe and responsible way.

Observing this global trend and understanding that, regardless of the pandemic, this new model of care has definitively transformed medical practice, the board of the Brazilian Association of Allergy and Immunology (ASBAI) created, in March 2021, the Digital Health Commission. In this way, ASBAI seeks to: 1) be up to date with society's digital revolution,

2) contribute at the national level to the debate and implementation of this method, and 3) provide allergists and immunologists with knowledge and regulations that ensure an ethical and effective practice. within the peculiarities of the specialty. Knowing the situation of professionals and the way they see and practice TM is essential for improvements in the regulation of telehealth practices.

In order to more assertively understand the specialist's current situation regarding their level of knowledge and the difficulties faced in the practice of TM, the ASBAI Digital Health Commission carried out a national survey on the subject in 2021. This article presents the results of this research.

Method

A cross-sectional study was carried out, through the application of an electronic questionnaire on the use of TM, applied to experts, through the GoogleForms platform® (Appendix 1).

A total of 2600 physicians associated with the Brazilian Association of Allergy and Immunology (ASBAI) were invited, by sending the questionnaire and the Free and Informed Consent Term (ICF) by emailing the months of August to October 2021, and on social networks like Instagram®, Facebook®, Linkedin®, Whatsapp®. In the networks, the survey was disseminated with an explanation of its objective, its importance and the time taken to respond to the instrument.

The project was approved by the Human Research Ethics Committee of the Hospital de Clínicas Complex of the Federal University of Paraná. Participants who signed the informed consent form were included in the study. Participants who did not complete the questionnaire in full or duplicate questionnaires answered by the same participant were excluded from the study.

Categorical variables were presented by frequency distribution and proportion.

Results

A total of 206 questionnaires were answered, one form being excluded due to data duplication, resulting in 205 participants. This amount represents about 7.9% of the total number of specialist professionals registered by ASBAI.

The distribution by age group is summarized in Figure 1.

Most of the participants who answered the questionnaire work in the Southeast region (59%); 12% work in the Northeast region, 10% in the South region, 11% in the Midwest region and 6% in the North region of Brazil.

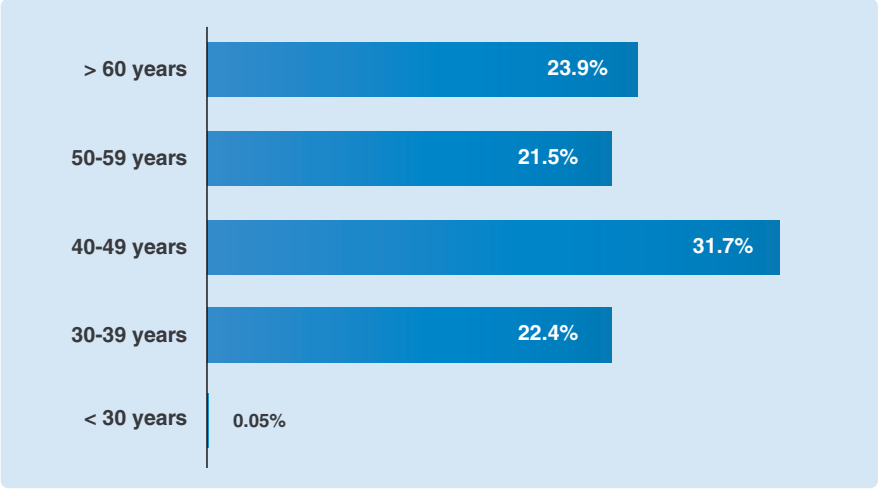

Figure 1
Age distribution of research participants

One hundred and forty-three (70.2%) answered that they attended TM. One hundred and eighty-nine (89.9%) did not use it before the COVID-19 pandemic, but 188 (91.7%) believe in the continuation of telemedicine care after the pandemic. Among those who used TM, 166 (81%) responded that only 25% or less of their patients used telemedicine.

Regarding ethical/legal issues, 105 (51.4%) of the participants who used TM used the informed consent, and 34 (16.7%) recorded the teleconsultation. It was evidenced that 122 (59.5%) of the participants read Resolution No. 1,643/2002 of the Federal Council of Medicine on telemedicine, while 119 (58%) of the interviewed specialists read the official position of ASBAI.

Most participants use the platform Whatsapp® for consultations via TM - 92 (45.1%). Other frequently used apps are Zoom® - 70 (34%), Own Electronic Medical Record - 65 (31.9%), Own Applications of the Agreement - 38 (18.8%), Google Meet® - 34 (16.7%) and Facetime® - 14 (6.9%). In total, 131 (64.1%) of the experts use at least one inappropriate platform for the use of TM.

As for consultation fees, almost three quarters of specialists charged the same amount as a face-to-face consultation - 147 (71.5%). Of these, 17 (28.5%) charged a different amount than the face-to-face consultation, all of them charged a lower amount for the TM consultation than for the face-to-face consultation. Among the participants, 120 (58.3%) answered that they did not have medical appointments for TM. Of the 41.7% who carry out consultations through the agreement, 67 (79.2%) receive the same amount as a face-to-face consultation.

When asked about the purposes they use telemedicine, 137 (66.7%) use it for the first consultation, 187 (91%) for return with exams and 192 (93.8%) for clinical follow-up. The most common diagnoses were: rhinitis (80.6%), urticaria and/or angioedema (74.3%), asthma (56.3%), food allergy (48.6%), atopic dermatitis (47.2%), drug allergy (38.9%), allergic conjunctivitis (30.6%), immunodeficiency (16%), COVID-19 (7%), need for immunobiologicals (1.4%) and chronic pruritus (0.7%). About 180 (88%) of physicians are able, most of the time or always, to determine the diagnosis with teleconsultation. Only 7 (3.5%) stated that they could not determine the diagnosis with this modality alone. Half of the specialists 104 (50.7%) request in vivo tests after the teleconsultation and 182 (88.9%) feel safe to handle the medications in use by the patient by telemedicine. Of the total, 144 (70.2%) feel safe to perform medical care by TM.

Physicians also pointed out the advantages and disadvantages of using telemedicine (Table 1).

As for the face-to-face consultation, the doctors considered the advantages pointed out in relation to TM, mainly, the performance of the physical examination - 198 (96.6%), the reception - 161 (79%) and adherence to treatment - 103 (50.3%) . Also listed were: doctor-patient relationship - 6 (3%), performing diagnostic tests (3.1%) and privacy, accessibility and security, with 1 (0.5%) each.

Discussion

In our study, most allergy and immunology specialists reported that they used TM in their clinical practice, demonstrating the spread of the modality among Brazilian professionals. This is in line with the global panorama: the digital world is increasingly present with the use of the internet on smartphones, social networks and health informatics. These advances have facilitated the dissemination of the use of TM globally.[7]

The COVID-19 pandemic played an important role in the process of TM[11] implementation. In fact, in our study, the vast majority of professionals did not use the modality before the COVID-19 pandemic, and believed in the continuation of telemedicine care after the pandemic. This was also corroborated in other studies, such as a recent work carried out in a Spanish allergy unit, which showed that half of the patients who had a telephone consultation during the first peak of the pandemic would like to continue with this practice after the epidemic.[7]

Several advantages of telemedicine in relation to face-to-face consultation are already consolidated. Some studies, even before the pandemic, already demonstrated an equivalence between TM and traditional consultations - as in the study conducted by Nguyenet al.,[3] which found similar control values for the asthma activity in children between the two treatment modalities. It is also worth mentioning a Brazilian study conducted by Giavina-Bianchi et al.,[12] which showed that teletriage in pediatric dermatology addressed 63% of the lesions without the need for a face-to-face visit. This is in line with the result of our research, where specialists reported being able to determine the patient's diagnosis most of the time, demonstrating that the potential viability of

Table 1
Attributes of telemedicine in the opinion of physicians

Benefits	**n (%)**
Accessibility in remote locations	159 (77.5%)
Avoid transportation	158 (77.1%)
Prevent the transmission of COVID-19	146 (71.2%)
Transfer of knowledge and experience between services	71 (34.6%)
Better quality of healthcare	52 (25.4%)
Integration of the assistance network	42 (20.5%)
Disadvantages	
Absence of physical examination	184 (89.8%)
Weakening of the doctor-patient bond	59 (28.8%)
Difficulty connecting to the Internet	45 (22%)
Lack of data security	45 (22%)
Little familiarity with the digital medium	29 (14.2%)
Inability to perform diagnostic tests	25 (12.2%)

telemedicine as an alternative to traditional face-to-face physicians for the treatment and management of allergic and immunological diseases.

Telemedicine has improved the frequency of consultations due to less use of transport, attendance at more flexible hours, which contributed to a better doctor-patient relationship.[13] In addition, several studies have shown that TM can be a reason for savings because the patient avoids commuting, lost working hours while waiting for the appointment, and absence from work.[3,7]

Despite numerous advantages, patient acceptance still seems to be low in Brazil: in our questionnaire, most experts reported that less than a quarter of their patients use telemedicine for consultations. This can be explained by the inherent disadvantages of the model, such as the absence of a physical examination and the loss of quality of care.[14,15] Second the European Society of Family Doctors, can negatively affect the quality of the physical examination and the quality of care.[11] As in the works cited, these were the two main disadvantages of TM highlighted by Brazilian allergists and immunologists in our questionnaire. There are still reports in the literature of a certain "fear" among physicians that telemedicine may harm their professional autonomy, increase their workload, cause a lack of organization, integrity, remuneration and flexibility, among other damages.[13]

Difficulty in accessing the Internet was also raised as a disadvantage by a quarter of respondents. In fact, telemedicine facilitates access where there are geographical barriers where there is no qualified professional.[11] However, despite data showing that 82.7% of Brazilian households have access to the Internet,[16] the quality of the connection in situations of high data volume, such as video calls, can be a limiting factor in our country, especially in these more remote areas.

Regarding the values attributed to the teleconsultation, one third of the participants reported charging a lower value for the teleconsultation, when compared to the face-to-face consultation. Also, it was noted that about half of the professionals carried out consultations through medical insurance, and a fifth of these received different values from a face-to-face consultation. In a document prepared by the Ethics and Professional Defense Commission of ASBAI, in May 2020,[17] it is concluded that the values must be maintained in relation to those that were already being practiced by the conventional method.

Regarding ethical/legal issues, there are some observations to be considered. In our questionnaire, half of the participants who used the TM used informed consent and the minority recorded the teleconsultation. According to Resolution No. 1,643/2002 of the Federal Council of Medicine on telemedicine[2] and the position of ASBAI,[17] these are two mandatory requirements. In addition, more than half of the participants used digital platforms not considered suitable for the use of telemedicine, such as the Whatsapp®. It is mandatory to use platforms or applications with digital certification that are exclusively appropriate for medical appointments by TM.[10,17] The data obtained show a lack of knowledge on the part of specialists about the TM regulation, and highlights the result that half of the allergists and immunologists interviewed did not read the documents that guide the practice in Brazil for the specialty.

In conclusion, our study shows the panorama of knowledge about the use of telemedicine in a portion of Brazilian allergists and immunologists. As electronic health innovations will be increasingly present in specialist practice, it is necessary that the protocols and guidelines formulated for the responsible use of TM are followed by professionals, in order to further optimize its advantages and minimize possible deleterious consequences, both for doctors and patients.

1. Email address: _____

2. I have read and understood the consent form, I voluntarily agree to participate in this study, and I understand that my identity will not be revealed.
   ( ) Yes, I agree with my participation
   ( ) No, I do not agree with my participation

3. What's your age?
   ( ) < 30 years
   ( ) 30 to 39 years
   ( ) 40 to 49 years
   ( ) 50 to 59 years
   ( ) > 60 years

4. In which City/State do you work? _____

5. Do you provide telemedicine services?
   ( ) Yes
   ( ) No

6. Were you using it before the COVID-19 pandemic?
   ( ) Yes
   ( ) No

Appendix 1
Form used in the research

7. What percentage of your patients currently use teleconsultation?
   ( ) Less than 25%
   ( ) 25 to 50%
   ( ) 50 to 75%
   ( ) Greater than 75%
8. Do you use the electronic medical record?
   ( ) Yes
   ( ) No
9. Do you use the Free and Informed Consent Form?
   ( ) Yes
   ( ) No
10. Do you record the Teleconsultation?
    ( ) Yes
    ( ) No
11. Which platform(s) do you use?*
    ( ) Google Meet®
    ( ) Zoom®
    ( ) Facetime®
    ( ) Whatsapp®
    ( ) Skype®
    ( ) Microsoft Teams®
    ( ) Own agreement application
    ( ) Electronic medical record (example: Doctoralia®, iclinic®, others)
    ( ) Other: _____
12. Do you charge the same amount as the face-to-face consultation?
    ( ) Yes
    ( ) No
13. If you answered no, what is the average percentage in relation to the value of the face-to-face consultation?
    ( ) 25%
    ( ) 50%
    ( ) 75%
    ( ) 100%
    ( ) Greater than 100%
14. Do you do Telemedicine through medical insurance?
    ( ) Yes
    ( ) No
15. For what purpose(s) do you use teleservice?*
    ( ) First consultation
    ( ) Return with exams
    ( ) Clinical follow-up
16. Can you determine the diagnosis with teleconsultation alone?
    ( ) Yes
    ( ) Mostly
    ( ) Few times
    ( ) No
17. What is the most sought after diagnosis?*
    ( ) Rhinitis
    ( ) Asthma
    ( ) Urticaria and/or Angioedema
    ( ) Drug allergy
    ( ) Food allergy
    ( ) Immunodeficiency
    ( ) Atopic dermatitis
    ( ) Contact dermatitis
    ( ) Allergic conjunctivitis
    ( ) Other

Appendix 1 *(continuation)*
Form used in the research

18. Do you feel safe to modify the medications used by the patient through teleconsultation?
    ( ) Yes
    ( ) No

19. Do you request in vivo tests (example: skin test) in the teleconsultation?
    ( ) Yes
    ( ) No

20. Do you feel safe to carry out the teleconsultation?
    ( ) Yes
    ( ) No

21. Have you read Resolution No. 1,643/2002 of the Federal Council of Medicine on telemedicine?
    ( ) Yes
    ( ) No

22. Have you read the official ASBAI position on telemedicine?
    ( ) Yes
    ( ) No

23. In your opinion, what are the biggest difficulties in this type of service?*
    ( ) Little familiarity with the digital medium
    ( ) Difficulty connecting to the internet
    ( ) Lack of data security
    ( ) Specialty exercise
    ( ) Absence of physical examination
    ( ) Inability to perform diagnostic tests at this time
    ( ) Weakening of the doctor-patient bond
    ( ) Other: _____

24. What is the advantage(s) of telemedicine in relation to face-to-face care?*
    ( ) No need to transportation
    ( ) Making the specialty more accessible (remote places)
    ( ) Safety regarding the transmission of COVID-19
    ( ) Integration of the assistance network
    ( ) Transfer of knowledge and experience between services
    ( ) Improving the quality of health care
    ( ) Other: _____

25. Do you think telemedicine care should continue after a pandemic?
    ( ) Yes
    ( ) No

26. What do you consider to be the advantage(s) of a face-to-face consultation?*
    ( ) Reception
    ( ) Physical exam
    ( ) Treatment adherence
    ( ) Other: _____

27. If you want to receive the result of the research, as well as the CFM Resolution and the ASBAI position, leave your e-mail address here: _____

Note: Questions marked with * could have multiple answers.

Appendix 1 *(continuation)*
Form used in the research

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Study of variants in the mTOR gene with asthma and therapeutic control in a population of Salvador/BA

Estudo de variantes no gene mTOR com asma e controle terapêutico em uma população de Salvador/BA

Ítalo Santos Uzêda[1], Raisa Coelho[1], Ryan Santos Costa[1], Camila Figueiredo[1]

ABSTRACT

Introduction: Asthma is an inflammatory airway disease that is influenced by several factors. An evolutionarily conserved serine/threonine kinase named mTOR plays a key role in the integration of environmental signals in the form of growth factors, amino acids, and energy. In the immune system, mTOR is a critical regulator. The mTOR pathway exerts central control over processes in the immune response and in T-cell proliferation, multiplication, and differentiation. Variations in the gene responsible for mTOR complexes have been associated with different critical levels of cytokines, increased likelihood of developing asthma, and increased prevalence of atopy. **Objective and method:** This study aimed to investigate the association of mTOR gene variants with asthma, asthma severity, and atopy, as well as to perform a cytokine analysis. **Result and conclusion:** The findings reinforce the importance of mTOR gene variants in the development of asthma.

Keywords: Asthma, TOR serine-threonine kinases, single nucleotide polymorphism.

RESUMO

Introdução: A asma é uma doença inflamatória das vias aéreas, com diversos fatores influenciando essa condição inflamatória. A mTOR, uma serina/treonina quinase evolutivamente conservada, desempenha um papel central na integração de sinais ambientais na forma de fatores de crescimento, aminoácidos e energia. No sistema imunológico, a mTOR se apresenta como um regulador crítico. A via mTOR se destaca pelo controle central na resposta do sistema imunológico, bem como na proliferação, multiplição e diferenciação das células T. Variações no gene responsável pelos complexos mTOR têm sido associadas a diferentes níveis críticos de citocinas, aumento da probabilidade de desenvolver asma e aumento da prevalência de atopia. **Objetivo e método:** O objetivo do presente estudo foi investigar a associação entre as variantes do gene mTOR com asma e sua gravidade, atopia, além da análise de citocinas. **Resultado e conclusão:** Os achados reafirmam a importância das variantes do gene mTOR no desenvolvimento da asma.

Descritores: Asma, serina-treonina quinases TOR, polimorfismo de nucleotídeo único.

Introduction

Asthma is an inflammatory disease of the airways of heterogeneous and chronic origin whose varied symptoms are cough, shortness of breath, wheezing and chest pain with variation in time and intensity in the air flow.[1] Because it is a complex disease, it is the result of many factors, whether genetic, environmental (dust, mites, animal hair or cigarette smoke), viral infections or use of drugs that culminate in the characteristic symptoms of asthma.[2] About 339 million people worldwide are affected by this disease, and the trend is for the prevalence to increase.[1]

Atopic asthma is characterized by the presence of specific IgE for these aeroallergens and by the action of cytokines and molecules that make up the

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profile of T helper 2 or Th2 lymphocytes, this being a subtype of effector CD4 + T cells, which lead to an inflammatory cascade.[3] The identification of allergens by Th2 cells in atopic asthma induces the interleukins (IL) of this profile, such as IL-4, IL-5 and IL-13, cytokines involved in the isotype change of the B cell heavy chain, which results in the release of Immunoglobulin E (IgE) by plasmocytes, in eosinophil chemotaxis, in airway hyperreactivity and mucus secretion. Non-atopic asthma, in turn, points to a distinct pattern of T cell activation, producing IL-5, IL-2 and IFN-γ.[4] The mTOR, or target of rapamycin in mammals, is a serine / threonine kinase whose function in the central regulation of cell metabolism, growth, proliferation and survival has already been reiterated.[5] In the activation cascade by extrinsic factors PI3K (p-PI3K) phosphorylates Akt, which activates mTOR and its effective ribosomal protein to S6 kinase 1 (S6K1). Phosphorylated S6K1 (p-p70S6k) promotes protein translation and cell growth. Aberrant mTOR signaling is involved in many diseases, including cancer, cardiovascular disease and diabetes.[6] The mTOR, which also regulates the cellular immunity of lymphocytes, stimulates the release of cytokines from inflammatory cells.[7] In addition, systemic lupus erythematosus was suppressed when patients were treated with the mTOR inhibitor rapamycin.

The mTOR pathway regulates the differentiation and activation of subsets of CD4 + T cells. Therefore, it is believed that the mTOR signaling pathway is strongly associated with the loss of balance between Th1 and Th2 cytokines and between Th17 and Treg cells in immunological diseases, as well as asthma, whose phenotypic profile is variable.[8] In this perspective, the objective of the study was to analyze the association of variants in the MTOR gene with asthma, atopy and therapeutic control of the disease in a population in Salvador, Ba.

Methods

Population

The present study was conducted in 1178 patients from ProAR (Program for the Control of Asthma and Allergic Rhinitis in Bahia) and these were divided into the following groups:

a) Patients with severe asthma: 401 patients with severe asthma, of both genders and age over 18 years, living in Salvador, were included. The cases were recruited consecutively among patients followed by ProAR for at least one year, with a confirmed diagnosis of severe asthma according to the classification of the Global Initiative against Asthma[9] by an audit carried out by two experts.

b) Controls (patients with mild asthma): 413 control patients with mild or intermittent persistent asthma[9], also resident in Salvador and matched to cases by gender, age and socioeconomic status, were evaluated.

c) Controls (patients without asthma): 364 individuals with no history of asthma, also resident in Salvador and matched to cases by gender, age, socioeconomic status and place of residence, were evaluated, undergoing a medical consultation to assess their condition, health supplemented by basic blood, feces and urine tests, to all procedures for obtaining environmental information and blood samples for DNA analysis and genetic study.

The diagnosis of asthma and the definition of severity, carried out by the doctor, followed the classification of the Global Initiative for Asthma.[1] Combined history, physical examination, spirometry, daytime airway variation and response to treatment lead to the diagnosis of the disease. The main associated symptoms included wheezing, chronic cough, chest tightness, dyspnoea, chest discomfort, at specific times and under certain circumstances: exposure to cold, post-exercise, respiratory infection, exposure to inhalers, respiratory irritants and / or exposure to allergens. Severity was based on reports of daily symptoms, exacerbations or frequent nocturnal symptoms, limitation in physical activities, reduced lung function (FEV_1 or peak expiratory flow ≤ 60%) or variability in FEV_1 or peak expiratory flow > 30%.

The individuals underwent a medical consultation to assess their general health condition, with basic tests (blood, feces and urine), a questionnaire to collect information on the home environment and blood samples for DNA analysis and genetic study.

Atopy was defined based on the dosage of allergen-specific IgE (asIgE) in the individuals' serum, combined with the results of skin tests. All cases and controls were subjected to skin prick tests (SPT) for the most common inhalable allergens in our region (mites – *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*; cockroach - *American periplaneta* and *Blatella germanica*; fungi - *Aspergillus fumigatus* and *Penicilliumnotatum*; animals - dog

and cat epithelium) (ALKAbello, Denmark), on the foreleg. The diameter of the papules was measured after 15 minutes. The test was considered positive if the average of the largest perpendicular diameters (excluding pseudopods) was at least 3 mm greater than the negative control.

Assessment of response to treatment

Asthma control is assessed considering the week prior to the date of the clinical evaluation and reflects the response to the treatment the patient is using. Asthma is considered uncontrolled if the patient has three or more of the following characteristics: symptoms more than twice a week that trigger limitations in his activities, nocturnal symptoms, FEV_1 or Peak Expiratory Flow < 80%. The patient is also considered uncontrolled if asthma exacerbation occurred in the week of the assessment[10].

The evaluation of asthma control was performed using the ACQ7 questionnaire. The ACQ, in its full version, consists of seven questions. Five questions refer to asthma symptoms (nighttime symptoms, morning symptoms, limitations in daily activities, dyspnea and wheezing), one question refers to the use of rescue β2-agonist medication and the seventh question takes into account a gauge measure of the airways: the percentage value of the forced expiratory volume in the first second (FEV_1) in relation to the predicted.

The final score of the questionnaire is the average score of the answers chosen by the patient, ranging from 0 (fully controlled) to 6 (uncontrolled) points. When validated in English, the ACQ presented two cutoff points to discriminate between controlled and uncontrolled asthma: the score of 0.75 is used in clinical practice, with a negative predictive value of 0.85 (meaning that if the score is < 0.75, there is an 85% chance of asthma being well controlled), and the score of 1.50 is used in clinical studies, with a positive predictive value of 0.88 (meaning that if the score is > 1.50, there is an 88% chance that asthma is not well controlled).

DNA Extraction and genotyping

DNA extraction was performed from blood samples according to the Gentra® Puregene® Blood Kit (Quiagen) protocol. All samples were standardized at a concentration of 5 ng/μL and stored at -30 °C until genotyping. 1 11166592 11333554

The genotyping was performed using the Illumina Infinium Multi-Ethnic AMR/AFR-8 kit. The data of the genetic variants to be studied were extracted considering the genetic location of the MTOR according to NCBI data (www.ncbi.nlm.nih.gov) [Chromosome 1, NC_000005.10 (11166592 - 11333554)].

After the tests were carried out, the results of the genotyped SNVs were stored in a database of phenotypes of the patients monitored and submitted to a quality control process. In this analysis, only individuals and SNVs with a genotyping rate "call rates" of at least 90% and presenting $p > 0.05$ in the Hardy – Weinberg balance analysis using healthy individuals of the population, as well as variants whose frequency of polymorphic allele (AMF) was greater than 0.5% in the population. As controls, wells without DNA were used to evaluate non-specific amplification and a family triad (mother, father and son) to evaluate inconsistencies in genotyping.

Dosage of cytokines and chemokine

The samples were tested for a panel of 11 cytokines and chemokines (IL1β, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17A, IFN-γ, TNF and CCL11) using okill MEXIPEX® (Merck, Darmstadt, Germany) and following the manufacturer's instructions. The assay was performed using the Luminex MAGPIX® system (LifeTechnology, USA), based on the measurement of fluorescent signals released by a suspension of microspheres with specific cytokine antibodies, in 96-well plates. The combination of the fluorimetric signal of the microspheres with that released by the secondary antibody allows the measurement of signals related to the concentration of cytokines converted by a processor. For this, a standard curve of eight points was used for each cytokine. The data were analyzed using the Analyst 5.1 MILLIPLEX® software (Merck, Darmstadt, Germany).

Analyzes in silica

The link disequilibrium (LD) analysis of the observed SNPs was also performed. LD measures the non-random association of alleles at different loci[11]. The observed associations can be affected by mutation, recombination, gene conversion, selection, genetic drift or demographic factors, such as inbreeding, migration and population structure.[12] Thus, LD patterns are used to infer genetic parameters of a population[13].

SNPs were also researched on the RegulomeDB and Ensembl platforms. RegulomeDB is a database for the interpretation of regulatory variants in the human genome. The platform identifies, through computational forecasts and manual annotations, the regulatory potential for productivity and functional variants. The score ranges from 1 to 6, where lower scores indicate increased evidence. Thus, a score of 1 indicates a likely effect on binding and gene expression, while scores 2 do not affect gene expression. Scores greater than 3 indicate a low probability of affecting the connection[14].

Statistical analysis

The phenotypes chosen in 3 genetic models (additive, dominant and recessive) for each SNP were analyzed. Empirical p-values were generated through a permutational approach for correction for multiple tests using the PLINK program. A series of current studies show that analyzing the 3 genetic models (additive, dominant and recessive) inserts more statistical power since the significance is determined by permutation. For adjusted association tests, we used logistic regression corrected for age, sex, BMI and main components of ancestry. For the analysis of quantitative traits (for example, specific IgE level as an outcome), the association tests were performed using a linear regression approach.

In addition, it was necessary to check the Hardy-Weinberg (H-W) balance. The H-W balance assumes that the genotype and allele frequencies are maintained randomly for generations and that there is a relationship between the allele and the gene frequency, their deviations or errors can be caused by genotyping errors. The tests are two-tailed and the statistical significance was established for the 95% confidence interval. The genetic associations followed analysis in the PLINK 1.9 program and the graphics produced in STATA 8.2 (StataCorp LP, CollegeStation, TX, USA).

Genotypic comparisons were made between the variants in the mTOR gene, in the three models (recessive, additive and dominant) and the dosed cytokines (IL-1β, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-17A, IFN-γ, TNF and CCL11). For data with normal distribution, we used the One-Way analysis of variance (ANOVA) and Tukey's test or Green House-Geisser correction as Post-test; for data with non-normal distribution, Kruskall Walis and Dunn's Post-test (multiple comparisons) or Mann-Whitney (comparisons between two groups), adopting a value of $P < 0.05$ to determine statistical significance between groups, using the Graph Program Pad v6 (Graph Pad Software Inc., San Diego, CA, USA).

Ethical considerations

This is a subproject of the project entitled "Risk factors, biomarkers and endemic phenotypes of severe asthma" coordinated by Prof. Álvaro Cruz, Faculty of Medicine, Federal University of Bahia in which he proposes to investigate the genetic mechanisms linked to asthma. This project was approved by the Research Ethics Committee of Maternidade Climério de Oliveira (MCO/UFBA), opinion No. 095/2012. The cell culture stage is a subproject of the project entitled "Assessment of Biological Pathway Markers in Endophenotypes and in the Therapeutic Response of Asthma and Allergy" coordinated by Prof[a] Camila Alexandrina Viana de Figueiredo Fontana, Institute of Health Sciences, Federal University of Bahia. This project was approved by the Research Ethics Committee of the Faculty of Medicine of Bahia, Federal University of Bahia, opinion No. 2,549,881/2018.

Results

The study population, PROAR, was analyzed according to asthma phenotypes, asthma severity and atopy. The data collected, in turn, in a system were analyzed for the prevalence of characteristics that could describe in an analytical way the different effects of the variables in the subsequent biostatistical analysis (Table 1).

Description of variants in the mTOR gene

74 variants were observed in the MTOR gene. Of the initial total of variants, 62 were excluded because they had FAM < 0.05 and 03 by the Hardy Weinberg (HWE) balance test. The low genotyping criteria (Mind > 0.1) did not exclude any variant. After the quality control steps, the study included 09 SNPs in the mTOR (Table 2).

Association of variants in mTOR with asthma

The analysis was performed using non-asthmatic individuals as a control group and all asthmatic individuals as a case group. In this sense, of the variants of the mTOR gene included in the study,

Table 1
Characteristics of the Proar population according to the asthma, gravity and atopy phenotypes

	Individuals (n)					Individuals with Asthma (n)				
Variables	**Not asthmatic (n=342)**	**%**	**Asthmatics (n=754)**	**%**	**p value**	**Light (n=385)**	**%**	**Serious (n=369)**	**%**	**p value**
Age										
Average±DP	43.84±12.9	–	43.36±15.1	–	0.271	36.27±12.8	–	50.75±13.63	–	0.000*
Sex										
Woman	294	26.8	598	54.6		298	39.5	300	39.8	
Man	48	4.4	156	14.2	0.09	87	11.5	69	9.2	0.187
Body mass index										
Average±DP	26.9±5.7	–	28.0±5.81	–	0.001	26.9±5.77	–	29.1±5.8	–	0.000*
Smoking index										
Yes	127	11.8	239	22.2		106	14.4	133	32.6	
No	216	20.1	495	46.0	0.150	260	35.4	235	67.4	0.033
Positive skin test (atopy)										
For at least one of the main allergens tested	80	9.0	404	45.7	0.000*	233	37.5	171	27.5	0.008

Table 2
Description of variants in the mTOR gene

Chromosome	SNP	Position	Alleles	MAF	HWE	Occupation	Score DB regulation
1	rs12139042	11167146	A/G	0.081	0.147	Intronic variant	5
	rs17036350	11171226	A/G	0.160	0.567	Intronic variant	5
	rs12122483	11193408	A/G	0.095	0.339	Intronic variant	3a
	rs1057079	11205058	A/G	0.392	0.072	Intronic variant	4
	rs12122605	11248020	A/G	0.152	0.552	Intronic variant	5
	rs28990992	11249789	C/G	0.056	0.380	Intronic losses variant	4
	rs61773703	11281952	A/G	0.072	1	Intronic variant	7
	rs2788570	11289466	A/G	0.113	0.304	Intronic variant	5
	rs7525957	11318236	A/G	0.485	0.825	Intronic variant	5

only two showed positive associations compatible with asthma, one identified by the additive model (rs1057079) and the other by the recessive model (rs7525957). The other variants (rs12139042, rs17036350, rs12122483, rs12122605, rs28990992, rs61773703, rs2788570) were not associated with the outcome in this population. Table 3 below shows such associations adjusted for sex, age, BMI, and main component 1.

Association of variants in mTOR with asthma control

Table 4 shows the significant association of the rs7525957 variant with severe asthma control. In this case, the analysis was done restricting the group of asthmatic individuals with a severe asthma profile, having as control the group whose asthma was controlled after treatment and the case the group whose control was not possible. In this sense, individuals with severe asthma who have the AA genotype are twice as likely to have the disease uncontrolled when compared with the other genotypes (OR 2.05; 95% CI 1.23-3.42). The other variants (rs12139042, rs17036350, rs12122483, rs12122605, rs28990992, rs61773703, rs1057079, rs2788570) were not associated with the outcome in this population.

Association of variants in mTOR with atopy

This immune response is promoted by the production of an antibody called immunoglobulin

Table 3
Significant association between SNPs in mTOR and asthma by logistic regression adjusted for sex, age, BMI and main component 1

SNP	Model	GENO	Control	Case	OR	95% CI	P value	P perm
rs1057079	ADD	GG	151 (45%)	272 (36.2%)	1.22	1.00-1.48	0.046	0.043
		GA	136 (40.5%)	336 (44.8%)				
		AA	48 (14%)	141 (18%)				
	DOM	GG	151 (45%)	272 (36.2%)	1.31	0.98-1.73	0.0062	0.069
		GA+AA	184 (54.5%)	477 (0.63%)				
	REC	GG+GA	287 (0.86%)	608 (0.81%)	1.28	0.19-1.88	0.190	0.184
		AA	48 (14%)	141 (18%)				
rs7525957	ADD	GG	102 (30.4%)	199 (26.5%)	1.18	0.98-1.42	0.087	0.100
		GA	168 (50.1%)	345 (46%)				
		AA	65 (19%)	205 (27%)				
	DOM	GG	102 (30.4%)	199 (26.5%)	1.084	0.81-1.45	0.592	0.555
		GA+AA	233 (69.1%)	550 (73%)				
	REC	GG+GA	270 (80.5%)	544 (72.5%)	1.45	1.05-2.01	0.002	0.026
		AA	65 (19%)	205 (27%)				

Table 4
Association between SNPs in MTOR and asthma control by logistic regression adjusted for sex, age, BMI and main component 1

Gene	SNP	Model	GENO	Control	Case	OR	95% CI	P value	P perm
			GG	71 (28.7%)	35 (30.4%)				
		ADD	AG	121 (48.9%)	39 (33.9%)	1.278	0.929-1.760	0.132	0.114
			AA	55 (22.0%)	41 (35.0%)				
mTOR	rs7525957	DOM	GG	71 (28.7%)	35 (30.4%)	0.745	0.557-1.554	0.783	0.857
			AA+AG	176 (70.9%)	80 (68.9%)				
		REC	GG+AG	192 (77.6%)	74 (64.3%)	2.05	0.261-3.421	0.006	0.009
			AA	55 (22.0%)	41 (35.0%)				

E (IgE), and some people are born with a genetic predisposition to show reactions due to the increase in this antibody. Of asthmatic patients, approximately half of them are atopic or allergic, the first symptoms occur in childhood and tend to regress in adolescence.

In this sense, the analysis is essential and was performed using non-asthmatic individuals as a control group and all asthmatic individuals as a case group. In this sense, three of the variants presented a significant association with the outcome atopy (rs1057079, rs7525957, rs12122483). As demais variantes (rs12139042, rs17036350, rs12122605, rs28990992, rs61773703, rs2788570) were not associated with the outcome in this population (Table 5).

The rs1057079 variant in the additive model and the recessive model, the rs7525957 variant in the additive and recessive model and the rs12122483 variant in the recessive model.

Eotaxin production among mTOR genotypes

Eotaxin production in patients with asthma was compared between mTOR genotypes. The rs1057079 variant was related to the serum increase in eotaxin. In this sense, the occurrence of allele A was significantly associated in the additive model, showing greater circulation of this cytokine when compared to polymorphic homozygosis and wild homozygosity as well as, in heterozygosis with p respectively 0.006 and 0.029 (Figure 1A).

There was also a difference in Eotaxin production between the rs7525957 genotypes, with the presence of the A allele, in heterozygote and wild homozygote different from the wild homozygote (p value 0.044 and 0.041, respectively) (Figure 1B).

The rs12122483 genotype showed a difference in Eotaxin production, with the wild homozygote ($p = 0.022$) having less expression compared to the heterozygote (Figure 1C).

Finally, the AA genotype of rs17036350 showed a reduction in eotaxin production when compared with the AG ($p < 0.01$) and GG ($p = 0.001$) genotypes (Figure 1D).

Cytokine production among MTOR genotypes

Individuals with asthma presenting the rs17036350 variant had lower IL-17 cytokine production between AA and heterozygous genotype ($p < 0.05$) and

between AA and GG genotypes (p < 0.05). As well as lower expression of IL-13 between genotype AA and AG (p < 0.01), between AA and GG (p < 0.01); IL-1B between genotype AA and AG (p < 0.05) and between AA and GG (p < 0.05); IL-8 between genotype AA and AG (p < 0.05); IL-6 between genotype AA and AG (p < 0.05), between AA and GG (p < 0.01); IL-5 between genotypes AA and GG (p < 0.05);

Table 5
Significant association between SNPs in mTOR and Atopy by logistic regression adjusted for sex, age, BMI and main component 1

SNP	Model	GENO	Control	Case	OR	95% CI	P value	P perm
rs1057079	ADD	GG	168 (43.2%)	163 (34.6%)	1.27	1.04-1.56	0.021	0.013
		GA	163 (42.0%)	210 (44.5%)				
		AA	57 (14%)	98 (20.0%)				
	DOM	GG	168 (43.2%)	163 (34.6%)	1.31	0.96-1.76	0.785	0.074
		GA+AA	220 (56%)	308 (65.5%)				
	REC	GG+AG	331 (85.3%)	373 (79.1%)	1.48	1.02-2.16	0.039	0.044
		AA	77 (20%)	98 (20%)				
rs7525957	ADD	GG	122 (31.4%)	117 (24.8%)	1.34	1.10-1.63	0.004	0.003
		GA	189 (49.3%)	207 (43.9%)				
		AA	77 (20.0%)	147 (31.0%)				
	DOM	GG	122 (31.4%)	117 (24.8%)	1.24	0.90-1.70	0.183	0.158
		GA+AA	266 (69.3%)	354 (54.9%)				
	REC	GG+GA	311 (80.7%)	324 (68.7%)	1.79	1.28-2.49	0.001	0.001
		AA	77 (20%)	147 (31%)				
rs12122483	ADD	GG	321 (82.7%)	387 (82.1%)	1.15	0.83-1.58	0.411	0.523
		GA	65 (16.7%)	73 (15.4%)				
		AA	2 (0.5%)	11 (2.3%)				
	DOM	GG	321 (82.7%)	387 (82.1%)	1.03	0.72-1.48	0.875	0.875
		GA+AA	67 (17.2%)	84 (17.7%)				
	REC	GG+AG	386 (99.4%)	460 (97.5%)	5.37	1.62-24.79	0.031	0.013
		AA	2 (0.5%)	11 (2.3%)				

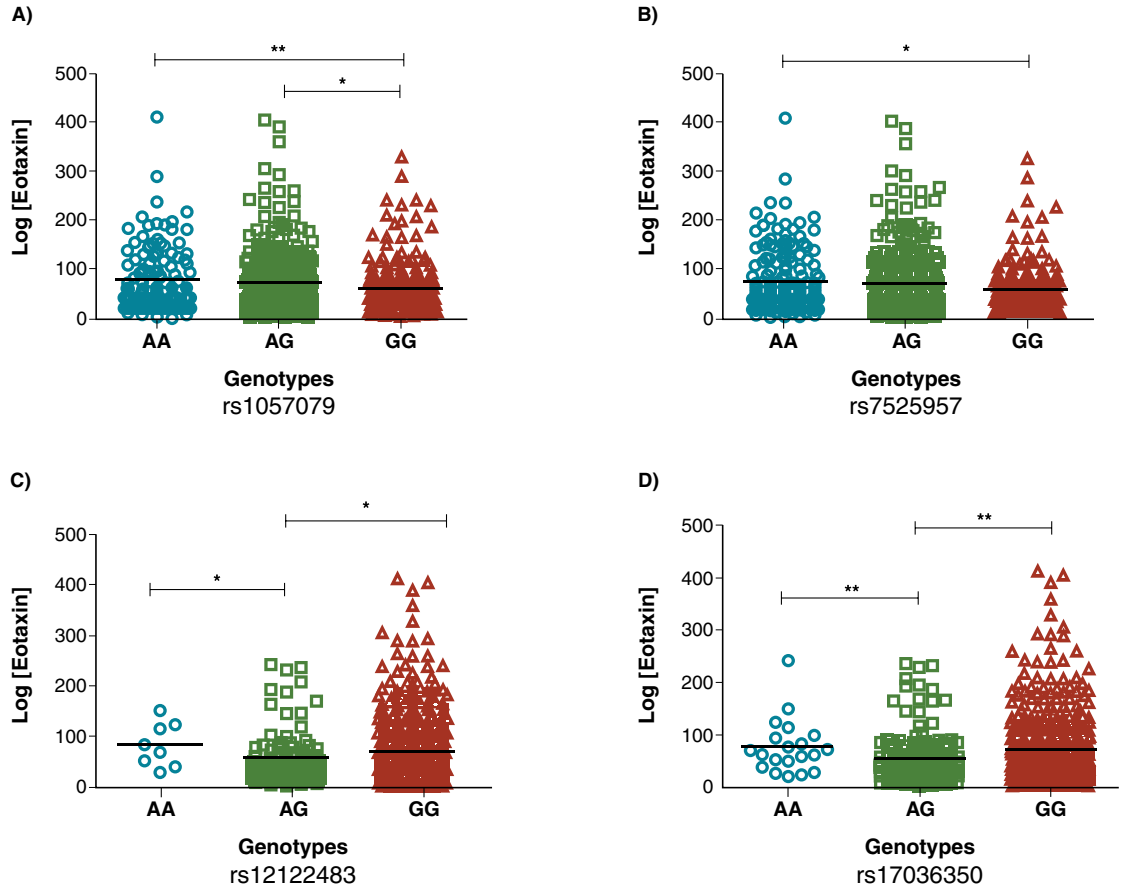

Figure 1
Average production of Eotaxin in individuals with asthma separated by rs1057079 (A), rs7525957 (B), rs12122483 (C) and rs17036350 (D), all with increased production in the polymorphic genotype. Tests used: Shapiro-Wilk; Kruskal-Wallis with Dunn and Mann-Whitney post-test

IL-12 between genotypes AA and GG ($p < 0.05$); IFN, between genotypes AG and GG ($p < 0.05$) and cytokine IL 10 between genotypes AA and GG ($p < 0.05$) (Figure 2A-I).

Additionally, the expression of Interleukin 8 (IL-8) is significantly reduced in the polymorphic genotype (AA) of the rs12122483 variant when compared to the heterozygous group ($p = 0.00061$) and when compared to the wild homozygote ($p = 0.0015$) (Figure 3).

Between the rs1057079 and rs7525957 genotypes there was no significant difference in the levels of the analyzed cytokines.

Tissue expression of mTOR among the studied genotypes

The in silico analysis by the gTex platform of the variants shows, in a global analysis, the expression of the variants in different tissues and their relevance is analyzed as to the significance value. Through this analysis it was observed that the expression of the variants in the blood and pulmonary tissues were significant in individuals with the AA genotype of the rs7525957 variant ($p = 1.2e\text{-}4$) presenting less expression of the mTOR gene in the blood. Also individuals with the AA genotype of the rs1057079 variant ($p = 5.1e\text{-}16$) showed lower expression of

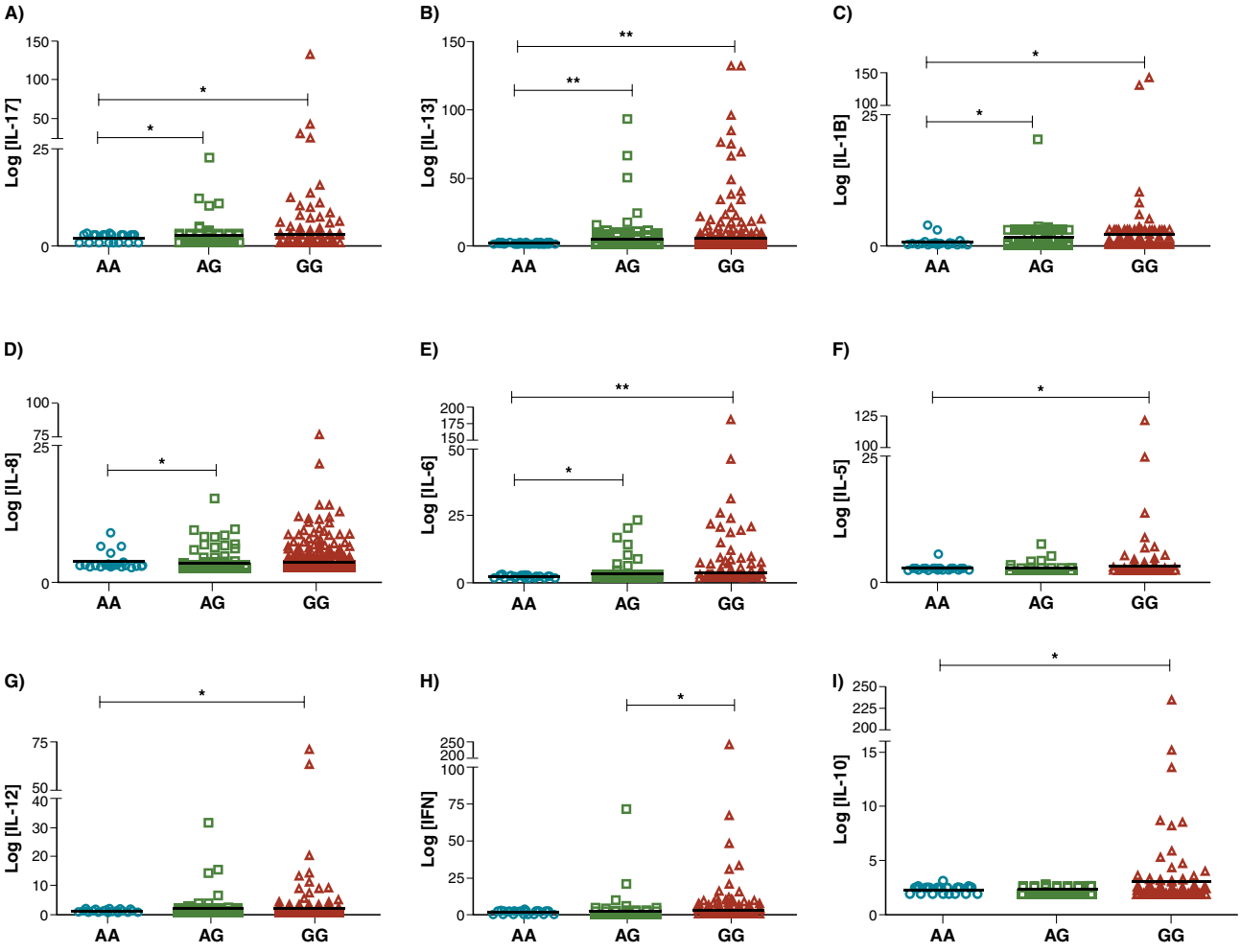

Figure 2

Average production of cytokines IL-17, IL-13, IL-1B, IL-8, IL-6, IL-5, IL-12, IFN (AH), IL-10 in individuals with asthma separated by genotype of rs17036350. All cytokines analyzed showed lower levels in the wild genotype group. Tests used: Shapiro-Wilk; Kruskal-Wallis with Dunn and Mann-Whitney post-test

mTOR in whole blood (p = 5.1e-16) and in lung tissue (p = 1.7e-6) when compared with the others genotypes (Figure 4).

Connection imbalance

Using Haploview, linkage imbalance analyzes were performed, which clarifies the non-random association of alleles in two or more loci. LD reflects historical events of natural selection, gene conversion, mutation and other evolutionary forces. In this scenario, it implies a joint heritability of the rs 1057079, rs7525057 variants of 60% in contrast to the rs 17036350 variant whose association with the aforementioned ones was less than 15% (Figure 5).

Discussion

Asthma is a chronic inflammatory disease with airway remodeling as one of the main symptoms. The PI3K/Akt/mTOR signaling pathway plays a central role in a broad spectrum of cellular activities, including cell proliferation, survival and differentiation[15]. Zhang et al.[16] demonstrated that the remodeling of the airways in mice was strongly associated with high levels of mTOR expression. MTORC1 can selectively inhibit the myeloid precursor to differentiate into

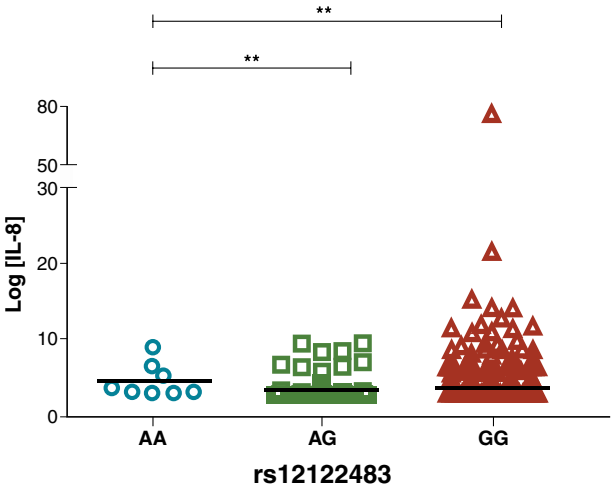

Figure 3
Average production of IL-8 in individuals with asthma separated by rs12122483 genotype. The group with the polymorphic genotype showed a higher level of cytokine ($p < 0.001$). Tests used: Shapiro-Wilk; Kruskal-Wallis with Dunn and Mann-Whitney post-test

eosinophil lineage, while promoting this differentiation in eosinophils. Activation of mTOR appears to be indispensable in controlling the excessive development of eosinophils, which can be a potential therapeutic target in the treatment of asthma.[17] On the other hand, Zhu et al.[18] demonstrated that inhibition of mTOR, either by gene deletion or by molecular antagonism, potentiated eosinophilia in a murine model of asthma, evidencing a dual role of mTORC1 and mTORC2 in the orchestration of the inflammatory process. In view of the complex role of mTOR in the immunological context, the present study evaluated variants in the mTOR gene in a population of patients with asthma.

In the analyzed population, the variant rs1057079 was significantly associated as a risk factor for asthma. This same variant was also associated with the risk of atopy, suggesting an impact on a common biological pathway for both outcomes. Similarly, the polymorphic homozygosis of the A allele of rs7525957 indicated a greater risk for asthma and atopy. Asthmatic patients carrying the polymorphic genotype presented airway obstruction determined by a spirometric test. Both variants are intronic, however, to date, they have no evidence of clinical significance in the literature related to their functional impact in asthmatic patients. On the other hand, single nucleotide varianters7525957 has been suggested as a marker of advanced esophageal tumor.[19] The link value and imbalance showed a 60% probability of heritability of these variants in the same individual, and the information may converge for both when observed in one of these, due to the chances of culminating in the association.

The in silico analysis of gene expression revealed that individuals who have rs7525957 or rs1057079 present a reduced tissue expression of mTOR, which suggests a negative regulatory role of these variants in the formation of mTORC1 and mTORC2. The inhibition of these complexes has already been simulated using substances such as Rapamycin, which specifically blocks mTORC1, while the use of Torina-1, which blocks both complexes, preventing the formation of the two complexes.[20] It has been shown that selective blocking of mTORC1 results in inhibition of eosinophilic differentiation. However, the blocking

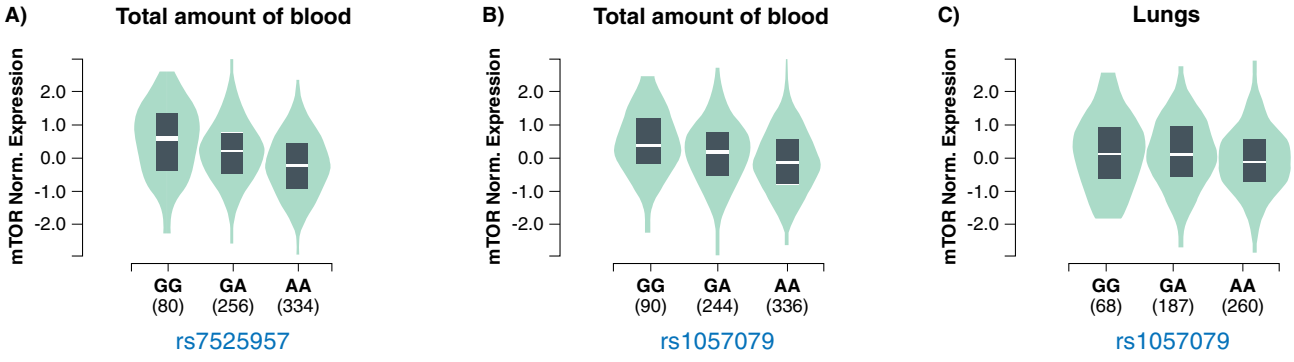

Figure 4
Image of the Violin Plot with the expression of the MTOR gene according to the genotypes of rs7525957 in whole blood (A), rs1057079 in whole blood (B) and rs1057079 in the lung (C). The polymorphic genotype showed reduced gene expression compared to the other genotypes ($p < 0.001$)

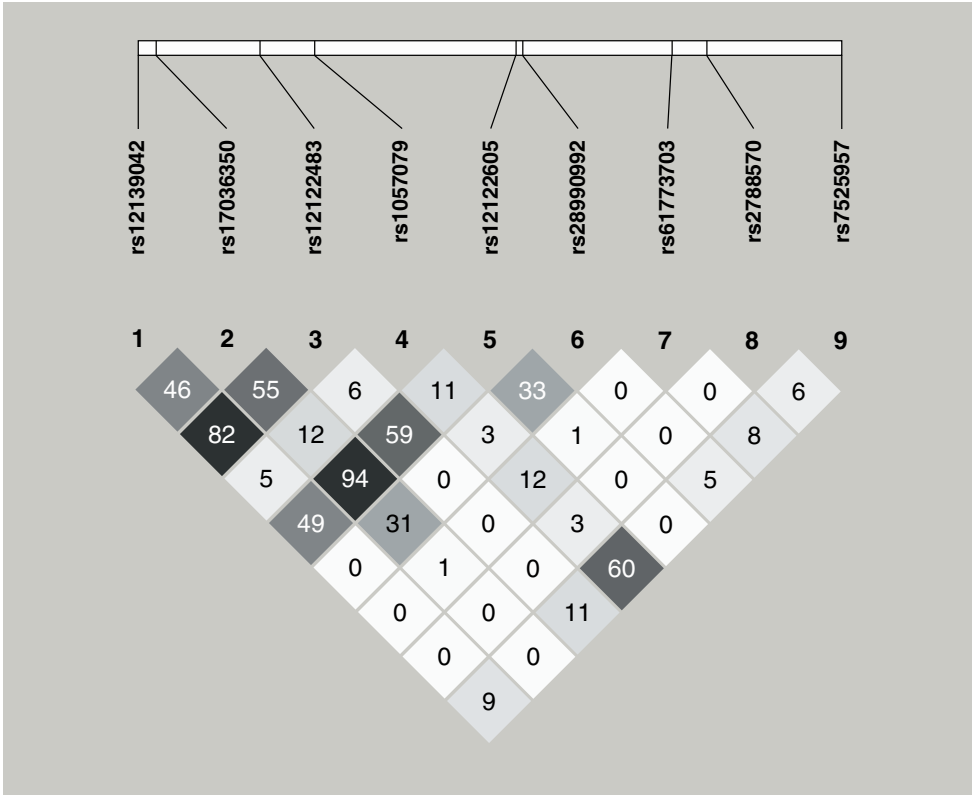

Figure 5
Graph of LD generated by Haploview using the R-squared statistic for SNPs in the mTOR gene

of both complexes has the consequence of increased eosinophilia, as demonstrated by Zhu et al.[18] Thus, it is believed that the variants rs7525957 and rs1057079, by reducing the expression of mTOR, contribute to the inflammatory process, increasing the susceptibility of individuals carrying the polymorphic alleles for the development of asthma and atopy.

The contribution of the rs7525957 and rs1057079 variants to the eosinophilic inflammatory process can be characterized, at least in part, by the level of production of Eotaxin, an eosinophilic chemotactic protein. In the population whose research was carried out, the variants were related to a higher level of Eotaxin in patients with asthma carrying the polymorphic allele, which may be associated with increased migration of eosinophils that potentiate the atopic process. Allergic diseases, such as asthma, allergic rhinitis and atopic dermatitis, are characterized by an increase in the number of eosinophils in the circulating blood and degranulation in the tissue.[21] The action of some cellular and molecular signals, including eotaxin, drives the exacerbated action of eosinophils. In this sense, eotaxin-1 binds with high affinity to the chemokine CC 3 receptor, which is expressed by a variety of inflammatory cells.[21]

In addition to the positive relationship with atopy whose influence of greater eotaxin expression has been previously reported, rs7525957 represented a twice as high risk for the lack of therapeutic control in patients with severe asthma. The uncontrolled asthma condition is thus defined when the use of inhaled corticosteroids only influences the reduction of exacerbations, but not the reduction of symptoms or the control of.[22] What is observed, particularly in this variant, is that its presence is attributed to the increased risk of asthma, atopy, eotaxin expression and possible resistance to inhaled anti-inflammatory drugs. The activity of mTORC1 has already been associated with insensitivity to corticosteroids[23] suggesting a greater expression of mTORC1.

The AA allele of rs12122483, also in homozygosis, was associated with a five times greater risk for atopy. In addition, it also presents higher levels of Eotaxin production, which leads us to think that the AA genotype of these variants has an impact on the expression of mTOR, similar to previous SNVs.

The aforementioned variant is also related to a higher level of production of Interleukin-8 (IL-8), being more produced in patients with AA genotype when compared with the other genotypes. The chemotactic cytokine IL-8 activates inflammatory cells by recruiting neutrophils, mononuclear phagocytes, mast cells and T cells.[24] Secreted by immune cells, bronchial epithelial cells, smooth muscle cells and macrophages, IL-8 is involved in the beginning of the acute and chronic inflammatory process.[25] This cytokine is associated with Th17 cells, as belonging to its secretion profile, which in turn, have been positively associated with difficult-to-control asthma in African-American children.[26] In a study of the mTOR pathway, the overexpression of these complexes was reversed by treatment with IL-8, demonstrating their regulatory role under this pathway.[27]

The rs17036350 variant was not associated with any of the study phenotypes, however there was an impact on the production of the tested cytokines. This variant, however, is not in imbalance of connection with the variants discussed earlier, rs1057079, rs7525957 and rs12122483, indicating reduced possibility of being inherited at the same time. Patients with asthma who have the AA genotype of this variant have a lower level of IL-17, IL-6, IL-13, IL5, IL-1B, IL-12 and IL-10 when compared to the wild genotype, which demonstrates its immunomodulatory impact. As for the cytokine IL-8, there was an average increase in its expression in asthmatic individuals, suggesting a possible activation of a feedback mechanism modulating the expression of mTOR in these individuals through the expression of cytokines, although this hypothesis was not tested in the study.

Conclusion

This study demonstrated for the first time that variants in the MTOR gene suggest risk factors for asthma, atopy and can influence the therapeutic control of asthma through the immunological regulation observed by the expression of cytokines. The variants have a direct influence on the immunogenic control that directly influences the responsiveness to asthma, mainly atopic, due to the strong relationship with the external environment. Further studies are needed to understand the functional impact of the variants associated here.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

House dust mite fauna characterization in the city of Rio de Janeiro and its importance in allergy diagnosis

Caracterização da fauna dos ácaros de poeira na cidade do Rio de Janeiro e sua importância em diagnósticos de alergias

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ABSTRACT

Introduction: The home environment is one of the most favorable spaces for the development of mites because of its low light, humidity, and temperature. Thus, it contributes to the growing cases of allergies among atopic individuals. **Objective:** To investigate the faunal profile of house dust mites in the city of Rio de Janeiro and the allergenic potential in this region. **Methods:** Thirty dust samples were collected from homes in the city of Rio de Janeiro, and the species found were classified according to their morphology, family, and genus by classification key. For the collection region, the total protein level was assessed by the Lowry method and electrophoresis under denaturing conditions (SDS-PAGE). **Results:** There was a predominance of *Pyroglyphidae* mites, accounting for 84.9% of samples; *Tyrophagus putrescentiae* accounted for 8%, *Blomia tropicalis* for 6%, *Cheyletus malaccensis* for 1%, and *Acarus siro* for 0.1%. The allergen protein content of the samples was the following: group 1 – 25 kDa (Der 1, Der p 1, and Blo t 1), group 2 – 15 kDa (Der f 2, Der 2, Tyr p 2, and Blo t 2), and group 3 – 29-30 kDa (Der f 3 and Blo t 3), which indicates that people in this region are susceptible to sensitization to these mites. **Conclusion:** Knowledge of the mite fauna in the region under study allows the guidance of health care professionals to perform skin tests for specific mites and conduct treatment according to the pool of mite extracts containing antigens, making immunotherapy more effective.

Keywords: Mites, identification, allergens.

RESUMO

Introdução: O ambiente domiciliar é um dos espaços favoráveis para o desenvolvimento de ácaros, tendo em vista a baixa luminosidade, umidade e temperatura, o que contribui para os crescentes casos de alergias em indivíduos atópicos. **Objetivo:** Investigar o perfil faunístico dos ácaros na cidade do Rio de Janeiro e o potencial alergêncio para essa região. **Métodos:** Foram coletadas 30 amostras de poeira em residências na cidade do Rio de Janeiro, e as espécies encontradas foram classificadas quanto à morfologia, família e o gênero por chave de classificação. Para as regiões das coletas, a carga total de proteínas contendo os alérgenos foi determinada pelo método de Lowry e eletroforese em condições desnaturantes (SDS-PAGE). **Resultados:** Os resultados mostram a predominância de 84,9% de ácaros da família *Pyroglyphidae*; para os demais ácaros o percentual corresponde a 8% *Tyrophagus putrescentiae*, 6% *Blomia tropicalis*, 1% *Cheyletus malaccensis*, e 0,1% de *Acarus siro*. O conteúdo proteico alergêncio constituinte das amostras foram, grupo 1: 25 kDa (Der 1, Der p 1 e Blo t 1); grupo 2: 15 kDa (Der f 2, Der 2, Tyr p 2 e Blo t 2); e para o grupo 3: 29-30 kDa (Der f 3 e Blo t 3), o que indica uma região passível à sensibilização de indivíduos por estes ácaros. **Conclusão:** O conhecimento da acarofauna nas regiões em estudo permite orientar a comunidade médica quanto à realização de testes cutâneos, além da terapêutica a partir do pool de extratos de ácaros contendo os antígenos, a fim de tornar a imunoterapia mais eficaz.

Descritores: Ácaros, identificação, alérgenos.

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Introduction

The city of Rio de Janeiro has the second largest population in Brazil, about 6.747 million inhabitants in 2021,[1] and has a tropical, hot and humid climate,[2] with local variations due to differences in altitude, vegetable life and proximity to the ocean. These factors can influence the existence and development of several species of dust mites and increase the proliferation of mites in the domestic environment.[3] Other contributions, such as evolutionary ecological and stochastic factors,[4] can also contribute to this differentiation.[5] The presence of these microorganisms in house dust particles exposes the population to aeroallergens constituted of mites' bodies and feces.[6,7] These antigens can sensitize atopic individuals, considering their genetic susceptibility, thus triggering respiratory allergies such as rhinitis, bronchitis and asthma.[1-3] This study aims to identify the faunal composition of mites in the region of the city of Rio de Janeiro, in order to provide information on the predominance of existing species, and consequently, the main allergens inserted in the household perimeter in potential sensitizers. This paper aims to identify the faunal composition of mites in the region of the city of Rio de Janeiro, to provide information on the predominance of existing species, and consequently, the main allergens inserted in the household perimeter in potential sensitizers. The theme promotes data that can help professionals in the field of medical allergology, as it presents information on the predominance of species in different regions, and therefore, the specific allergens to be included in the therapies offered to the population.

Material and methods

Dust mites collection and culture

Thirty dust samples (beds, sofas, rugs and surfaces) from homes were collected in the counties of Rio de Janeiro, Brazil. The collection was carried out with the aid of vacuum cleaners and the material was stored in pots and identified for further analysis. In a container, dust samples and a nutritional material (1:15), composed of rabbit feed, wheat bran and wheat germ in a 1:1:1 ratio were mixed. The container was kept in a dome containing a 5.0 mol/l sodium chloride solution, so that the mites, upon leaving the cultivation system, were collected in a 400-meche sieve. The mites were identified in compliance with the taxonomic classification according to the literature;[11,12] and separated for the cultivation of a pure culture. For the negative control, the same type of container received only the feed without a sample. The pure culture for the different species was kept for 90 to 180 days at a temperature of 30 °C, with a relative humidity between 70%-80%.

Clarification with Lactophenol

For better morphological visualization, the mites were clarified according to the procedure presented by Flechtmann,[13] with modifications. For the mass of mites, a solution of lactic acid (Sigma-Aldrich), phenol (Sigma-Aldrich), distilled water and methylene blue (Sigma-Aldrich) was applied in the proportions of 2:1:1:1:1, respectively, for a period of 48 h.

Preparation of protein extracts from mites

The preparation of protein extracts followed procedures described by Sánchez-Ramos et al.,[14] with modifications. 10% (w/v) of the mite mass was added in 0.1 mol/l saline buffer (Ultrasonic, frequency 20 kHz) for cell disruption for 30 minutes, under an ice bath. The pH of the extract was adjusted with a 2.0 mol/l sodium hydroxide solution to pH 8.5. After homogenization, the extract was left to rest at 8 °C for 48 h and then centrifuged at 1500 x g for 30 minutes at 25 °C. The supernatant was filtered on 0.22 µm pore membrane (Filtrile) and added with 40% glycerol (v/v) (Sigma-Aldrich).

Protein content - Lowry method

The protein contents of the extracts were determined using the Lowry method 15. Briefly, an analytical curve was constructed from a standard solution of BSA protein (bovine serum albumin - Sigma-Aldrich), in the range of 5 µg/mL to 100 µg/mL. The procedure was performed by adding in a test tube 3.0 mL of sodium carbonate (Sigma-Aldrich) 1% (w/v), 0.5 mL of copper sulfate (Sigma-Aldrich) 0.1% (w/v). After homogenization, the tubes were left to rest for 10 minutes at 25 ºC and 500 µL of Folin-Ciocalteu reagent (Sigma-Aldrich) (1:10) were added. Optical density (O.D.) was performed in a UV-Visible spectrophotometer (Spectrophotometer SP 1102 - Bel photonics - Brasil) at 750 nm.

Characterization by electrophoresis under denaturing conditions (SDS-PAGE)

The protein content of the mite extracts was obtained from the electrophoretic run of 20 µL of the homogenate samples in a reducing buffer solution containing TEMED (N,N,N',N'-tetramethylethylenediamine) and 2-mercaptoethanol, 20% (v/v) and bromophenol blue. The samples were reduced and denatured at 90 °C in a water bath and Applied on a 12.5% (v/v) acrylamide/bis-acrylamide gel. The Dual Xtra (Bio-Rad) standard was used with ranges between the molecular mass range of 250 to 10 kDa, which was used to construct the calibration curve in the Gel Analyzer software.

Characterization by Optical Microscopy and Scanning Electron Microscopy

For observation and identification of the mites, they were mounted on slides/coverslip in the presence of glutaraldehyde and then observed under an optical microscope (OPTON – TIM-208T). Also, the mite morphology was analyzed in a Scanning Electron Microscope (SEM) by a Jeol 7100FT Field Emission Cannon at 1 kV (LABNANO/CBBP), and a working distance of 8 mm. All samples were fixed to the surface of a metal blank with carbon tape. (Sputtercoater BAL-TEC, SDC 005). The samples were observed in low magnification and protected with a thin layer of Au, whose deposition was made using a very low amperage to cause minimal damage to the external structures of the mites.

Results and discussion

Dust mites characterization

Six species of mites were found in house dust: *Dermatophagoides pteronyssinus* (DP) and *Dermatophagoides farinae* (DF), *Blomia tropicalis* (BT), *Tyrophagus putrescentiae* (Tp), *Cheyletus malaccensis* and *Acarus siro*. The predominance was for the genus *Dermatophagoides* of the *Pyroglyphidae* family, as shown in Figure 1. The mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* are cited in the literature as the main representatives regarding their allergenic potential, triggering respiratory allergies worldwide.[16,17] Other studies also report their abundance and prevalence in domestic dusts.[18-20] These results are in agreement with Silva et al.,[19] the authors report that, for the city of Londrina (State of Paraná), southern Brazil, percentages of 82% for the *Pyroglyphidae* family, 9.4% for the *Glycyphagidae* family were found in house dust and 0.9% and for the

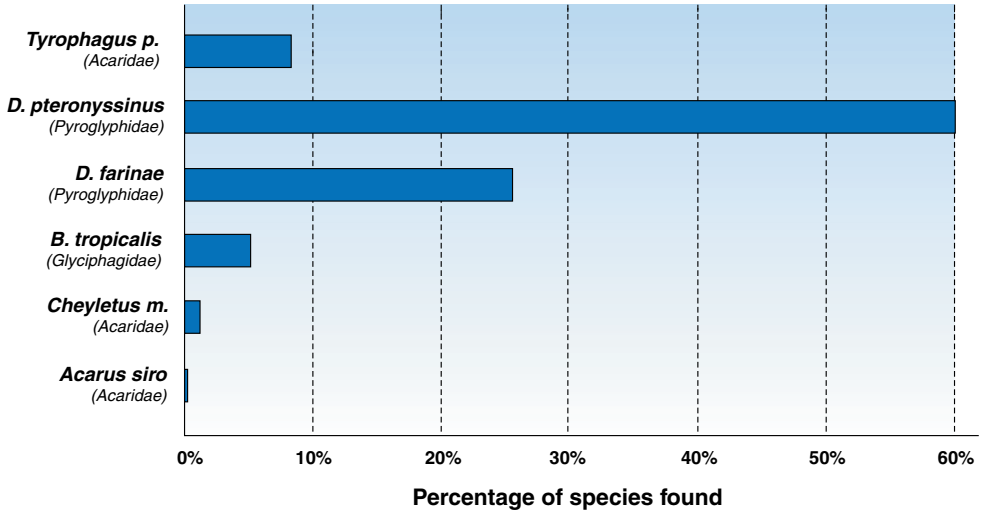

Figure 1
Faunistic profile and taxonomic classification for mites found in 30 house hold dust samples in the city of Rio de Janeiro

Acaridae family. It is important to consider that the other mites present also have significant relevance, as the literature reports the preparation of a mixture of these mites for immunotherapeutic desensitization purposes.[21]

The abundance of species found in the dust samples (Figure 1) is a factor that may be correlated with variable abiotic conditions present in the state of Rio de Janeiro, but these factors are unfavorable for the development of the species *Blomia tropicalis*, *Cheyletus malaccensis* and *Acarus siro*, for example, are found with less incidence in the samples and difficult to grow. However, opposite percentages to these were found by Serravalle et al.[22] in regions of the State of Bahia-BA (Brazil), in the percentages for *Dermatophagoides pteronyssinus* of 70%, *Cheyletus malaccensis* 50%, *Blomia tropicalis* 30%, *Dermatophagoides farinae* 8% and *Tyrophagus putrescentiae* 6%. This may be related to the abiotic conditions in this region. Baqueiro and collaborators,[23] report that for the city of Salvador - BA there is a prevalence of *Blomia tropicalis* (89%), compared to *Dermatophagoides* mites (31.6%) in the rainy season.

The Figure 2 shows the species found in the dust samples. In view of the small sampling of mites with lower incidences (*Acarus siru*, *Blomia tropicalis* and *Cheyletus malaccensis*) the images were obtained in an exceptional and scarce way.

In the collected powders, two species of mites of the Cheyletidae family were found: *Cheyletus malaccensis* and *Cheyletus bidentatus* (Figure 3). They were identified by the classification key of Fain et al.[23,24] These species are known to control the culture of other mites (predator), and may be present in grains, stored cereals and birds.[25] However, the *Cheyletus* species, considering their diet, can concentrate allergens from other mites.[26]

Dust Mites Allergen Extract

For the extracts of the mites under study, the protein content was 2.45 mg/mL for *Dermatophagoides farinae*; 4.12 mg/mL for *Dermatophagoides pteronyssinus*; 1.17 mg/mL for *Blomia tropicalis*; 2.83 mg/mL for *Tyrophagus putrescentiae* and 1.02 mg/mL for *Cheyletus malaccensis*. In the total protein content, the presence of protein fractions corresponding to allergenic antigens must be considered, which have already been identified in the literature with their respective equivalent molecular masses, in Kilodalton (kDa).[27-29,12] These pieces of information corroborate the data obtained by Soares et al.,[30] where the authors studied the sensitization profile to dust mite allergens in outpatients in the city of Rio de Janeiro. From skin tests, it was shown that 67.5% of individuals with rhinitis, with or without asthma, showed reactivity to the mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*.

These proteins were also identified by gel electrophoresis, as shown in Figure 4.

For the tropical *Dermatophagoides* and *Blomia* mites, the markings referring to the main allergens of group 1 are found in 25 kDa (Der 1, Der p 1 and Blo t 1), characterized as cysteine protease and group 2 in 15 kDa (Der f 2, Der 2, Tyr p 2 and Blot 2) represented by lipid-bound protein. Der f 3 and Blo t 3 allergens were identified for 29-30 kDa, characterizing trypsinlinked to the enzyme serine protease.[30,31] Cross-activity has already been observed between *Dermatophagoides pteronyssinus* (Der p 1), *Dermatophagoides farinae* (Der f 1) and *Blomia tropicalis* (Blo t 1), for example, a fact reported by Guilleminault et al.[32] For the mite family of *Cheyletus malacencis* proteins were identified at 20 kDa, 26 kDa, in agreement with Mihos et al.[33] Considering the low percentage in the samples of *Acarus siro*, the mass obtained in the culture was a limiting factor for the preparation of protein extracts for purposes of electrophoretic characterization. Based on these results, it is suggested the use of a mix of mite extracts (pool) as a more efficient immunotherapeutic treatment for the desensitization of atopic individuals.

Conclusion

It was possible to present a qualitative overview of the species found in the city of Rio de Janeiro, Basil, which indicates an indication of how susceptible individuals are in this region, regarding their exposure to allergens present in the residential environment. The *Dermatophagoides* species prevails over all other species, but there is the possibility of co-sensitization by other mites present in house dust, which makes this information relevant for the medical community and the body that manages public health.

Acknowledgment

We thank the Laboratory of Allergenic Extracts MQ and LABNANO facility in the Brazilian Center for Research in Physics (CBPF) for their laboratory support.

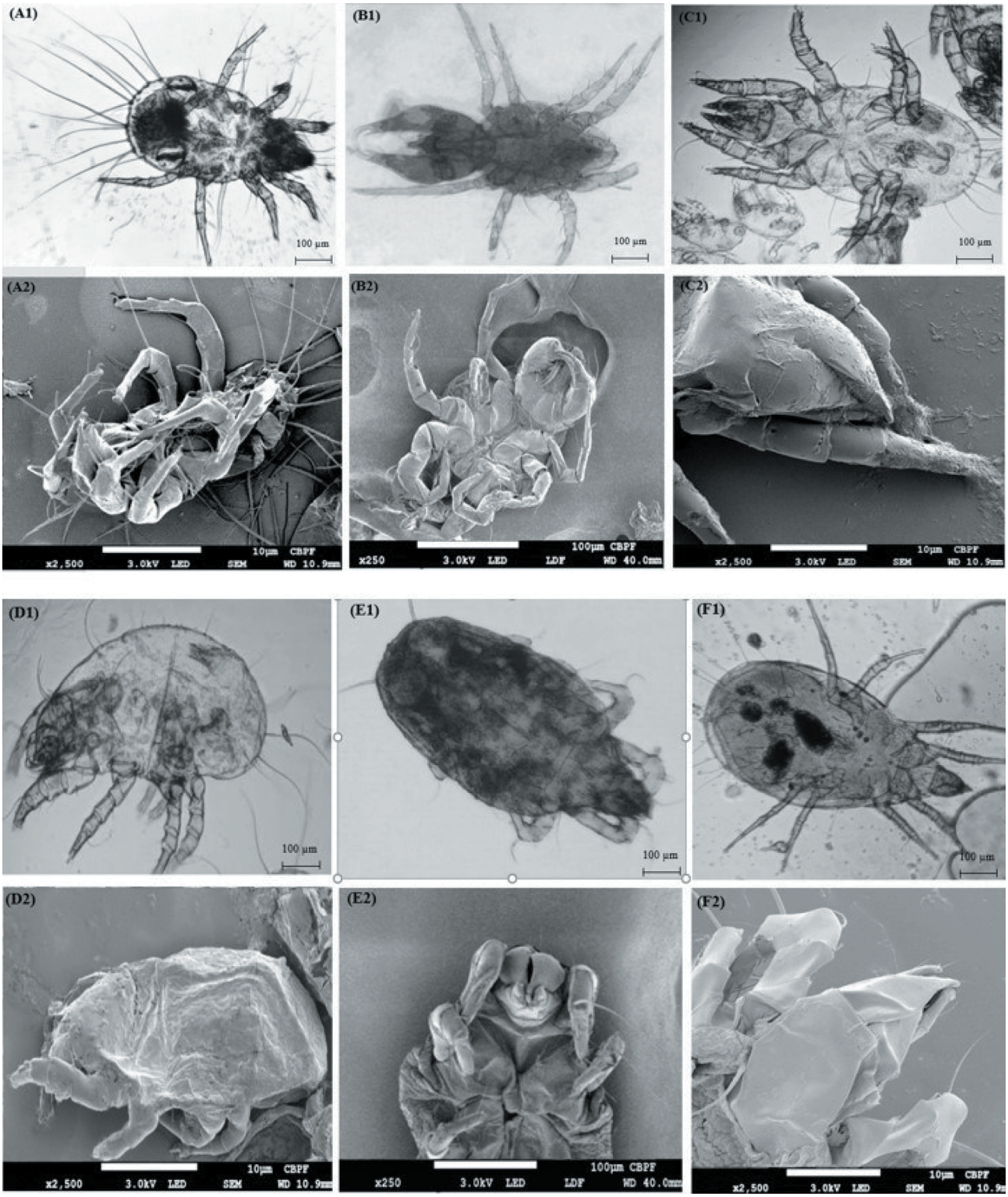

Figure 2

Opticalmicroscopy (OPTON – TIM-208T) and scanning electron micrographs (Joel, 1000 kv, LED) for mites found in the metropolitan region of the city of Rio de Janeiro - Brazil. (A1-A2): *Blomia tropicalis*, (B1-B2): *Cheyletus malaccensis*; (C1-C2 and D1-D2): *Dermatophagoides farina* and *pteronyssinus*, respectively; (E1-E2): *Acarus siro* and (F1-F2): *Tyrophagus putrescentiae*

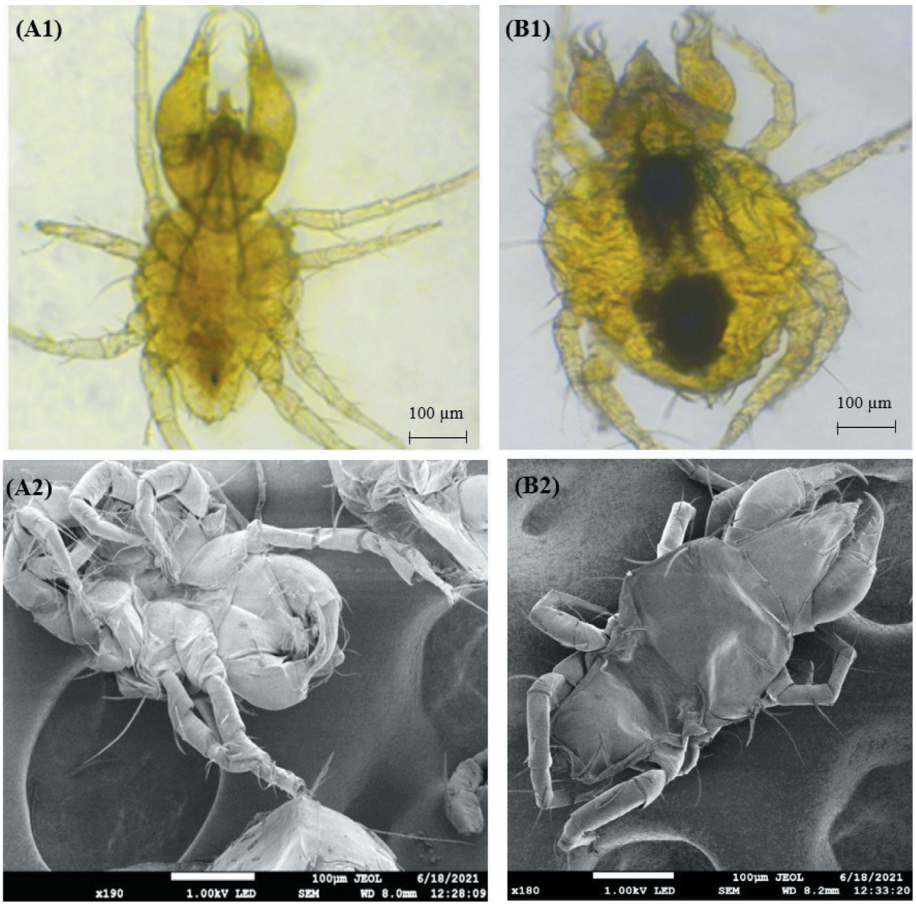

Figure 3
Optical microscopy (OPTON – TIM-208T) and scann in gel ectronmicrographs (Joel, 1000 kv, LED) for the mite species: (A1-A2) *Cheyletus malaccensis* and (B1-B2) *Cheyletus bidentatus*, found in the samples of house hold dust in the city of Rio de Janeiro - Brazil

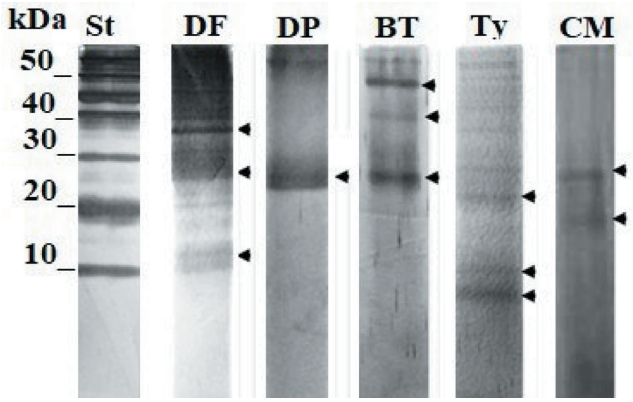

Figure 4
SDS-PAGE, 12.5% acrylamide/bis-acrylamide gel for the electrophoretic run of mite extracts present in house hold dust samples collected in the city of Rio de Janeiro - Brazil. (St) Standard marker proteins, (DF) *Dermatophagoides farinae*, (DP) *Dermatophagoides pteronyssinus*, (BT) *Blomia tropicalis*, (Ty) *Tyrophagus putrescentiae*, (CM) *Cheyletus malaccensis*

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Pityriasis lichenoides after COVID-19 vaccination: a case report

Pitiríase liquenoide pós-vacinação contra COVID-19: um relato de caso

Isabela Ceschin Maestri[1], Monica Preto Guimarães[1], Tsukiyo Kamoi[2], Rafaela Ceschin Fernandes[3], Renato Nisihara[1,2]

ABSTRACT

This study addresses the first case report of pityriasis lichenoides development after COVID-19 vaccination. A literature review found few studies describing pityriasis lichenoides as an adverse reaction to other vaccines. Although it is an immune-mediated inflammatory response, the development mechanism of this disease remains not well known. The diagnosis of pityriasis lichenoides is clinical and is considered a challenge due to the considerable number of differential diagnoses and the different forms of presentation of the disease. Thus, most cases require confirmation by biopsy and laboratory tests. Therapeutic options may include the use of antibiotics and immunosuppressants. The effectiveness of phototherapy is also highlighted as the treatment of choice for pityriasis lichenoides, as it can promote an almost complete resolution of lesions without causing systemic effects, unlike other therapies.

Keywords: Pityriasis lichenoides, COVID-19 vaccines, vaccines.

RESUMO

O artigo aborda o primeiro relato de caso que associa o desenvolvimento de pitiríase liquenoide com a vacinação contra a COVID-19. Em uma revisão literária foram encontrados escassos estudos que associam a pitiríase liquenoide como reação a outras vacinas. O mecanismo de desenvolvimento da doença ainda não é bem conhecido. Sabe-se apenas que se trata de uma reação inflamatória imunomediada. O diagnóstico da pitiríase liquenoide é clínico e é considerado um desafio, devido ao grande número de diagnósticos diferenciais e das diferentes formas de apresentação da doença. Desse modo, a maioria dos casos exige amparo na biópsia e em exames laboratoriais. As opções terapêuticas podem incluir o uso de antibióticos e imunossupressores. Destaca-se ainda a efetividade da fototerapia como tratamento de escolha da pitiríase liquenoide, podendo proporcionar uma resolução quase que completa das lesões e não causar efeitos sistêmicos que outras terapias poderiam trazer.

Descritores: Pitiríase liquenoide, vacinas contra COVID-19, vacinas.

Introduction

Pityriasis lichenoides (PL) is an uncommon immune-mediated dermatological disorder of unknown etiology. However, it is known that it can occur in association with exposure to drugs, infections, radiological contrast and vaccines.[1]

The disease can manifest in two ways: pityriasis lichenoid et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC).[2] The first refers to an acute condition characterized by multiple ulcerated lesions or crusted reddish papules, which usually heal leaving after effects, such as hyper/hypopigmentation or varioliform scars. It has variable remission periods, with a limited course. The second is manifested through reddish-brown scaly papules that can last for years and also generate sequelae. However, there are cases with lesions that refer to both diagnoses.[2,3] In

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addition, there is a clinical variant of PLEVA, febrile ulceronecrotic Mucha-Habermann disease (FUMHD), which is characterized by ulceronecrotic skin lesions associated with high fever and systemic symptoms. It is a more serious condition with malignant potential associated with T4 lymphoid proliferations.

The diagnosis of PL is clinical and requires differential investigations for chickenpox, lymphomatoid papulosis, secondary syphilis, vasculitis and pityriasis rosea.[5] Therefore, for the etiological differentiation, laboratory tests and/or histological analysis are necessary.

This study aims to report a case of post-vaccination PL with the SARS-CoV-2 CoronaVac® vaccine, describing the findings and clinical management.

Case report

A previously healthy 20-year-old female patient attends a dermatological consultation after noticing the appearance of red, non-pruritic papules on the entire body surface for about a week and a half. The appearance of the lesions occurred three days after the first dose of the vaccine against SARS-CoV-2 developed by Sinovac (China) and produced in Brazil by the Butantan Institute (Instituto Butantan).[6] CoronaVac is composed of the inactivated virus and an aluminum hydroxide solution.[7] The vaccine was performed by intramuscular injection in the right deltoid (0.5 mL). The patient reported that the lesions started slowly on the trunk, but quickly progressed to other areas of the body. It is noteworthy that the papules appeared in regions with less sun exposure, such as the internal and posterior regions of the limbs. On clinical analysis, the presence of erythematous papules is confirmed (Figure 1). Only in the popliteal fossa was the presence of three violaceous lesions observed. This fact suggests that the lesions were in different stages of development. On the thorax, there were larger lesions with scaling on the collarette. To control the lesions, it was recommended to use a cream manipulated with a low concentration of desonide (0.05 mk) in 100 mL of moisturizing lotion, applied once a day, but without response.

Treponemal and non-treponemal tests for syphilis were requested, which came back negative. After the second dose of vaccine, an increase in lesions was noticed, indicating biopsy and the start of lymecycline (300 mg) once a day.

Biopsy was performed in three different areas, with histopathological analysis showing similar changes. Among the findings, the epidermis showed mild irregular acanthosis, multifocal parakeratosis with serous lakes, moderate multifocal spongiosis, very rare lymphocyte exocytosis and necrotic keratinocytes. The superficial dermis showed edema and moderate lymphocytic perivascular inflammatory infiltrate with extravasated red blood cells. The findings suggest spongiotic and interface dermatitis. Thus, the hypothesis of PL was confirmed, ruling out differential diagnoses. At this time, treatment with tetracycline was started (500 mg) twice a day for ten days; however, no improvement.

According to the findings, the confirmed diagnosis was PLC, although the period between the onset and resolution of the lesions is compatible with PLEVA. Thus, the assistant physician opted for a milder treatment, with ten sessions of phototherapy, noting a significant resolution of the lesions after the second session.

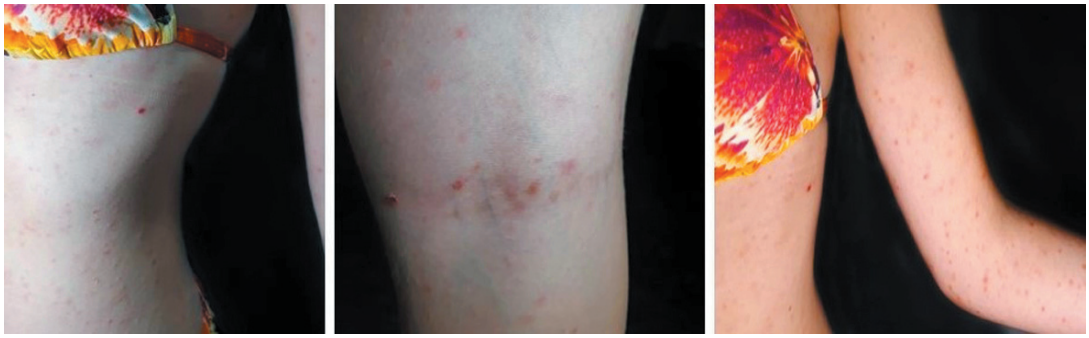

Figure 1
Aspects of chest and limb injuries

Discussion

In this case, the hypothesis is that the vaccine has triggered an immune-mediated inflammatory reaction. Therefore, the relevance of this study is remarkable as it is the first reported on the association of PL with COVID-19 vaccination. During the literature review, few studies were found relating PL with other types of vaccine, such as the MMR, influenza and adult vaccine.[1,8,9] It is therefore suggested that PL is triggered by an inflammatory response to extrinsic antigens. The SARS-CoV-2 Coronavac® vaccine is administered in two doses, with an interval of two to four weeks. As it is a recently developed vaccine, there is still no concrete data on the characterization and frequency of all its adverse effects.

PL is a dermatological disease related to the formation of lesions with wide variations in morphology. Primary lesions in PLEVA develop forming central necrosis with hemorrhagic crust and have gradual resolution.[3] In PLC, these lesions present as a monomorphic picture of erythematous-brown papules covered by an adherent scale. Both the chronic and acute conditions are more prevalent in males, and affect adolescents and young adults.[10]

The diagnosis is clinical and confirmed by biopsy, however it is a challenge due to the multiple differential diagnoses. In addition, there may be overlap between their classifications. Histopathological findings include superficial paravascular or lichenoid lymphocytic infiltrate with vacuolar alteration of the basal layer, parakeratosis, individual necrotic keratinocytes in the epidermis and extravasation of red blood cells.[3] Such alterations are more evident in PLEVA, whereas in PLC they are less exuberant. The histopathological description is compatible with the patient, and a PLC picture is suggested.

The disease has a variable course and common recurrences. PLEVA usually resolves in weeks, while PLC can take months.[2] Treatment may involve topical agents, antibiotics, phototherapy and immunosuppressants.[2] Antibiotic therapy with erythromycin or tetracycline may be beneficial in reducing the course of the disease.[3] In the case of the patient, lymecycline was started and then tetracycline was used. Although the former is derived from tetracycline, there are cases of unsatisfactory response, while the latter may be effective. Phototherapy is the treatment of choice when there is no response to the use of oral antibiotics.[2] This method was effective in the patient's case. In severe and refractory cases, systemic corticosteroids, methotrexate or cyclosporine are indicated.[2]

Conclusion

Pityriasis lichenoides is an uncommon disease, sometimes requiring biopsy support for differential diagnosis.

This case report addressed the first reported condition of pityriasis lichenoides chronica related to the CoronaVac® vaccine.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Dupilumab in the treatment of chronic rhinosinusitis with nasal polyps in adolescents

Dupilumabe no tratamento de rinossinusite crônica com pólipo nasal em adolescente

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ABSTRACT

The use of the monoclonal antibody dupilumab in adults has allowed the control of chronic inflammation, significantly reducing the size and recurrence of new polyps, improving nasal symptoms, and, consequently, quality of life. We report a successful case of dupilumab use in an adolescent for the treatment of chronic rhinosinusitis with nasal polyps.

Keywords: Sinusitis, asthma, monoclonal antibody.

RESUMO

O uso do anticorpo monoclonal dupilumabe em adultos tem possibilitado o controle da inflamação crônica, reduzindo significativamente o tamanho e a recorrência de novos pólipos, melhorando os sintomas nasais e, consequentemente, a qualidade de vida desses indivíduos. Relatamos o caso de uma adolescente que evidencia a eficácia de dupilumabe no tratamento da rinossinusite crônica com pólipo nasal.

Descritores: Sinusite, asma, anticorpo monoclonal.

Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the nasal mucosa and paranasal sinuses, presenting with or without nasal polyps (CRSwNP and CRSsNP, respectively).[1] Polyps are benign inflammatory masses that appear in the upper airways, often manifesting as nasal obstruction and hypo/anosmia.[2] The clinical diagnosis of CRSwNP is confirmed by the presence of sinonasal symptoms for more than 12 weeks and by the visualization of polyps in the nasal cavity by nasal endoscopy or computed tomography (Table 1).[2] Up to 60% of patients have lower airway involvement, coexisting with adult-onset asthma.[3,4] However, its association with childhood asthma is less common and, if present, cystic fibrosis and other secondary causes of CRS should be investigated.[5]

In most cases of CRSwNP, treatment is performed with topical corticosteroids and nasal lavage with saline solution. In addition to these, severe symptomatic patients require cycles of corticosteroids and systemic antibiotic therapy for prolonged periods, and endoscopic nasal polypectomy (ENP) is indicated for refractory cases.[6]

Cases resistant to steroid therapy and with recurrent polyps progress with progressive worsening of quality of life (assessed by the SNOT-22, Sino-Nasal Outcome Test),[7] requiring treatment with specific

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Table 1
Diagnostic criteria for chronic rhinosinusitis with nasal polyposis (two or more, with at least one main plus one additional criterion)

Main clinical criteria	Secondary clinical criteria	Complementary criteria
Nasal obstruction/congestion	Facial pain/pressure	Endoscopic signs of nasal polyposis (polyps and/or nasal discharge from the middle meatus and/or swelling with middle meatus obstruction)
Nasal discharge (anterior or posterior)	Hypo or anosmia	Tomographic evidence of nasal polyps (alterations of the nasal mucosa compromising the osteomeatal complex and/or the paranasal sinuses)

immunobiologicals. Such specificity is determined by the pathophysiological/immunological mechanism involved in the formation of polyps, and the type 2 immune response is found in almost 90% of cases.[8]

In this context, the first immunobiological agent approved for the treatment of uncontrolled CRSwNP in adults (≥ 18 years) was dupilumab (use authorized by the FDA in 2019, and by ANVISA in 2020), a human monoclonal antibody, immunoglobulin (Ig)G4, whose target is the subunit α interleukin (IL)-4 receptor (IL-4Rα), which is also common to the IL-13 receptor. Thus, the signaling of both fundamental cytokines in the development of the type 2 immune response is blocked.[8-10]

Case report

Female patient, 17 years old, student, with a history of asthma since childhood, controlled with the use of salmeterol xinafoate + fluticasone propionate (25 µg/125 µg; 1 inhalation 1x/day). Five years ago, he developed recurrent nasal obstruction and hyposmia. Initially, she was evaluated by the team from the Otorhinolaryngology Service, who performed a computed tomography scan of the paranasal sinuses (NSCT), which showed bilateral nasal polyps, left septal deviation and pansinus opacification, compatible with the diagnosis of CRSwNP. ENP was indicated and performed, whose histopathology was compatible with allergic inflammatory polyp. In the immediate postoperative period, he presented edema and hematoma in the right maxillary sinus, in addition to a positive nasal secretion culture for *Enterobacter* spp., with a satisfactory response to intranasal budesonide 400 µg/day associated with nasal lavage with mupirocin (5 times/day). After four months, there was a recurrence of polyps that extended beyond the middle meatus, being submitted to a new ENP. In the etiological investigation, sweat and genetic tests for cystic fibrosis were performed, both negative. Referred to the Immunology Department, sensitization to *Dermatophagoides pteronyssinus* and *Blomia tropicalis*, eosinophilia (1,103/mm^3), total IgE = 460 IU/mL, and low levels of IgM (P3-P10) were confirmed. After an oligosymptomatic period (about 24 months), it evolved with episodes of exacerbation of rhinosinusitis, refractory to conventional drug treatment, complicating with pneumonia and exacerbation of asthma. Clinical treatment for asthma and rhinosinusitis was optimized with formoterol fumarate dihydrate + beclomethasone dipropionate (6 µg/100 µg; 2 inhalations 12/12 h), in addition to montelukast sodium (10 mg; 1 tablet 1x/day) and nasal wash with glycerin budesonide solution 500 mL/day. Recently, even using nasal medications and, despite the new ENP, he still had an exacerbation of symptoms, with recurrent need for antibiotic therapy and frequent use of systemic corticosteroids (six cycles of 7-14 days in six months). In the last year,

the patient was symptomatic, with a predominance of nasal symptoms, refractory to treatment, in addition to complete veiling of the paranasal sinuses and ethmoid cells, extending to the nasal cavities, with progressive worsening of quality of life, when the use of dupilumab was indicated, despite not being licensed for CRSwNP in this age group. Started with 300 mg subcutaneously (SC) every two weeks. After eight weeks, the patient evolved with a significant improvement in the SNOT-227, VAS (visual analogue scale)[11] and NPS (nasal polyp score)[12] scores, maintaining asthma controlled by the ACT (asthma control test)[13] (Table 2 and Figure 1).

Discussion

About 90% of patients have CRSsNP mediated by type 2 immune response, with eosinophilia and IgE formation, in addition to significant eosinophilic infiltration of the mucosa and nasal polyps. There is synthesis of high levels of type 2 cytokines such as eosinophilic cationic protein, eotaxin, IL-4, IL-5 and IL-13. These interleukins play an important role in the pathophysiological mechanism of associated comorbidities, including asthma, which affects up to two thirds of patients with CRSwNP, impairing clinical control and worsening the quality of life of these patients.[14-15]

In clinical practice, evidence of inflammation of type 2 are the association with late-onset asthma and/or aspirin-exacerbated respiratory disease (ARD), in addition to greater severity in the presentation of CRSwNP itself, with recurrence of polyps after oral corticosteroid therapy and/or polypectomy. Other parameters are eosinophilia, high levels of serum IgE and eosinophilic infiltrate at the histopathology of polyps.[16,17]

The conventional therapeutic approach to CRSwNP aims to control the nasal inflammatory process. Topical intranasal corticosteroids and repeated courses of systemic corticosteroids may be necessary for more severe cases, leading to side effects from prolonged use. In addition, surgical treatment is more frequent due to the recurrence of polyps.[16,17]

Recently, the use of immunobiological agents have been indicated in patients with severe CRSwNP who have evidence of type 2 inflammation (tissue eosinophilia ≥ 10 cells/HPF or blood eosinophilia ≥ 250 cells/mcL or total IgE ≥ 100 IU/mL). In this context, patients with CRSwNP who need frequent courses of systemic corticosteroid therapy, with hypo/anosmia, association with asthma and significant reduction in quality of life. Dupilumab, as an anti-IL-4/IL-13 antibody, has a precise indication for CRSwNP. It is worth emphasizing that it is an IgG4, whose target is IL-4Rα, shared by IL-4 and IL-13, blocking their signaling and, consequently, attenuating the inflammatory response.[17-19]

In 2016, Bachert et al. evaluated the efficacy of dupilumab in CRSwNP, in subjects over 18 years of age, treated with a loading dose of 600 mg SC followed by 300 mg every two weeks. Patients showed

Table 2
Scores for clinical and nasal endoscopic assessment pre-dupilumab and at each application (2-week interval) up to 8 weeks of treatment

Scores	Pre-dupilumab	2 weeks	4 weeks	6 weeks	8 weeks
EVE	7.5	–	–	–	5
SNOT-22	41	50	41	44	27
ACT	25	25	25	25	25
NPS	6	8	–	–	6

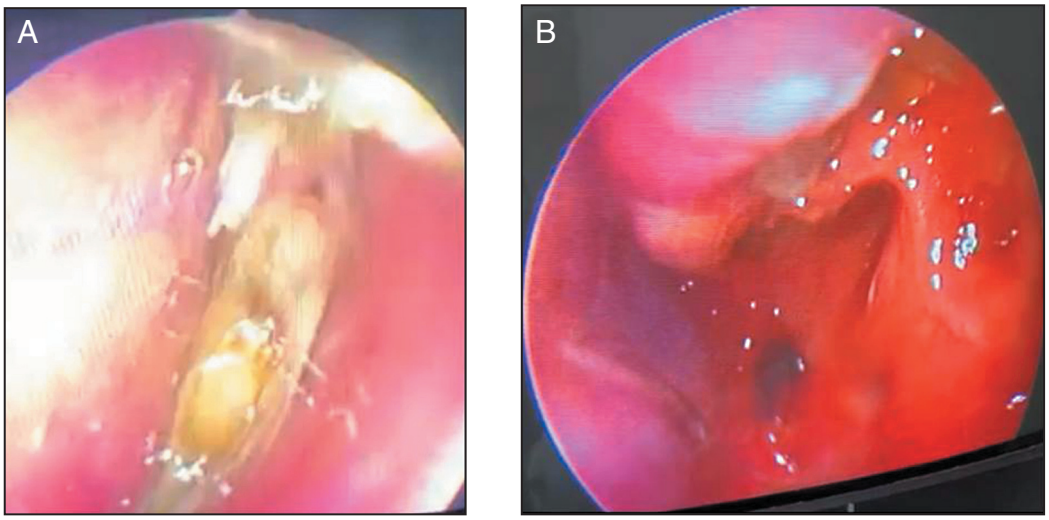

Figure 1
Nasal endoscopy pre-dupilumab (A) and after 8 weeks of treatment (B)

significant improvement in SNOT-22, endoscopic score and tomographic nasal polyp score (NPS and Lund-Mackay sinus – LMS, respectively). In addition, the use of dupilumab improved lung function and asthma control (ACT) in the subgroup of patients with asthma.[19]

Based on the positive results of this study, two other multicenter studies were carried out, SINUS-24 and SINUS-52 (with 24 and 52 weeks of follow-up, respectively), which also demonstrated that the use of dupilumab in adults ≥ 18 years with severe CRSwNP significantly reduced SNOT-22, NPS and LMS scores, with an increase in ACT, when compared to placebo. Thus, they evidenced the effectiveness of dupilumab in patients with CRSwNP refractory to clinical and surgical treatments, including those with associated asthma.[20]

In the case reported, the patient had all the clinical and laboratory criteria established for the diagnosis of CRSwNP with type 2 inflammation (Table 1, Figure 1).[16] He evolved with progressive clinical worsening, characterized by the recurrence of polyps, refractory to clinical and surgical treatments, coexistence of uncontrolled asthma, resulting in a significant loss of his quality of life. Considering the severity of the clinical picture, especially due to the recurrence of polyps and frequent use of systemic corticosteroids, it was decided to start dupilumab, 300 mg SC every two weeks, in an attempt to control the nasal inflammatory process. After eight weeks, the patient evolved with significant clinical improvement, corroborated by the SNOT-22, VAS and NPS scores, keeping the asthma controlled by the ACT (Table 2).

The dupilumab has been shown to be safe and clinically effective in the treatment of diseases with a type 2 immune response, including CRSwPN in adults. We report the case of an adolescent patient (17 years old), with severe CRSwNP, who achieved significant clinical control after eight weeks of use of dupilumab, at the dosage licensed for adults above 18 years old. Therefore, there is a need for further studies to show such efficacy in other age groups, avoiding future risks such as the development of osteoporosis and bone necrosis due to the frequent use of systemic corticosteroids.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

The Peruvian Association of Patients with Hereditary Angioedema and COVID-19 vaccination

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Hereditary angioedema (HAE) is a rare, potentially life-threatening disorder characterized by cutaneous and submucosal swelling attacks.[1] The coronavirus disease 2019 (COVID-19) pandemic has spread rapidly worldwide, and it can lead to death from respiratory failure or multi-organ compromise.[2] Vaccines against COVID-19 could cause adverse reactions or trigger HAE attacks in patients. The main objective of this study was to describe the features of adverse reactions following COVID-19 vaccination in patients with HAE.

We included 16 patients of the Peruvian Association of Patients with HAE, of whom 14 were women and 2 were men. Participants signed an informed consent form and completed a questionnaire about HAE history, COVID-19 infection, and COVID-19 vaccination. Mean patient age was 26.3 years (age range: 18-64 years). Eleven participants had HAE type I, and 5 had HAE with normal C1 inhibitor (HAE-nC1-INH). Genetic diagnosis was positive in 11 patients (2 FXII and 9 SERPING1) and unknown in 5. Patients with unknown mutations were only included in the study if they met the following criteria: clinical symptoms consistent with HAE with C1 inhibitor (HAE-C1-INH); presence of hormonal, trauma, and/or stress triggers; normal levels of C1-INH and C4; good response to tranexamic acid or danazol prophylaxis; and absence of mutations in FXII, plasminogen (PLG), angiopoietin-1 (ANGPT1), kininogen (KNG1), and SERPING1.

Before receiving the COVID-19 vaccine, 10 of 16 patients reported having mild to moderate attacks once a month, and 13 of 16 patients reported the abdomen as the most frequent region. Five had COVID-19 infection without worsening HAE crisis.

Fourteen patients received Pfizer®, 1 patient received Astrazeneca®, and 1 patient received Sinopharm®. After the first (11/16) and second (7/16) doses, patients had general discomfort, fatigue, headache, fever, and pain at the site of administration; some patients took acetaminophen, with good symptom control. There were 14 HAE crisis in total, 9 of which (65%) began after 24 hours of vaccine administration. The most frequent attacks were facial and upper airway angioedema, followed by abdominal crisis. Three patients had attacks only after the first dose; these patients received pre-treatment and did not have any attacks after the second dose. Four patients had a crisis only after the second dose; none were taking prophylaxis. Three patients had attacks after both doses and had not received any medication for prophylaxis.

Regarding the first dose, 3 of 16 patients had received short-term prophylaxis (2 tranexamic acid and 1 danazol), and 2 of them did not have attacks (1 with tranexamic acid and the other with danazol). Seven of 16 patients had a HAE crisis, of whom 6 were women and 1 was a man. Five of these 6 women had attacks during their menstrual period (range: 1 day before to 4 days after the beginning of menstruation). They reported worsening HAE crises during their periods. Three of 7 patients with mild/moderate HAE attacks did not received treatment, and the crisis lasted from 48 to 72 hours. The remaining 4 patients, all women with moderate/severe attacks, received specific treatments: 1 received icatibant (facial and tongue edema; attack remission in 24h); 2 received high doses of tranexamic acid (facial and hand edema; attack remission in 72h); and 1 received ecallantide (pharynx edema and difficulty to swallow; attack remission in 24h).

Regarding the second dose, 9 of 16 patients received short-term prophylaxis (500 mg tranexamic acid, 3 times a day, 5 days pre- and post-vaccination), and none of them had a crisis. Seven patients without prophylaxis had moderate/severe angioedema attacks, which began 3 to 48 hours after vaccine administration. Only 1 patient had severe abdominal crisis, 5 days after receiving the vaccine. Five of 7 patients received treatment: 1 received icatibant (facial and tongue edema; attack remission in 24h), and 4 were treated with high doses of tranexamic

acid (abdominal crisis and hands edema; attack remission in 96 h on average).

We conclude the following:

- Patients with HAE-C1-INH deficiency or HAE-nC1-INH may experience angioedema attacks after COVID-19 vaccination.
- The administration of COVID-19 vaccines during the menstrual period may induce HAE attacks. A possible recommendation would be to not administer COVID-19 vaccination immediately before or during the menstrual period.
- Patients with HAE included in this study had a positive response to prophylaxis with tranexamic acid.
- Specific treatments should be available to treat angioedema attacks after COVID-19 vaccination.
- The benefits of COVID-19 vaccination outweigh the risks of possible adverse events.
- To our knowledge, the present study has new findings. Further studies assessing COVID-19 vaccination in patients with HAE are needed.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Differential diagnosis between exercise-induced anaphylaxis and cholinergic urticaria

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Dear editor,

In the past, both cholinergic urticaria and exercise-induced anaphylaxis were called physical urticaria. Currently, cholinergic urticaria belongs to a group called chronic induced urticaria, and exercise-induced anaphylaxis is separated from other conditions inherent to the individual, in an adverse response to the practice of aerobic exercises.[1]

The prevalence of exercise-induced anaphylaxis is estimated at approximately 3% of the total anaphylaxis, and cholinergic urticaria in 5% of the total chronic urticaria, and 30% of the chronic induced urticaria.[2] The etiopathogenesis of both is still unknown, although they have in common a greater mast cell cytoplasmatic degranulation hyperreactivity. [3]

Different clinical presentations

Aerobic exercises can trigger four different modalities of anaphylaxis (Table 1). The main differences between exercise-induced anaphylaxis and cholinergic urticaria are listed in Table 2.[1-3]

Aerobic exercise is enjoyable, safe, and healthy, and therefore should always be encouraged. Physical desensitization with progressive and incremental exercises can be successful and occasionally proposed.[4]

Universal practice of aerobic exercises and of numerous sports makes it increasingly necessary to update the so-called “physical allergies”.[5]

Table 1
Exercise-induced anaphylaxis

Food-independent/Primary/Idiopathic
Food-dependent with specific IgE
Food-dependent without specific IgE
Drug-dependent

Table 2
Exercise-induced anaphylaxis and cholinergic urticaria

Characteristics	Exercise-induced anaphylaxis	Cholinergic urticaria
Symptoms	Flushing, warmth, malaise, diffuse pruritus, urticaria with large and coalescing wheals, angioedema, gastrointestinal symptoms, hypotension, syncope, laryngeal edema, anaphylaxis, and rarely asthma. Clinical history is very important for the diagnosis	Urticaria with small, punctate wheals (1-3 mm in diameter), exhibiting an adjacent erythematous and coalescing reaction ("fried egg" appearance), induced actively by exercise and/or passively by increasing body temperature (hot baths/ Hubbard bathtub, heavy clothing, spicy foods, and emotional stress)

Table 2 *(continuation)*
Exercise-induced anaphylaxis and cholinergic urticaria

Characteristics	Exercise-induced anaphylaxis	Cholinergic urticaria
Risk of anaphylaxis	Very common	Extremely rare
Provocation tests	Treadmill exercise for 30 minutes after eating suspicious foods or medications	Treadmill exercises for 30 minutes, followed by passive warm-up, inducing an increase in body temperature (usually less than 1°C). It can therefore be considered a variant of heat-induced urticaria
Management	Rule out associated food allergy. Measure baseline serum tryptase. Exercises always accompanied, and close to Hospital Emergencies. Medical alert bracelet. Carry activated mobile phone. Do not exercise 4-6 hours after eating or taking nonsteroidal anti-inflammatory drugs. Avoid aerobic exercise when the weather is very cold, hot or humid. Cease exercise immediately after symptoms begin. Omalizumab may be indicated in refractory cases	Symptomatic treatment with second-generation non-sedating antihistamines. Increase, if necessary, the dose of these antihistamines up to four times the usual recommended dosage. Omalizumab may be indicated in refractory cases
Need for auto-injectable epinephrine	Yes	No
Long term prognosis	Good	Good

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