

ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

ASBAI – Associação Brasileira
de Alergia e Imunologia

SLaai – Sociedad Latinoamericana
de Alergia, Asma e Inmunología

Volume 8 • Number 3 • July-September 2024

8/3

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July-September 2024

Volume 8, Number 3

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Perioperative anaphylaxis: very serious, not so rare, but still neglected and poorly understood

Anafilaxia perioperatória: muito grave, não tão rara, mas ainda negligenciada e pouco conhecida

Marcelo Vivolo Aun¹

Perioperative anaphylaxis is a serious immediate hypersensitivity reaction, with a mortality rate approaching 5% of cases.¹ This figure exceeds the estimates of mortality from other causes of anaphylaxis, which are less than 1%.² Conversely, immediate perioperative reactions are uncommon events, with an incidence ranging from 1:500 to 1:18,600 procedures.¹ The largest case series in the world were generated in the United Kingdom and France, where the incidence was about 1:10,000 procedures.^{3,4} There is only one (single-center, prospective) study conducted in Brazil, which has demonstrated a higher incidence in our setting. The study found 27.9 immediate grade 1 reactions (exclusively cutaneous) per 10,000 procedures and 7 anaphylactic reactions per 10,000 procedures, i.e., 7 times higher than the incidence rate from Western Europe.⁵ This suggests that, despite being an uncommon event, intraoperative anaphylaxis should not be considered a rare event. Nevertheless, anesthesiologists, the physicians who should recognize these reactions and promptly act to prevent fatal outcomes, are not well-informed on the subject.

Moura et al.,⁶ in a study published in this issue of the *Arquivos de Asma, Alergia e Imunologia*, demonstrated serious gaps in anesthesiologists' knowledge, which may compromise care for patients who develop an immediate reaction during the

procedure. Although they obtained a response rate of just over 10% to the online questionnaire sent to anesthesiologists in the state of Sergipe, the authors demonstrated that more than 10% of these specialists did not mention neuromuscular blockers as a possible cause of the reactions. It is important to note that this class of drugs is the most common cause of reactions in many of the published case series.⁷ Furthermore, regarding the management of anaphylaxis, 10.3% of respondents reported using crystalloid resuscitation as the first therapeutic measure in intraoperative anaphylaxis.

Apparently, anesthesiologists have insufficient knowledge not only of intraoperative reactions but also of drug hypersensitivity reactions. In another Brazilian study, published in the proceedings of a local event and presented at the Drug Hypersensitivity Meeting of the European Academy of Allergy and Clinical Immunology (DHM-EAACI 2022),⁸ 104 anesthesiologists completed an online questionnaire. There was clear evidence that current well-established concepts about hypersensitivity to beta-lactam antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) are unknown to those colleagues. The survey results showed that 40% believed in a high likelihood of cross-reactivity between penicillin and cefazolin, although it is currently known that this

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likelihood is less than 2%. Furthermore, more than 90% of anesthesiologists denied the existence of potential cross-intolerance between dipyrone and other NSAIDs,⁸ with the so-called “non-selective reactors” to NSAIDs clearly being the majority of these patients.

It can be postulated that the limited knowledge of anesthesiologists regarding drug allergy may be, at least in part, attributed to the minimal involvement of faculty members specialized in Allergy and Immunology in undergraduate medical education in Brazil. Most Brazilian medical schools do not have Allergy and Immunology as a course in their curriculum. Allergic and immunological diseases are often taught by other specialties with practical experience in these diseases, such as pediatrics, dermatology, pulmonology, otolaryngology, infectious diseases, and rheumatology, among others. However, some topics such as “Drug Hypersensitivity,” “Food Allergy,” “Anaphylaxis,” and “Inborn Errors of Immunity” encompass more than one organ or system, clearly showing that the participation of Allergy and Immunology specialists in the training of physicians would be of great value.

This deficient knowledge is clearly not limited to specialists in Anesthesiology but rather extends to most physicians who are not specialists in Allergy and Immunology. Two Brazilian studies, conducted in the states of Rio de Janeiro and Alagoas, showed that emergency physicians, although most of them had already treated cases of anaphylaxis during their shifts, were poorly trained and not up-to-date on the management of this life-threatening syndrome.^{9,10}

Regarding intraoperative anaphylaxis, it is important to highlight that, even after completing medical school, the physicians who specialize in anesthesiology (and who will deal with these complications) seem to continue to have little interaction with our specialty. Two medical societies, the Brazilian Association of Allergy and Immunology (ASBAI) and the Brazilian Society of Anesthesiology (SBA), have put a great deal of effort into improving the continuing medical education of their specialists. These societies have been collaborating, interacting during their annual congresses, and generating joint scientific production on the topic of perioperative hypersensitivity.^{11,12} However, these efforts still prove insufficient. We need to do more to reach colleagues who work face-to-

face with the patients who experience these severe reactions during surgery. This will lead to a reduction in morbidity and mortality from these events and to the correct referral of these cases to allergists and immunologists for investigation.

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Allergic bronchopulmonary aspergillosis: Brazilian Association of Allergy and Immunology guidelines for diagnosis and management

Aspergilose Broncopulmonar Alérgica (ABPA): guia da Associação Brasileira de Alergia e Imunologia para o diagnóstico e manejo

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ABSTRACT

Allergic bronchopulmonary aspergillosis (ABPA) is an immunoallergic lung disease caused by hypersensitivity reactions to antigens of the fungus *Aspergillus fumigatus*. The disease primarily affects individuals with asthma or cystic fibrosis and can lead to irreversible lung damage if not accurately diagnosed and treated. Despite being described nearly 70 years ago, the disease remains underdiagnosed. This may be related to the diagnostic methods used, the lack of standardized tests, and still imprecise diagnostic criteria. Standard therapy involves the use of systemic corticosteroids. Azole antifungals are indicated for the treatment of exacerbations and are the preferred strategy to reduce corticosteroid use. Biologics hold promise for treating ABPA due to their ability to inhibit type 2 inflammation, regulate IgE levels and eosinophil counts, and modulate inflammatory cytokines. Thus, in patients with asthma, especially those with difficulty in achieving disease control, the possibility of ABPA should be considered. Given the variability of diagnostic criteria and the need

RESUMO

A Aspergilose Broncopulmonar Alérgica (ABPA) é uma doença imunoalérgica pulmonar causada por reações de hipersensibilidade aos antígenos do fungo *Aspergillus fumigatus*. A doença afeta principalmente pessoas com asma ou fibrose cística e pode levar a dano pulmonar irreversível se não diagnosticada e adequadamente tratada. Apesar de descrita há quase 70 anos, a doença ainda é subdiagnosticada. Isso pode estar relacionado aos métodos de diagnóstico utilizados, à falta de testes padronizados e a critérios diagnósticos ainda imprecisos. O tratamento principal envolve o uso de corticosteroides sistêmicos. Antifúngicos azólicos são indicados para tratar exacerbações e são a estratégia preferencial para reduzir o uso de corticosteroides. Medicamentos biológicos prometem ser úteis no tratamento da ABPA, devido à sua capacidade de inibir a inflamação tipo 2, regular os níveis de eosinófilos e IgE e modular citocinas inflamatórias. Assim, frente a pacientes com asma, principalmente aqueles que têm dificuldade em alcançar o controle da doença, deve ser considerada a hipóte-

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Submitted Oct 28 2024, accepted Nov 01 2024.

Arq Asma Alerg Imunol. 2024;8(3):189-212.

to validate them in different populations, more studies are needed to better understand the disease, allowing its early detection and appropriate management. In these guidelines, we aim to update the data on ABPA epidemiology, clinical manifestations, diagnosis, differential diagnosis, and treatment.

Keywords: Allergic bronchopulmonary aspergillosis, pulmonary aspergillosis, asthma, bronchiectasis, eosinophilia, immunoglobulin E.

se de ABPA. Devido à variabilidade dos critérios diagnósticos e à necessidade de verificar a sua validação em populações distintas, são necessários mais estudos para um melhor entendimento da doença, possibilitando sua detecção precoce e manejo adequado. Nestas diretrizes procuramos atualizar dados sobre epidemiologia, manifestações clínicas, diagnóstico, diagnóstico diferencial e tratamento desta doença.

Descritores: Aspergilose broncopulmonar alérgica, aspergilose pulmonar, asma, bronquiectasia, eosinofilia, imunoglobulina E.

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disease first described in 1952 by Hinson et al. in England in individuals presenting with bronchitis/asthma, peripheral eosinophilia, bronchiectasis, and/or expectoration of mucus plugs containing the fungus *Aspergillus fumigatus*.¹ In 1968, the disease was reported in the United States,² and in 1974, França described nine cases in Brazil, eight in adults and one in a child.³

ABPA is the most common cause of allergic bronchopulmonary mycosis (ABPM), a noninvasive disease with high potential for lung destruction. It primarily affects individuals with conditions that favor the germination of *A. fumigatus* conidia, particularly patients with asthma or cystic fibrosis (CF).⁴

A. fumigatus is a ubiquitously distributed fungus, mainly found in environments rich in decomposing organic matter, such as dead plants and animals. Its atmospheric concentration, conidia size (2.5–3 µm), mutability, allergenic potential, environmental conditions, thermotolerance (12–52 °C), mycotoxin production, as well as the host's age and immunocompetence, are key determinants of its pathogenicity.^{4,5}

Inflammation of bronchial mucosa, as seen in asthma and CF, facilitates conidia retention and germination, leading to the formation of germ tubes and hyphae, which produce the main *A. fumigatus* antigens. Thus, depending on the individual's genetic background and immune status, type I and III hypersensitivity reactions may occur, resulting in ABPA. Clinical manifestations of ABPA range from mild bronchospasm to pulmonary fibrosis.^{4,6}

ABPA remains an underrecognized disease, with approximately 30% of patients initially misdiagnosed with tuberculosis, particularly in developing countries such as Brazil.⁶

Given the disease's potential to cause irreversible complications, it is crucial to establish screening policies for ABPA, as early detection is essential for adequate treatment and improved prognosis.

The objective of this study was to provide a comprehensive review of ABPA, including its epidemiology, clinical manifestations, diagnosis, differential diagnoses, and treatment.

Epidemiology

It is estimated that more than 4 million people are affected by ABPA worldwide.^{4,7} However, the exact prevalence of the disease remains uncertain and varies depending on the studied region. ABPA affects approximately 2.5% to 15% of patients with asthma and between 7% and 9% of patients with CF.^{4,8}

The prevalence of ABPA exceeds 40% in patients with asthma sensitized to *A. fumigatus*, being more common in those with severe asthma.⁸ In Brazil, the prevalence among adult asthmatics sensitized to *A. fumigatus* was reported at 20%.⁹ In children with CF (median age of 7.3 years), the rate of allergic sensitization detected by skin prick test or specific serum IgE ranged from 12.5% to 23%.^{10,11} Globally, the highest prevalence of ABPA has been reported in India.¹²

There is no age or sex predilection for the occurrence of ABPA, but it is more commonly observed in adults.¹³ Additionally, genetic predisposition, such as specific *HLA-DR* alleles, may contribute to the development of ABPA in susceptible individuals.¹⁴

Difficulties in determining the true prevalence of ABPA are related to the lack of standardized diagnostic tests and criteria, as well as variations in the characteristics of study populations.

Aspergillus fumigatus

Aspergillus is a fungus that plays a crucial role in maintaining ecological balance, contributing to the recycling of organic matter and nutrient availability.¹⁵ It is a eukaryotic, heterotrophic organism belonging to the domain *Eukarya*, kingdom *Fungi*, division *Ascomycota*, class *Eurotiomycetes*, order *Eurotiales*, family *Aspergillaceae*, genus *Aspergillus*, and species *A. fumigatus*.¹⁶

The genus *Aspergillus* is divided into six subgenera (*Circumdati*, *Nidulantes*, *Fumigati*, *Aspergillus*, *Cremeri*, and *Polypaecilum*), which include 27 sections and 446 species.¹⁷ Among these, *A. fumigatus* is the most clinically relevant pathogenic species due to its higher capacity to survive and thrive in a wide range of environmental conditions compared with other species.^{18,19}

The taxonomy of *Aspergillus* is complex and frequently revised.²⁰ Traditionally, classification was based on phenotypic characteristics; however, in recent decades, molecular and chemotaxonomic analyses have played a more significant role.²¹ These new approaches are necessary due to the large number of species within the genus, making precise identification challenging. A polyphasic methodology, which integrates both biotypic and genotypic characteristics, has proven to be the most effective for species identification. Biotypic analysis includes evaluating the conidia's shape, size, color, and thermotolerance.¹⁸

Thermotolerance is a key distinguishing feature, as *A. fumigatus* differs from other *Aspergillus* species in its optimal growth temperature. It thrives best at 37 °C but can grow between 20 °C and 52 °C, and it can survive prolonged exposure to temperatures as high as 55 °C. Consequently, *A. fumigatus* can be found worldwide, particularly in self-heating environments such as hay, corn, and compost.^{19,21}

Genotypically, different molecular biology techniques can be used for defining species, including ribosomal RNA sequencing, restriction fragment length polymorphism, protein-coding gene sequencing, and multilocus sequence typing.²⁰ The analysis of gene sequences encoding β -tubulin, calmodulin, or the RNA polymerase II second largest subunit (RPB2) appears to be the most suitable for distinguishing between *Aspergillus* species.²¹

The morphological characteristics of *Aspergillus* were first described in 1729 by Pietro Micheli, an Italian priest and biologist, who compared

its structure to a holy water sprinkler, hence the name *Aspergillus*.¹⁹ These fungi are composed of filamentous cells called hyphae, which can grow and form a network called mycelium, classifying them as filamentous fungi. The hyphae are septate and hyaline, varying in diameter, and branch into conidiophores, which are specialized asexual reproductive structures that produce asexual spores called conidia. The conidiophores emerge from the basal cell through the hypha, and terminate in a vesicle, which connects to the basal cell via a stalk (stipe). Phialides, the conidia-producing cells, arise from the vesicle. In *A. fumigatus*, the conidiophores are uniseriate, meaning they emerge directly from the vesicle.¹⁵

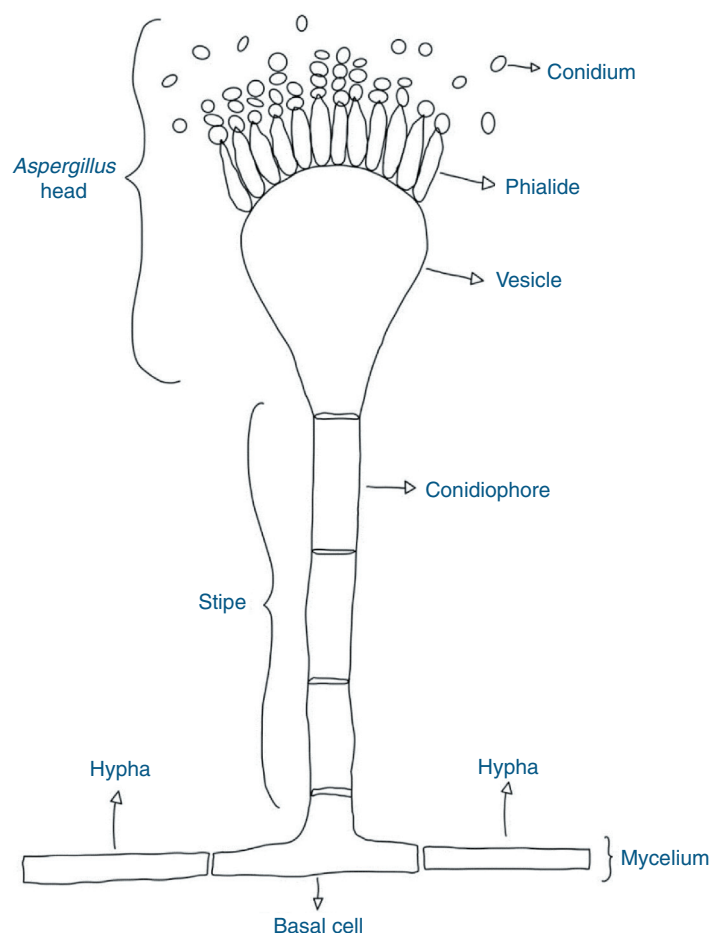
Aspergillus section *Fumigati* species are characterized by smooth conidiophores, balloon-shaped vesicles, columnar conidial heads, greenish globose conidia with textures ranging from smooth to rough, and are uniseriate.²² Conidiophores are simple, typically aseptate, and have septate hyaline hyphae that vary in diameter^{18,20} (Figure 1).

The *Aspergillus* life cycle consists of two phases: a somatic phase, during which it absorbs simple soluble nutrients for sustenance, and a reproductive phase.¹⁶ The genus *Aspergillus* is considered anamorphic, as it predominantly undergoes asexual reproduction in nature by producing chains of phialides and conidia.^{20,23}

Once germinated, the hyphae grow and form a colony. In the colony phase, *A. fumigatus* hyphae become embedded in an extracellular matrix and form a biofilm. Its rapid growth rate is a key factor promoting its dissemination.²³

Conidia detach and become airborne, with environmental concentrations ranging from 0.1 to 3 conidia per m³. This allows them to reach all levels of the respiratory tract. Additionally, they can remain dormant until they encounter adequate environmental conditions. *A. fumigatus* can grow on a wide variety of substrates and tolerate freezing temperatures or desiccation for prolonged periods.¹⁹

The first reported case of *Aspergillus* infection in humans was described by Sluyter in 1847.²⁴ The spectrum of diseases caused by *Aspergillus* includes mycotoxicosis, allergies, asthma, aspergilloma, necrotizing aspergillosis, invasive pulmonary aspergillosis, and ABPA.²⁵

**Figure 1**Morphological characteristics of *Aspergillus fumigatus*Adapted from Souza HG et al.¹⁵.

Pathogenesis

The pathogenesis of ABPA is complex, involving genetic factors, host-pathogen interactions, innate and adaptive immune responses, hypersensitivity reactions, and eosinophilic inflammation.

Genetic factors may contribute to susceptibility to ABPA. Human leukocyte antigen (HLA) genotyping studies have identified specific HLA-DR alleles, such as HLA-DR2 and HLA-DR5, which are associated with an increased risk of developing ABPA in patients with asthma and CF, respectively.²⁶ Conversely, HLA-DQ2 appears to confer protection against the disease.²⁷

The *ZNF77* gene variant rs35699176 has been reported to compromise the integrity of respiratory epithelial cells, exposing extracellular matrix proteins and thereby promoting the adhesion, germination, and growth of *A. fumigatus* conidia.²⁸ Polymorphisms in innate immune response pathways, including surfactant protein A2 and Toll-like receptors 3 and 9, have also been described in patients with ABPA.²⁹⁻³¹

Aspergillus is a ubiquitous saprophytic fungus found in the air and soil, thriving in decaying vegetation.²³ The small size of *Aspergillus* spores allows deep penetration and deposition in the airways. Inhalation

of these spores can lead to airway colonization and germination in susceptible individuals, particularly those with asthma or CF.³²

Normally, *A. fumigatus* does not elicit an immune response because its conidia possess a hydrophobic layer composed of RodA protein, which prevents recognition by dendritic cells, rendering the spores immunologically inert.³³ However, if the conidia persist in the respiratory tract, they germinate and produce hyphae, losing their hydrophobic layer. This triggers pathogen-associated molecular patterns, which activate pattern recognition receptors on pulmonary epithelial cells, leading to the release of alarmins such as interleukin (IL)-33, IL-25, and thymic stromal lymphopoietin (TSLP). These alarmins stimulate type 2 innate lymphoid cells (ILC2), which produce type 2 (T2) cytokines, including IL-4, IL-5, and IL-13, resulting in eosinophilia, mucus production, and bronchial hyperreactivity. Evidence suggests that ILC2s interact with CD4+ T lymphocytes, promoting adaptive immune responses and persistent airway inflammation.³⁴

Impaired mucociliary clearance and local immune responses in these individuals facilitate the persistence of *Aspergillus* hyphae in the airways, triggering an exaggerated immune response. The release of several fungal proteins and proteases (catalase, aspartic protease, metalloprotease, elastase, and collagenase) contributes to fungal colonization and perpetuates respiratory epithelial damage.³⁵⁻³⁷

In addition, *A. fumigatus* hyphae produce its key antigens. The World Health Organization (WHO) and the International Union of Immunological Societies (IUIS) have identified 30 *A. fumigatus* allergenic proteins,³⁸ of which five (Asp f1, Asp f2, Asp f3, Asp f4, and Asp f6) are available as recombinant proteins for testing.³⁹ Asp f1, described by Arruda LK et al., is a ribotoxin protein specific to *A. fumigatus*, which is expressed and secreted exclusively by germinating spores.⁴⁰ Asp f3, Asp f4, and Asp f6 are somatic proteins. Although Asp f1 is considered the most allergenic, all of these antigens have the potential to elicit IgE- and IgG-mediated immune reactions.³⁹

Thus, ABPA pathogenesis is characterized by a marked type 2 (T2) inflammatory response involving a combination of type I (immediate) and type III (immune complex-mediated) hypersensitivity reactions.⁴¹ In type I hypersensitivity, *Aspergillus* antigens bind to IgE on the surface of mast cells and basophils, leading to the release of inflammatory mediators such as histamine, leukotrienes, and prostaglandins. This results in bronchoconstriction, increased vascular permeability,

and mucus production.⁴² In type III hypersensitivity, immune complexes formed by *Aspergillus* antigens and IgG are deposited in lung tissue, activating the complement system and attracting inflammatory cells, leading to tissue damage and marked eosinophilic inflammation.⁴³

The T2 inflammatory process in ABPA is characterized by massive eosinophilic infiltration of the airways and high levels of polyclonal IgE. Eosinophils play a central role in ABPA pathogenesis, contributing to airway inflammation, mucus production, and bronchial hyperresponsiveness.⁴¹ Cytokines such as IL-4, IL-5, and IL-13, produced by Th2 cells, promote eosinophil recruitment, activation, and survival.⁴⁴ Furthermore, IL-4 and IL-13 promote IgE production by B cells and induce goblet cell hyperplasia, increasing mucus secretion. Airway inflammation leads to the formation of dense eosinophilic mucus containing Charcot-Leyden crystals, which obstruct the airways. Variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene may play a role in ABPA, even in the absence of CF, although this is not fully elucidated.⁴⁵

Clinical presentation

The most common clinical findings in ABPA are related to the symptoms of the underlying diseases that predispose to it, as well as those directly caused by ABPA itself. These manifestations can range from mild bronchospasm to pulmonary fibrosis. Patients may experience recurrent and paroxysmal coughing, dyspnea, increased sputum production, wheezing, frequent exacerbations, and exercise intolerance. Depending on the disease stage, symptoms such as the expectoration of brownish mucus plugs, occasional hemoptysis, fever, and general malaise may be present. Digital clubbing is uncommon and typically observed in patients with longstanding bronchiectasis.^{44,46}

A subset of patients with ABPA may present without underlying asthma, with chest imaging findings being the key factor leading to the suspicion of the disease.⁴⁷ The diagnosis of ABPA may take up to 10 years to be suspected and established, often considered only in cases of severe, treatment-resistant asthma requiring high doses of inhaled corticosteroids combined with long-acting bronchodilators or even oral corticosteroids (corresponding to steps 4 or 5 of the Global Initiative for Asthma [GINA]).⁴⁸ Rarely, allergic fungal rhinosinusitis caused by *Aspergillus*

may occur simultaneously, presenting with symptoms such as nasal obstruction and thickened and dark nasal discharge.⁴⁹

Clinical findings are crucial for the diagnosis of ABPA and, when combined with characteristic radiological features on chest computed tomography (such as mucoid impaction and parenchymal opacities), the presence of biomarkers (elevated total IgE, specific serum IgE against *A. fumigatus*, or a positive immediate hypersensitivity skin test), as well as other supporting criteria such as elevated blood eosinophils, specific IgG, or serum precipitins against *A. fumigatus*, they can confirm the diagnosis.⁴⁹⁻⁵⁰

Several clinical stages of ABPA have been described, initially proposed by Patterson et al. in 1982⁵⁰ and more recently revised by Agarwal et al. in 2024.⁴⁹ These are summarized in Table 1.

Diagnosis

Diagnosing ABPA is challenging and requires the assessment of clinical, immunological, and radiological criteria to differentiate it from other pulmonary conditions.⁵¹ The first diagnostic criteria for ABPA were proposed by Rosenberg et al. in 1977 (Table 2). These included seven primary components (asthma, peripheral blood eosinophilia, immediate skin reactivity to *Aspergillus* antigen, presence of precipitating antibodies against *Aspergillus* antigen, elevated serum IgE concentrations, history of transient or fixed pulmonary infiltrates, and central bronchiectasis) and three secondary components (*A. fumigatus* culture in sputum, history of expectoration of brown plugs or flecks, and Arthus reactivity).⁵² These criteria were the most used for the diagnosis of ABPA. However, in 2013, the ABPA working group of the International Society for Human and Animal Mycology (ISHAM) proposed updated criteria to establish standardized diagnostic guidelines for ABPA.⁵³

Subsequently, new evidence emerged regarding the sensitivity and specificity of the ISHAM criteria. A study evaluating the performance of different diagnostic criteria⁵⁴ demonstrated that specific serum IgE tests were more sensitive than skin tests in detecting *Aspergillus* sensitization. It also showed that the sensitivity and specificity of the ISHAM criteria improved with a lower total IgE threshold. Additionally, a cutoff level for *A. fumigatus*-specific IgG was proposed, leading ISHAM to modify its diagnostic criteria in 2021.⁵⁴ Despite validation, the revised ISHAM criteria still showed low sensitivity in

cases of ABPM caused by fungi other than *Aspergillus*. To address this, Asano et al. proposed and validated new diagnostic criteria, which demonstrated higher sensitivity and specificity compared to the Rosenberg-Patterson and ISHAM criteria, even in atypical ABPA cases and other forms of ABPM.⁵⁵

Given these evolving insights and remaining gaps in knowledge, new guidelines have recently been published to aid clinicians and researchers in the management of ABPA.⁴⁹

The currently proposed diagnostic criteria are shown in Table 3, along with their advantages and disadvantages.

Clinical criteria

The clinical criteria for diagnosing ABPA involve the presence of characteristic symptoms and risk factors, particularly asthma and CF, along with warning signs that may indicate ABPA, such as: uncontrolled asthma despite appropriate treatment; (ii) persistent respiratory symptoms, including cough, dyspnea, wheezing, and sputum production; (iii) recurrent acute exacerbations with pulmonary eosinophilia; and (iv) bronchiectasis.^{51,55}

Immunological criteria

Immunological markers may help confirm hypersensitivity to *Aspergillus* and provide insights into disease activity.

According to the latest ABPA guidelines, a total serum IgE level of ≥ 500 IU/mL is considered sufficient for an ABPA diagnosis, while a threshold of ≥ 417 IU/mL is used for ABPM.^{49,55} An increase of $\geq 50\%$ in total serum IgE levels is indicative of ABPA exacerbation⁴⁹ (Table 3).

The detection of specific IgE against *Aspergillus* antigens plays a crucial role in diagnosis. However, variability in test methods and allergen quality can impact the accuracy of results. To address these challenges, the use of recombinant allergens has been proposed. These proteins, produced using genetic engineering techniques, provide more controlled and standardized production compared with natural allergens, enhancing test sensitivity and specificity for ABPA diagnosis. The presence of IgE against rAsp f1 or rAsp f3 has demonstrated high sensitivity, while rAsp f4 and rAsp f6 showed high specificity for diagnosing ABPA in patients with asthma and CF.³⁹ The presence of IgE against rAsp (f1, f2, and f4) was considered specific for ABPA in two studies.^{56,57}

Table 1

Clinical classification of ABPA/ABPM

Stage	Definition	Findings
1	Acute ABPA	New diagnosis - Previously undiagnosed ABPA that meets diagnostic criteria. Exacerbation - In a patient with diagnosed ABPA: – Sustained clinical worsening (> 14 days); OR – Radiological deterioration; AND – Increase in total serum IgE by $\geq 50\%$ compared to the last recorded IgE value during clinical stability; AND – Exclusion of other causes of worsening. Asthma exacerbation - Worsening of respiratory symptoms for at least 48 hours without immunological or radiological deterioration of ABPA. Infectious exacerbation/bronchiectasis - Clinical deterioration for at least 48 hours with increased cough, dyspnea, sputum volume or consistency, sputum purulence, fatigue, malaise, fever, or hemoptysis, without immunological or radiological worsening of ABPA.
2	Responsive	Symptomatic improvement of at least 50% (on a Likert scale or visual analog scale) after 8 weeks; AND Significant radiological improvement (> 50% reduction in radiological opacities) or a $\geq 20\%$ decrease in total serum IgE after 8 weeks of treatment.
3	Remission	Clinical and radiological improvement for > 6 months without the use of systemic corticosteroids. No increase in total serum IgE $\geq 50\%$ compared to the last recorded IgE value during clinical stability. <i>Patients on long-term biologic agents or antifungal therapy may also be considered in remission if they meet the above criteria.</i>
4	Treatment-dependent ABPA	≥ 2 consecutive exacerbations within 3 months after discontinuation of systemic corticosteroids. Worsening of respiratory symptoms AND worsening in imaging findings or a 50% increase in total serum IgE within 4 weeks of stopping oral corticosteroids on two separate occasions.
5	Advanced ABPA	Extensive bronchiectasis (≥ 10 segments) on imaging due to ABPA. <i>Cor pulmonale</i> or chronic type 2 respiratory failure.

ABPA = allergic bronchopulmonary aspergillosis, ABPM = allergic bronchopulmonary mycosis.

Adapted from Agarwal R et al.⁴⁹

The European Academy of Allergy & Clinical Immunology ABPA Task Force proposed changes to the diagnostic algorithm, incorporating the research of recombinant allergens, while emphasizing the need for appropriate recommendations for countries with limited resources.⁵⁸ However, a Brazilian study found no advantages in using recombinant allergens (rAsp f1, rAsp f2, rAsp f3, rAsp f4, and rAsp f6) over conventional immunological tests, highlighting persistent challenges in ABPA diagnosis.⁵⁹

Skin testing for immediate hypersensitivity using *Aspergillus* extracts can assess immune response to fungal antigens, serving as an alternative to specific IgE testing.^{6,49,53}

The detection of specific IgG antibodies through serological tests, such as double immunodiffusion or enzyme immunoassay, is another key criterion for ABPA diagnosis. A study conducted in the Indian population proposed a specific IgG threshold for

Aspergillus of > 27 mgA/L.⁶⁰ However, this cutoff varies depending on assay methodology and population, with thresholds of > 60 mgA/L in Japan and > 40 mgA/L in the United Kingdom.^{61,62}

Peripheral blood eosinophilia is common in ABPA, but its presence alone is not sufficient to differentiate it from eosinophilic asthma or other eosinophilic lung diseases. An eosinophil count >500 cells/ μ L is considered an additional diagnostic marker for ABPA.^{6,49,53,55} Eosinophilia in sputum may also be observed; however, recent guidelines emphasize that sputum eosinophil count remains an unmet need in ABPA diagnostics.⁴⁹

Additionally, direct visualization of the fungus (using Gram or Grocott–Gömöri staining), as well as fungal culture can be performed on sputum, induced sputum, or bronchoalveolar lavage (BAL) samples. The presence of *Aspergillus spp.* in culture can support the diagnosis.⁴⁹

Table 2
Differential diagnoses of ABPA⁷¹

Diseases associated with bronchiectasis
– Asthma without ABPA – Cystic fibrosis without ABPA – Post-infectious (mycobacteria, pertussis, adenovirus) – Immunodeficiencies – Ciliary dyskinesia – Yellow nail syndrome – Tracheobronchomegaly (Mounier-Kuhn syndrome) – Collagen diseases (rheumatoid arthritis, Sjögren’s syndrome)
Diseases associated with eosinophilia
– Asthma without ABPA – Eosinophilic pneumonia – Drug hypersensitivity – Eosinophilic granulomatosis with polyangiitis (EGPA) – Hypersensitivity pneumonitis – Primary or secondary malignancy – Granulomatous lung disease – Parasitic infections (Löfﬂer’s syndrome)

ABPA = allergic bronchopulmonary aspergillosis.

Table 3
Evolution of ABPA diagnostic criteria

	ABPA diagnostic criteria	Advantages and disadvantages
Rosenberg-Patterson (1977)	Primary criteria 1. Asthma. 2. Peripheral eosinophilia. 3. Immediate skin hypersensitivity to <i>Aspergillus</i> antigens. 4. Presence of precipitins to <i>Aspergillus</i> antigens. 5. Elevated total serum IgE. 6. History of pulmonary infiltrates (transient or fixed). 7. Central bronchiectasis. Secondary criteria – <i>Aspergillus fumigatus</i> in sputum. – History of expectoration of brownish mucus plugs. – Delayed skin reactivity to <i>Aspergillus</i> antigens (Arthus reaction). Definitive ABPA diagnosis: Presence of all primary criteria.	Advantages: Facilitated diagnosis when the disease was largely unknown. Flexible and easy-to-use criteria. Disadvantages: Not applicable for ABPA-CF. Not applicable for patients with ABPM.
ISHAM criteria (2013)	Predisposing conditions – Asthma or CF. Mandatory criteria – Total serum IgE (> 1000 IU/mL).* – Specific IgE for <i>Aspergillus fumigatus</i> > 0.35 kUA/L or positive skin test. Additional criteria – Peripheral eosinophilia > 500 cells/μL.** – Positive precipitins or specific IgG for <i>Aspergillus</i>. – Bronchiectasis on CT scan. – Mucoid impaction on CT scan. Definitive ABPA diagnosis: At least two mandatory criteria and at least two additional criteria. * If all other criteria are met, total IgE < 1000 IU/mL is acceptable. ** Without systemic corticosteroid use.	Advantages: More clearly defined and objective criteria. Useful in both clinical and research settings. Allows diagnosis of ABPA even in the absence of bronchiectasis. Applicable to ABPA-CF. Disadvantages: Not applicable for patients with ABPM.

^a Or clinical-radiological presentation consistent with ABPA.
^b Total serum IgE < 500 IU/mL is acceptable if all other criteria are met.
^c In the absence of a population-specific cutoff, follow manufacturer recommendations.
^d High-attenuation mucus confirms ABPA even if other criteria are not met.
Specific IgE for rAsp f1, f2, and f4 confirms ABPA diagnosis and can be used as a diagnostic criterion.

ABPA = allergic bronchopulmonary aspergillosis; ABPA-CF = ABPA in cystic fibrosis; ABPM = allergic bronchopulmonary mycosis; CT = computed tomography; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease.
Adapted from Agarwal R et al.⁷⁵, Valle SOR et al.⁶⁷ and Agarwal R et al.⁴⁹.

Table 3 (continuation)

Evolution of ABPA diagnostic criteria

ABPA diagnostic criteria		Advantages and disadvantages
Modified ISHAM criteria (2021)	Predisposing condition – Asthma. Mandatory criteria – Total serum IgE > 500 IU/mL. – Specific IgE for <i>Aspergillus fumigatus</i> > 0.35 kUA/L or positive skin test. Additional criteria – Peripheral eosinophilia > 500 cells/μL. – Positive precipitins or IgG for <i>Aspergillus</i> > 27 mgA/L. – Bronchiectasis on CT scan. – Mucoid impaction on CT scan. Definitive ABPA diagnosis: At least two mandatory criteria and at least two additional criteria.	Advantages: Clearly defined and objective criteria. Useful in both clinical and research settings. Allows diagnosis of ABPA even in the absence of bronchiectasis. Disadvantages: Not applicable for ABPA-CF. Not applicable for patients with ABPM. Requires evaluation across different geographic regions.
Modified ISHAM criteria (2024)	Predisposing condition^a – Asthma, CF, COPD, or bronchiectasis. Mandatory criteria – Total serum IgE $\geq$ 500 UI/mL^b – Specific IgE for <i>Aspergillus fumigatus</i> $\geq$ 0.35 kUA/L or positive skin test. Additional criteria – Positive IgG for <i>Aspergillus fumigatus</i>^c – Peripheral eosinophilia > 500 cells/μL. – Chest CT with findings suggestive of ABPA (bronchiectasis, mucoid impaction, and high-attenuation mucus^d) or transient infiltrates on chest X-ray. Definitive ABPA diagnosis: At least two mandatory criteria and at least two additional criteria.	Advantages: More clearly defined and objective criteria. Useful in both clinical and research settings. Allows diagnosis of ABPA even in the absence of bronchiectasis. Applicable for diagnosing ABPA in various predisposing conditions. Considers regional differences. Disadvantages: Not applicable for patients with ABPM.

^a Or clinical-radiological presentation consistent with ABPA.^b Total serum IgE < 500 IU/mL is acceptable if all other criteria are met.^c In the absence of a population-specific cutoff, follow manufacturer recommendations.^d High-attenuation mucus confirms ABPA even if other criteria are not met.

Specific IgE for rAsp f1, f2, and f4 confirms ABPA diagnosis and can be used as a diagnostic criterion.

ABPA = allergic bronchopulmonary aspergillosis; ABPA-CF = ABPA in cystic fibrosis; ABPM = allergic bronchopulmonary mycosis; CT = computed tomography; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease.

Adapted from Agarwal R et al.⁷⁵, Valle SOR et al.⁶⁷ and Agarwal R et al.⁴⁹.

Molecular biology techniques, such as polymerase chain reaction (PCR) on different clinical samples (sputum, lung tissue), may be particularly useful in cases of ABPA with negative cultures or for early diagnosis.^{51,55}

The sensitivity of sputum cultures for detecting *Aspergillus* in ABPA is low, as is the accuracy of serum galactomannan antigen testing. However, in suspected cases of ABPM, current guidelines recommend performing fungal cultures on sputum samples collected before initiating treatment to characterize the fungal species and later assess treatment failure.⁴⁹

Radiological criteria

The characteristic radiological findings of ABPA may vary according to the disease stage and can help differentiate it from other pulmonary conditions.^{6,49,51,53} High-resolution computed tomography (HRCT) is the gold standard for detecting the broad spectrum of lung alterations associated with ABPA. One of the hallmark findings is the presence of recurrent and migratory pulmonary infiltrates, which may appear in different lung lobes and can be either unifocal or multifocal. Ground-glass opacities, defined as areas of increased lung attenuation without complete obscuration of blood vessels, are frequently observed and may indicate alveolar inflammation with or without eosinophilic and mucoid exudate. Bronchiectasis, characterized by permanent and irreversible bronchial dilation, is another key radiological feature of ABPA. In ABPA, bronchiectasis predominantly affects central airways, especially in the proximal segments of the upper and middle lobes.^{6,49,52,53}

High-attenuation mucus (HAM) in the bronchi, often associated with bronchial dilations resembling a “finger-in-glove” pattern, is another characteristic finding.⁵³ HAM is defined as mucus visually denser than paraspinal skeletal muscle and may be associated with the presence of calcium salts and metal ions (manganese or iron)⁶³ or dehydrated mucus.⁶⁴ Other common findings include bronchial wall thickening and parenchymal scarring, indicative of long-term inflammation and tissue damage.^{46,65}

Centrilobular nodules with a “tree-in-bud” pattern, suggestive of small airway inflammation and often associated with chronic inflammation, are frequently seen in ABPA.⁶⁶

The final stage of ABPA is characterized by fibrosis, which can be recognized by the presence of architectural distortion predominantly affecting

the upper lobes. Pulmonary fibrosis may appear on HRCT as traction bronchiectasis, honeycombing, and volume loss.^{65,66}

Early recognition and treatment of ABPA are crucial to prevent disease progression, including the development of bronchiectasis, pulmonary fibrosis, and advanced lung disease. In its initial stages, when only serological markers are present, ABPA is referred to as serologic ABPA. Unfortunately, ABPA is often diagnosed only after years of disease progression, when fibrosis and airway remodeling become evident. The diagnosis of ABPA is challenging for several reasons, such as⁶⁸:

- There is no single biomarker for diagnosing and monitoring the disease. Several criteria have been proposed based on clinical, immunological, and radiological parameters (Table 3).
- Some criteria are not specific to ABPA and may not always be present simultaneously.
- ABPA symptoms are characterized by periods of remission and exacerbation.
- The lack of standardization in allergens used for diagnosis affects the reproducibility of test results.
- Treatment of patients with asthma with corticosteroids and other anti-inflammatory medications may mask several diagnostic criteria.
- Other fungi can colonize the lower airways and induce a disease similar to ABPA, termed ABPM.

In this context, following a diagnostic flowchart is recommended to improve diagnostic accuracy (Figure 2).

Differential diagnoses

The differential diagnoses of ABPA include conditions associated with elevated peripheral blood eosinophil counts, recurrent pulmonary infiltrates, increased total serum IgE levels, or bronchiectasis.⁶⁹ In this context, the primary differential diagnoses are CF, pulmonary tuberculosis, sarcoidosis, infectious pneumonia, acute and chronic eosinophilic pneumonia, *Aspergillus*-induced asthma, eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss syndrome), bronchocentric granulomatosis, tropical pulmonary eosinophilia, and parasitic infections with pulmonary involvement (Löfller's syndrome).^{12,70} Table 2 lists the main differential diagnoses of ABPA related to the presence of bronchiectasis or eosinophilia.⁷¹

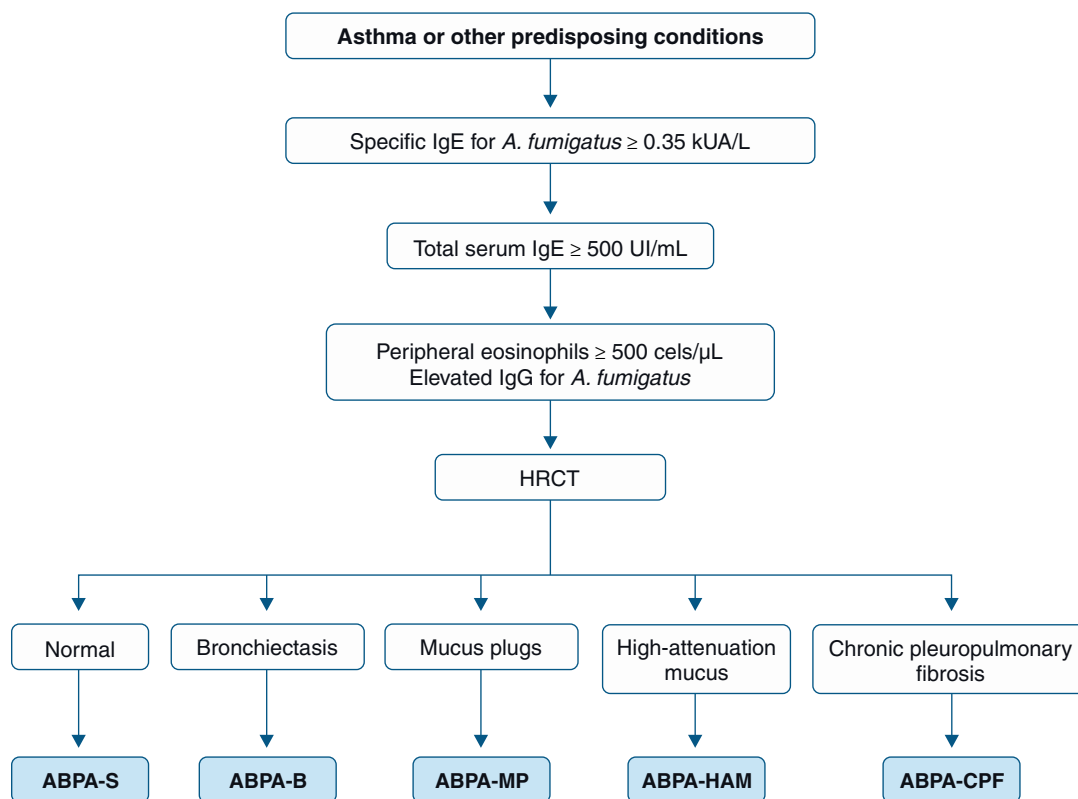
Due to the frequent involvement of the posterior segments of the upper lung lobes in ABPA and the high prevalence of tuberculosis in Brazil, ABPA cases are often misdiagnosed as tuberculosis.⁷²

EGPA typically presents with uncontrolled asthma associated with purpura (cutaneous vasculitis), commonly on the hands or legs, and, in some cases, with sensory or motor neuropathy. It may also manifest with pulmonary infiltrates, extravascular granulomas, small vessel vasculitis on lung biopsies, and peripheral blood eosinophilia.⁶⁹

Other pulmonary diseases caused by *Aspergillus* should also be considered in the differential diagnosis of ABPA, including⁷³:

- *Aspergillus*-induced asthma.
- Hypersensitivity pneumonitis.
- Aspergilloma.
- Chronic cavitary and fibrotic pulmonary aspergillosis.
- Acute and subacute invasive aspergillosis (chronic and necrotizing).

Among these, *Aspergillus*-induced asthma is particularly notable. This condition involves asthma with an IgE-mediated hypersensitivity reaction to *Aspergillus* antigens but without other ABPA manifestations, particularly without bronchiectasis, mucoid impaction, or specific IgG for the fungus.⁷³



ABPA = allergic bronchopulmonary aspergillosis; *A. fumigatus* = *Aspergillus fumigatus*; HRCT = high-resolution chest computed tomography; ABPA-S = ABPA with positive serology; ABPA-B = ABPA with bronchiectasis; ABPA-MP = ABPA with mucus plugs; ABPA-HAM = ABPA with high-attenuation mucus; ABPA-CPF = ABPA with chronic pleuropulmonary fibrosis.

Figure 2

ABPA diagnosis flowchart

Adapted from Agarwal R et al.⁴⁹

Aspergillus sensitization may also occur in severe fungal asthma, which affects a subgroup of asthmatic patients sensitized to *Aspergillus* or other fungal antigens. These patients experience frequent exacerbations requiring recurrent hospitalizations. Diagnostic criteria for severe fungal asthma include⁷³:

- Severe (or poorly controlled) asthma.
- Positive skin tests for fungi or elevated specific IgE ≥ 0.4 kU/L.

Treatment

The goals of ABPA treatment are to prevent permanent lung damage, improve prognosis, and enhance the patient's quality of life.⁷⁴ Treatment varies according to disease stage and involves systemic corticosteroids, antifungal therapy, biologic agents, and respiratory physiotherapy tailored to individual patient needs (Table 4). In patients with asthma or CF, management should also include treatment of the underlying disease. Inhaled corticosteroids and bronchodilators should be maintained and/or optimized in patients with asthma.

Systemic corticosteroids

Oral corticosteroids are the first-line treatment for ABPA.^{49,50} However, several treatment regimens exist, differing in dosage and duration.⁷⁵ The most commonly used regimen starts with a daily dose of 0.5 mg/kg of prednisolone for 14 days, followed by 0.5 mg/kg/day on alternate days for 8 weeks, with a subsequent taper of 5 mg every 2 weeks until completing 3 to 5 months of treatment.⁵

Although disease remission is achieved in most cases treated with systemic corticosteroids, relapse occurs in a significant proportion of patients (13.5% to 45%), and some may become corticosteroid-dependent.^{6,50}

Pulse corticosteroid therapy may be used as an alternative to oral administration. Methylprednisolone at 15 mg/kg/day (not exceeding 1 g) for 3 days has been used in children to minimize the side effects of daily corticosteroid therapy⁷⁶ and in cases of exacerbations refractory to oral treatment.⁷⁷

Antifungal therapy

Antifungal agents reduce fungal load in the airways, decrease antigenic stimulation, and mitigate

the inflammatory response, potentially reducing the need for systemic corticosteroids. The use of azole antifungals, either alone or in combination with corticosteroids, is an option for ABPA treatment.⁷⁸ Azoles such as itraconazole are typically prescribed at a dose of 200 mg twice daily for 16 weeks.⁷⁵ The combination of itraconazole with prednisolone results in a greater reduction in exacerbation rates over 1 year compared to monotherapy with either agent.⁷⁸

Other azoles, including voriconazole, posaconazole, and isavuconazole, have also demonstrated efficacy in treating ABPA, particularly in cases of intolerance or resistance to itraconazole.^{49,79} However, drug interactions, hepatotoxicity, and variable bioavailability can limit their use.⁸⁰

The efficacy of nebulized amphotericin B for treating ABPA exacerbations appears to be limited and should only be considered when other therapeutic options have been exhausted.^{49,81}

Biologic therapy

Post-treatment recurrences are common, regardless of whether corticosteroids, antifungal therapy, or a combination of both is used. In addition, prolonged treatment can lead to adverse effects, underscoring the need for new, safe, and effective therapeutic strategies. Given ABPA pathogenesis, biologic agents developed for severe asthma targeting T2 inflammation are considered potential treatment alternatives for ABPA.⁸² Although evidence remains limited, recent case reports and series have demonstrated their efficacy.⁸²⁻⁸⁵

The monoclonal anti-IgE antibody omalizumab has shown promise in reducing corticosteroid use, improving lung function, and preventing exacerbations.⁸⁴ It is administered subcutaneously every 2–4 weeks, with the dosage determined based on patient weight and total serum IgE levels.⁸⁴ However, due to the high IgE levels observed in ABPA, the doses used may be suboptimal.

The two biologics targeting IL-5, mepolizumab and reslizumab, along with the anti-IL-5R α monoclonal antibody (MAB) benralizumab, have demonstrated efficacy in treating eosinophilic lung diseases, including ABPA. These anti-IL-5/IL-5R α MABs have been successful in reducing exacerbation frequency, minimizing oral corticosteroid requirements, and improving lung function, even in patients unresponsive to omalizumab.⁸²

Table 4

Medications used in the treatment of ABPA

Medication		Indication
Oral corticosteroids^a	– Prednisolone: 0.5 mg/kg/day for 14 days, followed by 0.5 mg/kg/day on alternate days for 8 weeks, then taper by 5 mg every 2 weeks until completing 3 to 5 months. OR – Prednisolone: 0.5, 0.25, and 0.125 mg/kg/day for 4 weeks each, then taper by 4 mg/week until completing 4 months. OR – Deflazacort: 0.75 mg/kg/day for 4 weeks, reduce by half every 4 weeks for the next 2 months, then taper gradually by 6 mg every 2 weeks until discontinuation at 4 months.	– Acute or exacerbated ABPA.
Intravenous corticosteroids	– Methylprednisolone: 15 mg/kg/day (max 1 g) intravenously for 3 consecutive days	– To minimize side effects of daily corticosteroid use.
Antifungal therapy	Oral antifungals^b: – Itraconazole 200 mg twice daily for 16 weeks. OR – Voriconazole 200 mg twice daily for at least 24 weeks. Nebulized antifungals^c: – Liposomal Amphotericin B 25–50 mg once or twice per week. – Deoxycholate Amphotericin B 10 mg twice daily 3–6 times per week	– Acute or exacerbated ABPA.
Biologic therapy^d	– Omalizumab: 150 mg, approved for patients ≥ 6 years, administered SC. Dose and frequency depend on weight and total IgE levels. Max IgE level: 1500 UI/mL. OR – Mepolizumab: 40 mg or 100 mg, approved for patients ≥ 6 years. For children (6–11 years): 40 mg SC every 4 weeks and for patients ≥ 12 years: 100 mg SC every 4 weeks. OR – Benralizumab: 30 mg, approved for patients ≥ 12 years, administered SC every 4 weeks for the first 3 doses, then every 8 weeks. OR – Dupilumab: 200 mg or 300 mg, approved for patients ≥ 6 years, administered SC every 2 weeks. For children (6–11 years): dose and frequency depend on weight. For patients ≥ 12 years: 300 mg for corticosteroid-dependent severe asthma. OR – Tezepelumab: 210 mg, approved for patients ≥ 12 years, administered SC every 4 weeks.	– Treatment-dependent ABPA. – Adverse events of contraindication to the use of corticosteroids or antifungals.

^a First-line treatment. For the first exacerbation, corticosteroids can be used alone, while subsequent exacerbations may require combination therapy with azoles.

^b Itraconazole can be used alone in patients with contraindications to corticosteroids. Combining it with prednisolone may reduce the risk of exacerbation.

^c Nebulized Amphotericin B may be considered when systemic corticosteroids and/or azoles are required.

^d Clinical studies are needed to clarify the role of biologics in ABPA treatment.

Dupilumab, an anti-IL-4R α MAB, has shown beneficial therapeutic effects on symptoms and lung function in ABPA.^{83,86} Some patients with ABPA refractory to omalizumab or mepolizumab have responded favorably to dupilumab.^{83,87}

Tezepelumab, a human IgG2 MAB targeting TSLP, has proven effective in improving asthma control.⁸⁸ A recent case report described a patient using tezepelumab who experienced symptom improvement, reduced mucus plugs, and resolution of pulmonary opacities associated with ABPA.⁸⁵

Respiratory physiotherapy techniques and positive expiratory pressure devices can benefit patients with ABPA, especially those with CF.⁸⁰ These techniques help remove mucus plugs, improve lung function, and reduce the risk of recurrent infections.

The treatment of ABPA in CF is largely similar to that in asthma. However, patients with CF often experience concomitant malabsorption, making treatment more complex. Oral medications, particularly itraconazole capsules, may have reduced absorption.⁸⁰

Remission is defined as the absence of asthma and ABPA exacerbations, no dependence on systemic corticosteroids, and optimal lung function. This goal can be achieved through a combination of corticosteroids, antifungals, and biologic agents.⁴⁹

Figure 3 presents the currently recommended treatment algorithm for ABPA.⁴⁹

Treatment monitoring

Treatment response should be monitored using clinical parameters, chest radiography, and total serum IgE measurements every 8 weeks. A successful response is indicated by the resolution of radiographic opacities and a minimum 25% reduction in total serum IgE levels, establishing a new baseline. Clinical and/or radiological worsening, along with a 50% increase in IgE levels, suggests an exacerbation.⁸⁰ For patients receiving omalizumab, monitoring total IgE levels is unreliable, as IgE concentrations increase during therapy.

ABPA and CF

CF is an autosomal recessive genetic disorder characterized by reduced or absent function of the CFTR protein. CF affects approximately 89,000 individuals worldwide, including more than 6,000 Brazilians registered in the Brazilian CF Registry (REBRAFC).⁸⁹

The CFTR protein is located in the apical portion of the cell membrane and functions as an ion channel that facilitates chloride ion transport into the epithelial lumen. The dysregulation of CFTR-mediated ion transport results in depletion of the periciliary liquid layer and hyperconcentration of mucin. This severely impairs ciliary movement and mucus clearance, resulting in secretion buildup and recurrent infections. Over time, these infections damage the epithelium and airway structures, particularly the bronchi and bronchioles. This process leads to the formation of sac-like dilations (bronchiectasis) and initiates a vicious cycle of mucus accumulation, infections, structural damage, pulmonary function decline, and disease progression.⁹⁰

CF-related respiratory symptoms include chronic productive cough, recurrent infections (*Staphylococcus aureus*, non-encapsulated *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*), airway obstruction symptoms, recurrent sinusitis and otitis, and digital clubbing. Radiological findings commonly include small airway disease, bronchiectasis, and sinusitis. Infection and colonization by *P. aeruginosa* are typically associated with more rapid disease progression.⁹⁰

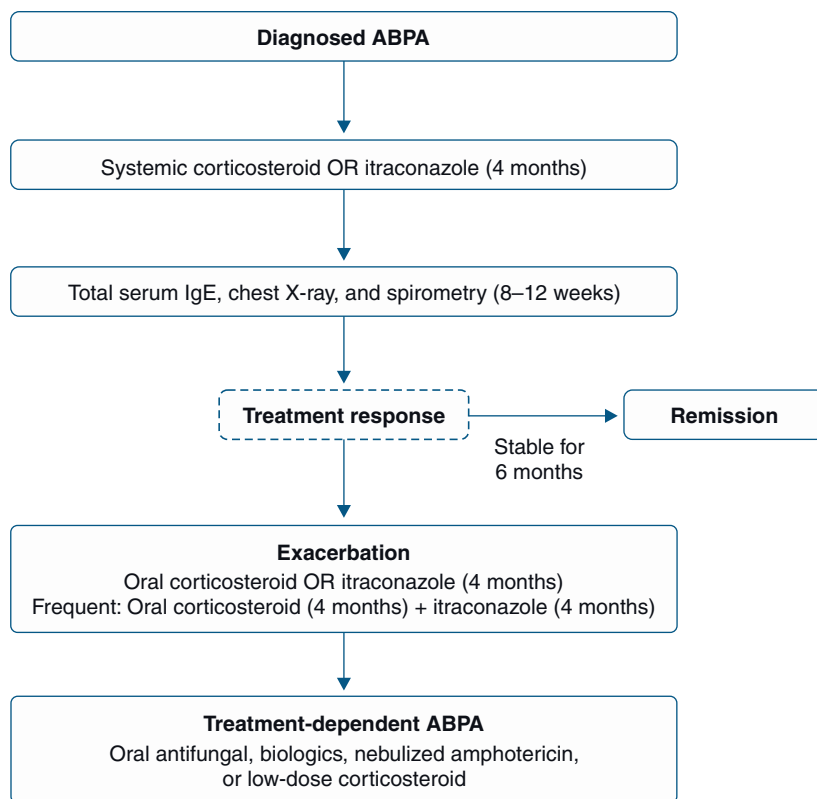
Due to the altered airway physiology in CF, fungal species are frequently found in sputum samples, with *A. fumigatus* being the most common. However, unlike *P. aeruginosa* colonization, the impact of *A. fumigatus* on CF disease progression remains uncertain. In some cases, inhaled *A. fumigatus* conidia may colonize the respiratory tract, leading to ABPA, which significantly increases morbidity, accelerates lung function decline, and worsens bronchiectasis and pulmonary fibrosis.⁹⁰

Diagnosis of ABPA in patients with CF

The diagnostic criteria for ABPA in patients with CF, as proposed by the CF Foundation Consensus Conference (CFFCC) in 2003,^{91,92} are similar to the 2024 ISHAM criteria⁴⁹ (Table 5). Fungal colonization, especially of *A. fumigatus*, in sputum is common and does not necessarily indicate disease unless clinical deterioration occurs, in which case the criteria in Table 3 should be applied.

CFFCC recommendations include^{91,92}:

- Screening for ABPA in patients with CF aged > 6 years old with clinical deterioration.
- Measure total serum IgE annually:



ABPA = allergic bronchopulmonary aspergillosis.

Figure 3

ABPA treatment flowchart

Adapted from Agarwal R et al.⁴⁹.

- If IgE > 500 IU/mL – Test for specific IgE against *A. fumigatus* or perform skin test for immediate hypersensitivity. If positive, consider ABPA and conduct further diagnostic testing (specific IgG for *A. fumigatus* or serum precipitins, chest CT).
- If IgE between 200 and 500 IU/mL – Repeat testing. If levels increase, conduct additional diagnostic tests (specific IgE or skin test, specific IgG for *A. fumigatus* or serum precipitins, chest CT).

Treatment of ABPA in patients with CF

The treatment suggested by the Brazilian Guidelines for the Diagnosis and Treatment of Cystic Fibrosis follows a structured approach, although

the level of evidence is considered low.⁹³ The treatment strategy aligns with the recommendations in Table 4⁹³:

- *Prednisone*: 0.5–2.0 mg/kg/day (max 60 mg/day) for 1–2 weeks, followed by gradual tapering to alternate-day dosing, with withdrawal over 2–3 months.
- *Itraconazole*: 5 mg/kg/day (max 400 mg/day), administered every 12 hours if the dose exceeds 200 mg, for 3–6 months; alternatively, *Voriconazole*: 4 mg/kg every 12 hours (max 400 mg/day) for 3–6 months.

Alternative/adjunctive treatments include pulse corticosteroid therapy, biologic agents, and inhaled amphotericin B.⁹³

The role of CFTR modulators in ABPA treatment remains unclear, as does their interaction with antifungal therapies.⁹⁴

A recent retrospective study of 65 patients with CF treated for ABPA found that a regimen of decreasing doses of prednisone over 18 days combined with itraconazole for 1 year (with serum monitoring) successfully prevented lung function decline associated with ABPA, without corticosteroid-related adverse effects.⁹⁵

Allergic Bronchopulmonary Mycosis (ABPM)

ABPA was the first ABPM described and remains the most commonly reported in the literature. However, several other airborne fungi have been identified as capable of inducing chronic inflammatory responses

in the lungs, causing cough, dyspnea, and excessive mucus production. Due to the overlapping antigenic repertoire among *Aspergillus* species, the term ABPA is recommended when any *Aspergillus spp.* (not just *A. fumigatus*) is involved. The broader term ABPM is used when other fungal species are responsible for the disease.

Although detailed information on ABPM remains limited, it is known that if left undiagnosed and untreated, the condition can lead to bronchiectasis, lung function decline, and pulmonary fibrosis.⁹⁶

The prevalence of ABPM is increasing in several regions, particularly in countries with hot and humid climates such as Brazil, India, Australia, and parts of Europe.⁷³ Similar to ABPA, ABPM primarily affects young and middle-aged adults with asthma, CF, or

Table 5
Criteria for diagnosing ABPA in patients with cystic fibrosis

CFFCC diagnostic criteria ^{91,92}
– Diagnosed CF with acute or subacute deterioration. – Total serum IgE > 1000 IU/mL (unless the patient is on systemic corticosteroids). – Positive specific IgE or positive skin prick test for <i>A. fumigatus</i>. – Positive precipitins or serum IgG for <i>A. fumigatus</i>. – New or recent infiltrates on chest X-ray or CT that do not respond to antibiotics and conventional physiotherapy.
2024 ISHAM diagnostic criteria ⁴⁹
– Diagnosed CF. Mandatory criteria - Both criteria must be present: – Total serum IgE > 500 IU/mL.^a – Specific IgE for <i>Aspergillus fumigatus</i> > 0.35 kUA/L or positive skin test. Additional criteria - At least two of the following must be present: – Peripheral eosinophilia > 500 cells/μL.^b – Elevated specific IgG for <i>A. fumigatus</i>.^c – Chest CT findings suggestive of ABPA (bronchiectasis, mucoid impaction, or high-attenuation mucus) or transient infiltrates on chest X-ray.
^a If all other criteria are met, total IgE < 500 IU/mL is acceptable. ^b Without systemic corticosteroid use. ^c In the absence of a population-specific cutoff, follow manufacturer recommendations.

ABPA = allergic bronchopulmonary aspergillosis; CF = cystic fibrosis; CT = computed tomography.
CFFCC = Cystic Fibrosis Foundation Consensus Conference. ISHAM = International Society for Human and Animal Mycology.

other underlying lung disease, with no significant sex preference. Since these fungi are airborne, their growth and distribution depend on local environmental conditions, leading to regional variations in ABPM incidence.⁵⁵

Causative agents

Several fungi in addition to *A. fumigatus* are known to cause ABPM (Table 6). *Candida albicans* is the most frequently identified non-*Aspergillus* agent, but other fungi can colonize the respiratory tract, proliferate, trigger immune-mediated inflammation, and promote airway damage.⁹⁶

Disease mechanisms

The pathogenesis of ABPM is essentially the same as ABPA, involving genetic factors, host-pathogen interactions, and innate and adaptive immune responses. Genetic variants contribute to ABPM susceptibility.²⁶⁻³¹ Fungi colonize the airways in susceptible individuals, triggering a T2 inflammatory response, type I and III hypersensitivity reactions, eosinophilia, and mucus hypersecretion.³⁴⁻⁴⁴ This inflammatory process is exacerbated by factors such as mucociliary clearance impairment and fungal protein secretion, which perpetuate damage to the respiratory epithelium.

The resulting inflammatory process leads to the destruction of the bronchial walls, resulting in the development of bronchiectasis, a hallmark feature of ABPM. The local anatomical changes caused by bronchiectasis predispose patients to recurrent infections, persistent inflammation, progressive lung damage, and fibrosis.⁹⁷

Clinical presentation

Allergic fungal diseases present a heterogeneous spectrum of symptoms and clinical manifestations.⁹⁸ Clinical characteristics of ABPM are similar to those of uncontrolled asthma. Patients typically experience cough, dyspnea, and expectoration of mucus plugs. Other nonspecific symptoms include fever, malaise, chest pain, and hemoptysis. A detailed medical history may reveal the chronic nature of symptoms and a history of radiological tests showing images consistent with past pneumonia. Studies have shown an association between ABPM and asthma (32% of cases) as well as other allergic conditions, such as rhinosinusitis, atopic dermatitis, and urticaria (41%).⁹⁶

Physical examination is often normal, although auscultation of the lungs may reveal coarse crackles during periods of acute exacerbation or in patients with fibrosis, and digital clubbing may be present in some cases.

Imaging studies may reveal atelectasis due to mucus plugging and bronchiectasis. Laboratory investigations often provide crucial diagnostic information.^{96,97}

The new clinical classification for ABPA/ABPM describes five clinical stages: acute ABPA, response to therapy, remission, treatment-dependent ABPA, and advanced ABPA (Table 1).

Laboratory investigation

After a thorough evaluation of the patient's clinical history, laboratory and imaging tests may play a decisive role in confirming ABPM.

The laboratory assessment of ABPM follows the same approach as ABPA and includes total IgE and specific IgE for fungi, specific IgG or serum precipitins for fungi, and HRCT. In addition, fungal culture from sputum or BAL may be helpful in identifying the causative fungus.^{96,97}

Diagnosis

Accurate diagnosis of ABPM is as challenging as ABPA. Given the variability in clinical presentation, antifungal treatment response, and disease prognosis depending on the causative agent, accurate identification of the fungus (not *Aspergillus*) is crucial for optimal management.⁹⁹ The presence of specific IgE for certain allergenic components confirms sensitization and can help identify the causative fungus. However, cross-reactivity with crude fungal extracts makes the accuracy of the etiological diagnosis more difficult.⁹⁹ Repeated microbiological isolation from respiratory samples is another important resource, but obtaining high-quality biological specimens remains a challenge.¹⁰⁰

Tests assessing cellular immune response, such as basophil and lymphocyte activation tests, have been studied and are considered a promising alternative to currently used diagnostic tests for ABPM in patients with underlying lung disease.¹⁰¹

The identification of new biomarkers for ABPM is of great interest, particularly since traditional clinical diagnostic criteria are more specific for ABPA,¹⁰² and molecular fungal diagnostics are only available for *A. fumigatus*.¹⁰⁰

Table 6
Fungi recognized as causative agents of ABPM

Causative agents of allergic bronchopulmonary mycosis
<i>Candida albicans</i> ^a
<i>Bipolaris spp.</i> ^a
<i>Schizophyllum commune</i> ^a
<i>Curvularia spp.</i> ^a
<i>Alternaria alternata</i>
<i>Cladosporium spp.</i>
<i>Penicillium spp.</i>
<i>Fusarium vasinfectum spp.</i>
<i>Mucor spp.</i>
<i>Rhizopus spp.</i>
<i>Trichosporon spp.</i>
<i>Saccharomyces cerevisiae</i>
<i>Bipolaris spp.</i>
<i>Pseudallescheria boydii</i>
<i>Stemphylium spp.</i>
<i>Paecilomyces spp.</i>
<i>Geotrichum spp.</i>

ABPM = allergic bronchopulmonary mycosis.
^a More frequently described causative agents.⁴⁹

A study published in 2021 demonstrated improved sensitivity and specificity using new diagnostic criteria for ABPM compared with conventional methods.⁵⁵ These criteria were recently revised in 2024⁴⁹ and are summarized in Table 7.

Treatment

The treatment principles for ABPM are similar to those for ABPA, with the difference being that identifying the causative fungus can help guide the choice of antifungal therapy.⁴⁹

The goals of ABPM treatment are:

- Inflammation control.
- Eradication of fungal colonization from the airways.
- Removal of bronchial mucus plugs.
- Identification and elimination of the causative agent from the patient’s environment.

Systemic corticosteroids remain the cornerstone of ABPM treatment but may be less effective in preventing exacerbations and lung function decline, similar to ABPA. The recommended dosage is 0.5 mg/kg for the first 2 weeks, followed by a gradual taper over 3 months, with complete withdrawal if the patient remains stable without complications. The treatment goal is to reduce total IgE levels by 35% to 50% within 6 to 8 months and achieve complete resolution of pulmonary infiltrates.

Antifungal therapy may be necessary to eradicate fungal colonization from the airways. The choice of antifungal agent and treatment duration depend on effectiveness and availability.

Mucus impaction can be relieved via bronchoscopy.⁹⁶

For patients with asthma, chronic obstructive pulmonary disease (DPOC), or CF, management should also include treatment of the underlying

Table 7
Evolution of ABPM diagnostic criteria

Criteria for allergic bronchopulmonary mycosis
Criteria (2021) 1. Current or past history of asthma or asthma-like symptoms. 2. Peripheral blood eosinophilia (≥ 500 cells/μL). 3. Elevated total serum IgE (≥ 417 IU/mL). 4. Positive skin test or specific IgE > 0.35 kUA/L for filamentous fungi. 5. Presence of precipitins or specific IgG for filamentous fungi. 6. Growth of filamentous fungi in sputum or bronchoalveolar lavage. 7. Presence of fungal hyphae in mucus plugs. 8. Central bronchiectasis on CT. 9. Presence of mucus plugs on CT, bronchoscopy, or history of mucus plug expectoration. 10. High-attenuation mucus on CT. Definitive ABPM diagnosis: At least 6 criteria present. Probable ABPM diagnosis: At least 5 of the 10 criteria.
Criteria (2024) Predisposing condition^a – Asthma, CF, COPD, bronchiectasis, or clinical-radiological presentation consistent with ABPM. Mandatory criteria – Specific IgE or positive skin test for the fungus. – Total serum IgE > 500 UI/mL.^b Additional criteria – Specific IgG or positive precipitins for the fungus.^c – Peripheral eosinophilia > 500 cells/μL (previous test result acceptable). – Two sputum cultures or one bronchoalveolar lavage with a positive fungal culture. – Chest CT showing findings suggestive of ABPA (bronchiectasis, mucoid impaction, or high-attenuation mucus^d) or transient infiltrates on chest X-ray. Definitive ABPM diagnosis: At least two mandatory criteria and at least two additional criteria.
^a Mucus plug expectoration, finger-in-glove sign, transient infiltrates on radiography, pulmonary collapse, among others. ^b Total serum IgE < 500 IU/mL is acceptable if all other criteria are met. ^c IgG cutoff values should be established for each population. If unavailable, follow manufacturer recommendations. ^d High-attenuation mucus is pathognomonic for allergic bronchopulmonary fungal disease and confirms the diagnosis even if other criteria are not met. The absence of specific IgE for rAsp f1, f2, and f4 excludes ABPA and supports an ABPM diagnosis.

ABPM = allergic bronchopulmonary mycosis; ABPA = allergic bronchopulmonary aspergillosis; *A. fumigatus* = *Aspergillus fumigatus*, rAsp = recombinant *A. fumigatus*; COPD = chronic obstructive pulmonary disease.

disease. Inhaled corticosteroids and bronchodilators should be maintained and/or optimized in patients with asthma and in some cases of DPOC.

Biologic therapy, particularly omalizumab and anti-IL-5 agents, appears promising in ABPM treatment, as demonstrated in recent studies.⁴⁹

Broad-spectrum antibiotics may be necessary in cases of pulmonary infection, especially in patients with bronchiectasis or underlying lung diseases.

Additionally, complementary therapeutic measures, such as pulmonary rehabilitation and physiotherapy, should be part of the treatment plan for patients with ABPM.⁹⁷

Conclusion

ABPA occurs in genetically predisposed individuals, primarily those with asthma or CF, although its exact prevalence remains unknown. The diagnostic criteria involve clinical, serological, and radiological parameters, which have evolved since the disease was first described. However, widespread awareness of these criteria remains limited, contributing to underdiagnosis. Moreover, ABPA can mimic common pulmonary diseases such as tuberculosis. Regarding treatment, multiple therapeutic protocols have been proposed, with oral corticosteroids as the first-line therapy, either alone or in combination with azole antifungals. Biologic agents targeting T2 inflammation have shown benefits in some cases. Further research is needed to establish diagnostic criteria for different populations, as well as clinical trials of targeted therapeutic agents for patients with ABPM.

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No conflicts of interest declared concerning the publication of this article.

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Management of perioperative anaphylaxis from the anesthesiologist perspective

Manejo da anafilaxia perioperatória sob a visão dos anestesiológicos

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ABSTRACT

Perioperative anaphylaxis is a severe systemic reaction that can occur at any point during the surgical procedure, typically minutes after induction of anesthesia, and can also be caused by agents administered via other routes (such as chlorhexidine, latex, and methylene blue). Global epidemiology suggests an increase in the incidence of drug-induced anaphylaxis, highlighting the need for improved diagnosis and management of this condition. This study aims to describe anesthesiologists' knowledge of perioperative anaphylaxis management. This is a descriptive, exploratory, quantitative study conducted from May to October 2023. Data were collected through an online questionnaire aimed at assessing anesthesiologists' knowledge of triggering agents, risk factors, clinical manifestations, diagnosis, treatment, and prevention of perioperative anaphylaxis. The questionnaire was developed based on a review of the literature on the topic. The study included 29 anesthesiologists. Although anesthesiologists were aware of certain etiologic agents involved in anaphylaxis, 10.3% of them did not mention neuromuscular blockers, and only 48.3% considered chlorhexidine an option. Only 27.6% and 6.9% identified female sex and beta-blocker use as significant risk factors. Hypotension was reported as the main clinical manifestation by 93.7% of participants. The use of epinephrine for treatment was reported by 89.7%, and despite the lack of convincing evidence, 48.3% of anesthesiologists recommended the use of corticosteroids. No significant difference in scores was found between those who graduated in anesthesiology more than 5 years ago and those who graduated less than 5 years ago, nor in relation to age, first contact with the topic, or years of experience as a specialist. No significant differences were found in scores related to the variables of interest. Many participants had deficient knowledge of perioperative anaphylaxis, posing a potential risk to patients.

Keywords: Anaphylaxis, hypersensitivity, anesthesia, intraoperative complications, perioperative period.

RESUMO

A anafilaxia perioperatória é uma reação sistêmica grave que pode ocorrer em qualquer período durante as etapas cirúrgicas, geralmente minutos após a indução anestésica, podendo ocorrer também com agentes administrados por outras vias (como clorexidina, látex e azul de metileno). A epidemiologia global sugere um aumento na incidência da anafilaxia induzida por drogas, destacando a necessidade de melhoria no diagnóstico e manejo de tal condição. O objetivo deste artigo é descrever o conhecimento sobre o manejo da anafilaxia perioperatória pelos anestesiológicos. Trata-se de um estudo descritivo, exploratório, quantitativo, realizado de maio a outubro de 2023. Os dados foram coletados via questionário online e visou avaliar o conhecimento dos anestesiológicos sobre agentes desencadeantes, fatores de risco, manifestações clínicas, diagnóstico, tratamento e prevenção da anafilaxia perioperatória. O questionário foi construído após revisão da literatura sobre as principais informações acerca do tema. Participaram da pesquisa 29 anestesiológicos. Apesar de haver conhecimento acerca de determinados agentes etiológicos envolvidos na anafilaxia, 10,3% dos anestesiológicos não assinalou os bloqueadores neuromusculares e apenas 48,3% considerou a clorexidina como opção. Apenas 27,6% e 6,9% indicou o sexo feminino e o uso de medicamentos betabloqueadores como fatores de risco relevantes. A hipotensão foi descrita como principal manifestação clínica por 93,7% dos participantes. O uso de adrenalina no tratamento foi afirmado por 89,7% e, apesar de não haver evidências convincentes, 48,3% dos médicos indicou o uso de corticoide. Não houve diferença significativa de pontuação entre formados em anesthesiologia há mais de 5 anos e formados há menos de 5 anos, nem em relação à idade, primeiro contato com o tema ou tempo de atuação como especialista. Não foram encontradas diferenças significativas nas pontuações relativas às variáveis avaliadas. Muitos participantes apresentaram déficits no conhecimento sobre anafilaxia perioperatória, representando um risco potencial para os pacientes.

Descritores: Anafilaxia, hipersensibilidade, anestesia, complicações intraoperatórias, período perioperatório.

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Submitted Apr 21 2024, accepted Nov 02 2024.

Arq Asma Alerg Imunol. 2024;8(3):213-24.

Introduction

The safety of anesthetic procedures has increased significantly in recent decades, but they are still considered high-risk. This is due to the fact that several medications are administered simultaneously or near-simultaneously over a short period of time. Among potential anesthesia-related complications, immediate hypersensitivity reactions to drugs—which may or may not be allergic in nature—stand out. When such reactions are severe and occur during the perioperative period, they are known as intraoperative or perioperative anaphylaxis.¹

Perioperative anaphylaxis is a rare hypersensitivity reaction that may occur at any time during the patient's surgical experience, most commonly within minutes of intravenous administration of an anesthetic agent, but also to agents administered by other routes (such as chlorhexidine, latex, and methylene blue) due to absorption through the skin, mucosa, or tourniquet removal.²⁻⁴

These reactions pose a diagnostic and clinical challenge, due to their wide range of clinical manifestations and the multiple underlying mechanisms involved. This is compounded by the technical limitations of the perioperative environment, which amplify the complexity of diagnosis. The capacity for objective assessment to identify hypersensitivity reactions is also greatly restricted in the anesthetized patient.^{5,6}

Epidemiological data suggest an increase in the global incidence of drug-induced anaphylaxis, which highlights the urgency of improving allergy reporting systems. The incidence of anaphylaxis is estimated to range from 1 in 386 to 1 in 13,000 anesthetic procedures³, which translates into 1 case for every 7 years of professional activity over an anesthesiologist's career; mortality rates vary between approximately 3% and 10%. This wide variation in incidence rates is mainly attributable to a lack of uniform clinical and diagnostic criteria, as well as to the diversity of studied populations.^{3,6-8}

Due to the low incidence of perioperative anaphylaxis, this serious condition is often unexpected by anesthesiologists and is sometimes neglected by those who fail to identify it and to provide immediate, appropriate treatment—which explains its high mortality rate. In addition to the difficulty in recognizing this condition, a lack of hospital protocols to guide the approach to perioperative anaphylaxis makes the extremely complex management of this disorder even more challenging.⁹

Analysis of anesthesiologists' knowledge about perioperative anaphylaxis can provide important inputs to inform the scientific community regarding how this condition is diagnosed and managed in practice. Furthermore, it encourages an early approach to anaphylaxis.

Given the complexity of clinical diagnosis of perioperative anaphylaxis, compounded by the absence of protocols to assist anesthesiologists in managing this complication, the objective of this study is to describe the knowledge of anesthesiologists working in private and public settings regarding the diagnosis and management of patients with perioperative anaphylaxis.

Methods

This is a descriptive, exploratory, quantitative study, carried out entirely in a virtual environment, from May through October 2023. Data were collected with a questionnaire (Appendix 1) posted on the Google Forms platform and designed to assess anesthesiologists' knowledge about perioperative anaphylaxis. The questionnaire was constructed after a literature review of core information on the topic.

The sample of interest consisted of anesthesiologists working in the state of Sergipe, Brazil. Contact with prospective participants was established through the Sergipe Anesthesiologists Cooperative (Coopanest-SE), which maintains a registry of and information on all anesthesiologists practicing in the state. Participants showed interest in taking part in the study by signing an Informed Consent Form (ICF).

Approval was obtained from the Universidade Federal de Sergipe Research Ethics Committee (Certificate of Submission for Ethical Appraisal: 66854822.2.0000.0217) before any study procedures were performed. The study was conducted in accordance with the guidelines of Brazilian National Health Council Resolution No. 466/12. Only those prospective participants who had signed an ICF were allowed to take part. To ensure anonymity, neither the form nor the database contained any nominally identifying information. Strict confidentiality was also preserved regarding the information acquired, and respondents were free to choose to refuse to participate in the study if they felt uncomfortable in any way.

The Google Forms survey link was divided into sections. The first section consisted of the ICF, presented with the options “I agree” (which allowed respondents to proceed to the survey) and “I do not agree” (which terminated their participation). The subsequent sections presented the questionnaire itself (Appendix 1), with the second section consisting of seven questions to characterize the sample while the third and fourth sections addressed the pathophysiology, clinical presentation, and management of perioperative anaphylaxis.

The third section consisted of three questions. Question 1 listed 10 agents potentially related to perioperative anaphylaxis. Question 2 listed 15 risk factors potentially related to this condition. Question 3 listed 15 potential clinical manifestations of perioperative anaphylaxis. In this third section, participants were asked to select the items that they believed to be associated with perioperative anaphylaxis; they were required to select at least 1 item in each question. The fourth section of the questionnaire presented 8 multiple-choice questions about the diagnosis, treatment, and prevention of perioperative anaphylaxis.

The level of knowledge of the respondents was calculated based on their scores for the last two sections. The third section score ranged from 3 to 40 points, while the fourth section score ranged from 0 to 80 points. Final assessment of the level of knowledge was based on the sum score for sections three and four, with a minimum of 3 points and a maximum of 120 points.

Collected data were tabulated in Microsoft Excel (version 16.3) and analyzed in Jamovi (version 2.3). Absolute (n) and relative (%) frequency measures were generated and the Shapiro-Wilk test was used to verify the normality of distribution of the variables of interest. Spearman's correlation test was used for quantitative variables with a non-normal distribution.

Comparison of knowledge scores in relation to seniority (time since completion of training) was performed using the Mann-Whitney test after dividing the sample into two groups (> 5 years or < 5 years since graduation). The Kruskal–Wallis test was used to analyze the timing of first contact with the topic of perioperative anaphylaxis.

Results

Invitations were sent to the 261 anesthesiologists who met the criteria for inclusion. Of these, only 29

(11%) agreed to take part in the study, of whom 20 (69%) were under age 40 and had < 10 years of experience. The sample profile is described in Table 1.

Table 1

Sample profile of anesthesiologists in the state of Sergipe, Brazil

Characteristics of the sample		
Age range	N	%
31-40	20	69.0
41-50	6	20.6
> 50	3	10.3
Year of completion of anesthesiology training	N	%
1990-2000	3	10.3
2001-2010	4	13.8
2011-2020	18	62.0
> 2020	4	13.8
Years in practice	Public health care facilities	Private facilities
< 5 years	9	9
5-10 years	11	11
11-15 years	3	2
> 15 years	6	7

* The maximum variation in years worked in public vs. private facilities for the same respondent was 3 years.

Most participants had been practicing as anesthesiologists for at least 5 years (96.6%) and had diagnosed at least one case of perioperative anaphylaxis (65.5%). Medical residency was the first point of contact with the topic of perioperative anaphylaxis for 21 (72.4%) participants.

Regarding specific knowledge about perioperative anaphylaxis, no participants achieved the maximum score of 120 points; scores ranged from 64 to 114 points among the respondents, with an average score of 85.9.

The results were distributed into percentiles, with the 25th percentile (p25) delimited by a score of 76, the 50th percentile (p50) by a score of 88, and the 75th percentile (p75) by a score of 92. Table 2 shows the distribution of scores across the percentiles described above.

Table 2

Perioperative anaphylaxis knowledge score achieved by anesthesiologists in the state of Sergipe, Brazil

Score achieved	Percentile	N	%
< 76	< 25	7	24.1
76-87	25-50	7	24.1
88-92	50-75	5	17.2
> 92	> 75	10	34.4

The sample was divided into anesthesiologists with more than 5 years of experience and those with less than 5 years of experience (time since completion of anesthesiology training), with the intention of assessing whether this parameter would interfere with the scores achieved. Anesthesiologists with more than 5 years of experience had an average score of 84, while those with less than 5 years of experience had an average score of 90; the difference was not statistically significant ($p = 0.21$). This analysis was hampered by the small number of respondents with < 5 years of training. The average score among anesthesiologists who encountered perioperative anaphylaxis for the first time during medical residency was 86.28, while the group who first came into contact with the topic during medical school had an average score of 86.57 ($p = 0.5$). The number of years of practice as an anesthesiologist in public and/or private hospitals, year of completion of anesthesiology training, and age had no influence on scores.

Regarding agents possibly implicated in perioperative anaphylaxis, all respondents identified antibiotics and latex-derived products as such, while 28 (96.6%) selected non-steroidal anti-inflammatory drugs, 26 (89.7%) selected neuromuscular blocking agents, and 17 (58.6%) selected opioids. The most well-known risk factors were frequency of exposure,

selected by 28 respondents (96.6%); asthma, selected by 27 respondents (93.1%); and food allergy, chosen by 26 respondents (89.7%). The frequency of selection of other agents and risk factors is shown in Tables 3, 4, and 5.

Regarding the diagnosis of anaphylaxis, all participants reported being aware that the surgical environment can make the manifestations of perioperative anaphylaxis less readily apparent, and the vast majority (96.6%) stated that the diagnosis of perioperative anaphylaxis is a clinical one. Regarding laboratory tests, 16 (55.1%) of respondents reported not knowing whether an increase in tryptase could occur in anaphylaxis or not being familiar with this test at all.

When asked about the treatment of anaphylaxis, 26 (89.7%) responded that epinephrine should be the first medication to be administered, while 3 (10.3%) answered that crystalloids should be administered first. According to 23 (79.3%) of the participants, the dose of epinephrine should be chosen according to the severity of the patient's clinical condition, and 14 (48.3%) believed that early administration of steroids and antihistamines could improve clinical outcomes.

Regarding preventive management in patients who had recent episodes of perioperative anaphylaxis, 27 (93.1%) of respondents stated that proper management would be to refer the patient to an immunologist for a skin test; only 2 (6.9%) would perform a skin test immediately after the patient's recovery. As for management after diagnosis and reversal of the initial episode of perioperative anaphylaxis, 22 (75.9%) would opt for admission to an intensive care unit and observation for 24 hours, while 7 (24.1%) would keep the patient under observation for 6 hours on a regular ward.

Discussion

This is the first study to assess and describe the knowledge of anesthesiologists regarding diagnosis and management of perioperative anaphylaxis in Brazil, a topic that is often neglected and insufficiently discussed, including by academic institutions and specialists. Similar studies have been carried out in Petrópolis (state of Rio de Janeiro)¹⁰ and Maceió (state of Alagoas)¹¹; these, however, investigated physicians' knowledge about the management of anaphylaxis overall (not limited to perioperative anaphylaxis) in the urgent care/emergency department setting.

Table 3

Agents that anesthesiologists believed to be associated with perioperative anaphylaxis

Agent	N	%
Latex-derived products (e.g., sterile gloves and urinary catheters)	29	100
Antibiotics (e.g., cephalosporins and penicillins)	29	100
Non-steroidal anti-inflammatory drugs (NSAIDs)	28	96.6
Neuromuscular blocking agents (e.g., rocuronium and vecuronium)	26	89.7
Local anesthetics	18	62.1
Dyes (e.g., methylene blue)	18	62.1
Opioids (e.g., morphine and pethidine)	17	58.6
Chlorhexidine	14	48.3
Hypnotics (e.g., propofol)	14	48.3
Heparin	11	37.9

Table 4

Risk factors that anesthesiologists believed to be associated with perioperative anaphylaxis

Risk factors	N	%
Frequency of exposure to antigen	28	96.6
Asthma or history of asthma	27	93.1
Food allergies	26	89.7
Multiple surgical procedures	25	86.2
Family history of atopy	24	82.8
Parenteral administration of antigen	20	69.0
Systemic mastocytosis	19	65.5
Time of exposure to antigen	18	62.1
Female sex	8	27.6
Chronic lung disease (e.g., COPD)	6	20.7
Recent intracranial surgery and hyperthyroidism	5	17.2
On angiotensin-converting enzyme inhibitors (ACEi)	4	13.8
Cardiovascular disease	3	10.3
On beta blockers	2	6.9

COPD = Chronic obstructive pulmonary disease.

Table 5
Clinical manifestations that anesthesiologists believed to be associated with perioperative anaphylaxis

Clinical manifestation	N	Percentage (%)
Angioedema	27	93.1
Hypotension	27	93.1
Cutaneous manifestations	27	93.1
Hypoxemia (desaturation)	23	79.3
Urticaria	22	75.9
Cardiac arrest (pulseless)	21	72.4
Dyspnea	24	82.8
Tachycardia	20	69.0
Bradycardia	14	48.3
Decreased EtCO ₂	13	44.8
Cyanosis	13	44.8
Nausea	11	37.9
Vomiting	11	37.9
Rhinorrhea	10	34.5
Abdominal pain	7	24.1

EtCO₂ = end-tidal carbon dioxide.

IgE-mediated anaphylactic reactions can be triggered by various agents. Neuromuscular blockers are the most frequently reported in most studies, followed by latex and antibiotics.^{2,12} Although most respondents reported that neuromuscular blockers are a cause of anaphylaxis, 10.3% did not select this option, thus failing to recognize one of the main factors involved in immune-mediated reactions in the perioperative period.¹³ No data were found from other studies to compare whether anesthesiologists from other regions share this perception.

NSAIDs are a recognized cause of drug-induced anaphylaxis, although rarely in the perioperative setting.¹⁴ The *6th National Audit Project* (NAP 6), the largest study of anaesthesia- and surgery-related anaphylaxis, found only one case of ibuprofen-induced anaphylaxis in 356 European hospitals.¹⁴ However, despite being an uncommon cause of perioperative anaphylaxis, NSAIDs do play a major role in anaphylaxis overall. In the Latin American literature, they are often cited as the main cause of non-allergic anaphylactic reactions. In a study by the Latin

American Society of Allergy, Asthma and Immunology (SLAAI) with 634 participants from 15 Latin American countries, 31.2% of systemic anaphylactic reactions were drug-induced, with 22.7% of these cases being attributed to NSAIDs.¹⁵ In a large Brazilian study, aspirin, metamizole, and diclofenac were the drugs most commonly implicated in non-allergic anaphylactic reactions.¹⁶ Given this epidemiology, it is justified that 28 (96.6%) of our respondents considered NSAIDs as possible causes of perioperative anaphylaxis.¹⁶

Regarding chlorhexidine, NAP 6 reported an increase in the role of this substance and of contrast agents in perioperative anaphylaxis. In the United Kingdom, chlorhexidine was identified as the third most common cause of perioperative anaphylaxis. In Asia and Belgium, it was the fourth leading cause.¹⁷ Despite the substantial number of reactions associated with this compound, only 14 (48.3%) respondents in our sample believe that chlorhexidine can be implicated in immediate hypersensitivity reactions in the perioperative period.

Due to the large number of possible agents, the causal factor is never identified in approximately half of all cases, which has implications for the subsequent prevention of these reactions.³ In addition, there are exceedingly rare triggers of anaphylactic reaction, such as heparin^{2,13,18}, which despite being implicated in few cases, was named as a possible trigger by 11 (37.9%) respondents.

Female sex is one of the leading risk factors, with a threefold higher incidence of perioperative anaphylaxis in this group compared to male patients. This difference only occurs during childbearing age, which suggests a relationship with sex hormones.¹⁹⁻²¹ Despite its importance, this factor was recognized by only 8 (27.6%) respondents.

A history of asthma, food allergies, multiple surgical procedures, family history of atopy, and frequency of antigen exposure were recognized as potential risk factors by more than 80% of anesthesiologists in the survey. These are also important factors, but are more relevant in the pediatric population.^{14,19-21} Systemic mastocytosis, time of exposure to antigen, and parenteral administration of the antigen are known to be associated with an increased risk of perioperative anaphylaxis^{14,21}; however, less than 70% of respondents recognized them as such.

Comorbidities that may contribute to greater severity of anaphylaxis include cardiovascular diseases, chronic lung diseases, hyperthyroidism, and recent intracranial surgery.² The latter, despite being cited in several articles, lacks robust evidence proving its relationship with a worse prognosis. The mechanism is unclear, but it has been suggested that such surgeries may disrupt the integrity of the blood-brain barrier, potentially increasing permeability to various substances²² and thus predisposing to an exacerbated inflammatory response and a greater risk of cerebral edema. Furthermore, the release of inflammatory mediators such as bradykinin, histamine, and substance P can compromise blood–brain barrier junctions, facilitating the passage of potentially harmful agents.^{23,24}

In addition to comorbidities, some medications such as ACE inhibitors and beta blockers are also considered to increase the severity of symptoms and reduce the response to treatment.^{19-21,25} Furthermore, studies have shown that the odds ratio for developing anaphylaxis is 6.8 when on beta blockers and 13 when on ACE inhibitors. However, other studies have indicated that they are significant risk factors only when used simultaneously; further research is needed

to analyze the impact of these medications as risk factors.^{21,26,27}

Although many reports in the literature mention the aforementioned factors as being associated with the severity of perioperative anaphylaxis, comorbidities were reported by less than 25% of our participants, and use of medications by less than 15%, with the use of beta blockers being recognized as a risk factor by only 2 (6.9%) respondents. It is possible that part of the sample failed to select these options because there is still ongoing debate about the actual impact of these drugs.

The main signs and symptoms of anaphylaxis and the objective diagnostic criteria for its diagnosis are highly varied, with a wide range of possible presentations; the major manifestations are cardiovascular, respiratory, and cutaneous. Hypotension is found in most, if not all, patients with perioperative anaphylaxis.²⁵ This sign was recognized by 93.7% of respondents, as were cutaneous manifestations and angioedema. The latter, despite being absent in some cases or even going unnoticed when the patient is covered by surgical drapes, were present in 70% of IgE-mediated reactions and in 95% of non-IgE reactions in a 2011 French study.^{13,28} Cutaneous manifestations were considered to be among the most common by 27 of the 29 respondents.

A study published in 2015 reported that cardiac arrest is the only sign of anaphylactic reaction in 51.7% of cases², although this has not been replicated in other research; 72.4% of our respondents were aware that this is a possible presentation of perioperative anaphylaxis. Bronchospasm is another common sign, present in 49% of cases in the United Kingdom and 43% in the USA, potentially manifesting as cyanosis, dyspnea, hypoxemia, and reduced end-tidal carbon dioxide (EtCO₂).^{2,25,29} Among our respondents, 79.3% selected hypoxemia with desaturation, 69% selected dyspnea, and only 44.8% considered cyanosis and reduced EtCO₂ as possible signs of perioperative anaphylaxis.

Hypotension, tachycardia, and bradycardia may be merely side effects of anesthetic agents rather than manifestations of anaphylaxis, and, although common, tachycardia may not occur in anaphylactic reactions in patients who are on beta blockers. Furthermore, patients with severe hypovolemia may not present with tachycardia with hypotension but rather with bradycardia, due to the Bezold–Jarisch reflex.^{19,30} Intuitively, tachycardia, being a more common manifestation of anaphylaxis, was reported by 69%

of participants; conversely, less than half (48.3%) believe that bradycardia is among the most common symptoms of this reaction.

Stated by several authors and very well consolidated in the literature, masking of the clinical manifestations of perioperative anaphylaxis by the surgical environment^{18,25} was recognized by 100% of participants in this survey. The concept that diagnosis of this condition is clinical¹⁸ was also recognized by the majority of the sample (96.6%).

Although the diagnosis is indeed based on the signs and symptoms exhibited by the patient, there are laboratory tests that can assist in the workup of a suspected reaction, such as tryptase—one of the mediators released by the mechanisms of drug-induced anaphylaxis, whether IgE-mediated or otherwise, due to degranulation of mast cells and basophils.²⁵ However, tryptase levels may increase under other conditions and, therefore, false-positive results are possible.²

When assessing knowledge about this alternative method of diagnosis, we found that 37.9% of respondents were not even aware of this test, and only 37.9% gave a response consistent with the literature. The low level of knowledge of this option among anesthesiologists is justified, as all guidelines agree that laboratory tests are not useful for the diagnosis of anaphylaxis, due to the delay in measuring mediators such as total serum tryptase. Furthermore, this test is largely unavailable in clinical practice in both the public and private sectors, given that there is no provision for its coverage by insurance companies in Brazil.³¹

Regarding management of anaphylaxis, 89.7% of respondents selected epinephrine as the first-line drug of choice medication, while 10.3% stated that intravenous crystalloids should take precedence. In the Petrópolis study, 63.4% of anesthesiologists cited epinephrine as their first-line drug of choice¹⁰, versus 78.9% of those in the Maceió study¹¹, corroborating our findings. According to the literature, epinephrine should always be the first drug administered in cases of anaphylaxis, since its alpha- and beta-adrenergic effects have a broad effect on the pathophysiological mechanisms of anaphylaxis—reducing edema, urticaria, and upper airway obstruction; promoting bronchodilation; and suppressing mediators generated by the degradation of mast cells and basophils.³²

Despite its narrow therapeutic window, failure to use epinephrine appropriately outweighs any of its adverse effects, even in patients with heart disease;

the heart is a target organ for anaphylaxis – the released mediators can cause myocardial infarction and/or arrhythmias – even without administration of epinephrine, so there is no contraindication to its use.³¹

Other measures do include resuscitation with intravenous fluids, although this should not be the first action taken.^{18,25}

The most recent studies on the management of anaphylaxis provide no evidence that corticosteroids and antihistamines improve clinical outcomes; therefore, these drugs should not be a priority.³² Antihistamines can reduce itching and edema, but despite causing smooth muscle relaxation, they are unable to relieve bronchospasm. Corticosteroids have an anti-inflammatory effect with onset of action between 4-6 hours, and are thus not effective in an anaphylactic emergency.³³ Furthermore, a systematic review of 31 studies suggests that use of corticosteroids for the prevention of biphasic reactions is not recommended, as there is no convincing evidence and well-known adverse effects.³²

Nevertheless, 48.3% of our respondents stated that steroids improve clinical outcomes, which is inconsistent with the published evidence. These drugs can be used to reduce symptoms once the patient is stable, although it should be noted that there are no studies demonstrating their benefits and that adverse effects such as worsening hypotension have been reported.

Regarding management after stabilization of the patient, 22 (75.9%) respondents would opt for admission to an intensive care unit and observation for 24 hours, while 7 (24.1%) would keep the patient under observation for 6 hours on a regular ward. According to the literature, patients must remain under observation in an intensive care unit (ICU) setting for at least 6-8 hours if the anaphylactic reaction involved respiratory symptoms alone and for 12-24 hours if there were cardiovascular manifestations. After all, biphasic reactions—a recrudescence of symptoms without further exposure to the precipitating trigger—occur in up to 20% of cases, are unpredictable, and can last up to 36 hours.¹⁸

Based on the data collected herein, most participants scored high on the perioperative anaphylaxis knowledge questionnaire. Nevertheless, a substantial portion of the sample demonstrated outdated knowledge on this topic, failing to recognize the agents most commonly responsible for anaphylactic

reactions and advocating for the use of corticosteroids and antihistamines, which is still controversial. Furthermore, the failure to identify known risk factors and the failure to use epinephrine as the first-line drug of choice may jeopardize patient management and prognosis.

One limitation of this study was the low questionnaire response rate, which means our sample may not accurately reflect the knowledge of anesthesiologists on this topic. Despite the small sample and use of a questionnaire that has yet to be validated, our findings highlight an urgent need for greater attention to perioperative anaphylaxis. It is imperative that new studies be conducted and continuously updated strategies be developed to mitigate the risks associated with this condition in the surgical setting. Finally, promoting a more effective collaboration between medical specialties is crucial for advancing and enhancing knowledge on this topic.

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No conflicts of interest declared concerning the publication of this article.

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Appendix 1

Questionnaire to assess anesthesiologists' knowledge of perioperative anaphylaxis

**Management of perioperative anaphylaxis from the perspective of anesthesiologists
in the state of Sergipe, Brazil**

SAMPLE PROFILE

Age: _____ Year of completion of Anesthesiology training: _____

1 - Of your time practicing as an anesthesiologist, how long has been spent in public and private practice? Fill in below as follows:

Public _____ years Private _____ years

Note: if you spent less than 1 year in either, enter "0" (zero)

2 - Have you practiced as an Anesthesiologist in the last 5 years?

☐ Yes ☐ No

3 - Have you ever diagnosed a case of perioperative anaphylaxis?

☐ Yes ☐ No

4 - Do you feel confident in diagnosing a case of perioperative anaphylaxis?

☐ Yes ☐ No

5 - When did you first become aware of the topic of perioperative anaphylaxis? _____

☐ Medical school ☐ Residency ☐ Congress/Course/Conference ☐ Other: _____**QUESTIONNAIRE**

Description: The European Academy of Allergy and Clinical Immunology defines anaphylaxis as a severe, life-threatening, generalized or systemic hypersensitivity reaction. Perioperative anaphylaxis is a systemic reaction that occurs during induction of anesthesia, within minutes of intravenous (IV) administration of induction agents. However, certain agents administered by other routes may also cause such a reaction, during maintenance of anesthesia (approximately 15 minutes after induction) or during recovery (due to absorption through the skin or mucosa or removal of tourniquets).

1 - Based on your knowledge as an anesthesiologist, select the option(s) that describe agents you believe to be associated with Perioperative Anaphylaxis:

- ☐ Neuromuscular blocking agents (e.g., rocuronium and vecuronium)
- ☐ Latex-derived products (e.g., sterile gloves and urinary catheters)
- ☐ Antibiotics (e.g., cephalosporins and penicillins)
- ☐ Chlorhexidine
- ☐ Hypnotics (e.g., propofol)
- ☐ Opioids (e.g., morphine and pethidine)
- ☐ Non-steroidal anti-inflammatory drugs (NSAIDs)
- ☐ Heparin
- ☐ Local anesthetics
- ☐ Dyes (e.g., methylene blue)

2 - Based on your knowledge as an anesthesiologist, select the option(s) that describe risk factors you believe to be associated with Perioperative Anaphylaxis:

- ☐ Cardiovascular disease
- ☐ Chronic lung disease (e.g., COPD)
- ☐ Recent intracranial surgery
- ☐ Hyperthyroidism
- ☐ Multiple surgical procedures
- ☐ Female sex
- ☐ Asthma or history of asthma
- ☐ Food allergies
- ☐ Family history of atopy
- ☐ Systemic mastocytosis
- ☐ On angiotensin-converting enzyme inhibitors (ACEi)
- ☐ On beta blockers
- ☐ Time of exposure to antigen
- ☐ Frequency of exposure to antigen
- ☐ Parenteral administration of antigen

Appendix 1 (continuation)

Questionnaire to assess anesthesiologists' knowledge of perioperative anaphylaxis

3 - Among the potential manifestations of anaphylaxis, which are most common in cases of perioperative anaphylaxis?

(You may select more than one choice)

- ☐ Urticaria
- ☐ Angioedema
- ☐ Hypotension
- ☐ Cardiac arrest (pulseless)
- ☐ Dyspnea
- ☐ Hypoxemia (desaturation)
- ☐ Decreased EtCO₂
- ☐ Cyanosis
- ☐ Abdominal pain
- ☐ Nausea
- ☐ Vomiting
- ☐ Rhinorrhea
- ☐ Tachycardia
- ☐ Bradycardia
- ☐ Cutaneous manifestations

4 - Can general anesthesia, as well as the surgical environment, make the manifestations of perioperative anaphylaxis less apparent?

- ☐ Yes
- ☐ No
- ☐ I don't know

5 - Based on your opinion as an anesthesiologist, is perioperative anaphylaxis a clinical diagnosis?

- ☐ Yes
- ☐ No
- ☐ I don't know

6 - In your opinion, can perioperative anaphylaxis be diagnosed from an elevated total plasma tryptase measurement in a single (spot) specimen?

- ☐ Yes
- ☐ No
- ☐ I don't know
- ☐ I am unfamiliar with this test

7 - In your opinion, among the medications listed below, which should be the first-line drug of choice for management of perioperative anaphylaxis?

- ☐ Epinephrine
- ☐ Intravenous crystalloids
- ☐ Norepinephrine
- ☐ Glucagon
- ☐ Vasopressin
- ☐ Glucocorticoids
- ☐ Antihistamines
- ☐ Other

8 - When administering epinephrine for treatment of perioperative anaphylaxis, does the dose depend on the severity of anaphylaxis and should it be titrated to clinical response?

- ☐ Yes
- ☐ No
- ☐ I don't know

9 - Does early administration of steroids (e.g., dexamethasone, hydrocortisone) and antihistamines in the treatment of perioperative anaphylaxis improve clinical outcomes?

- ☐ Yes
- ☐ No
- ☐ I don't know

10-Regarding preventive management of patients who have had a recent episode of perioperative anaphylaxis, which of the following is recommended?

- ☐ Refer to an immunologist for skin testing
- ☐ Perform a skin test immediately after the patient recovers
- ☐ Neither skin tests nor any preventive measures are necessary

11-After diagnosis and reversal of a first episode of perioperative anaphylaxis, what would be your subsequent management?

- ☐ Immediate discharge with referral to an allergist
- ☐ Observation for 6 hours on a regular ward
- ☐ Observation for 24 hours in the intensive care unit

Anaphylaxis: updating Practice Parameter 2023 recommendations

Anafilaxia: atualizando as recomendações do Practice Parameter 2023

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ABSTRACT

Anaphylaxis is a potentially life-threatening medical emergency that requires prompt and effective intervention. Understanding and updating clinical practices is crucial to ensure optimal patient care. This update is based on evidence and expert clinical experience and discusses aspects focusing on 7 different areas with new evidence and different from those of previous practice guidelines. The text summarizes aspects related to the diagnosis of anaphylaxis, mastocytosis, with emphasis on the indication rate of bone marrow biopsy and hereditary alpha tryptasemia, investigation of perioperative anaphylaxis, and influence of beta blockers and angiotensin-converting enzyme inhibitors, in addition to the important prescriptions for epinephrine auto-injectors, highlighting practical aspects in the management of self-medication.

Keywords: Anaphylaxis, epinephrine, diagnosis, mastocytosis.

RESUMO

A anafilaxia é uma emergência médica potencialmente fatal que requer intervenção rápida e eficaz. Compreender e atualizar as práticas clínicas é crucial para garantir os melhores cuidados aos pacientes. Esta atualização baseada em evidências e experiência clínica de especialistas mostra uma discussão de aspectos focados em sete diferentes áreas com novas evidências e diferentes das diretrizes práticas anteriores. O texto resume desde aspectos do diagnóstico da anafilaxia, mastocitose, com destaque para o escore de indicação de biópsia de medula óssea e alfa triptasemia hereditária, investigação da anafilaxia perioperatória, influência dos betabloqueadores e inibidores da enzima de conversão da angiotensina, além das importantes indicações da prescrição dos autoinjetores de adrenalina, destacando-se aspectos práticos no manejo da autoprescrição.

Descritores: Anafilaxia, epinefrina, diagnóstico, mastocitose.

Introduction

The ICD-11 defines anaphylaxis as a serious, life-threatening systemic hypersensitivity reaction, characterized by the rapid onset of changes in the airways, breathing, or circulation, usually associated

with changes in the skin and mucous membranes.¹ The diagnosis is clinical, without definitive markers or quintessential symptoms.² In 2019, the World Allergy Organization (WAO) proposed modifications to

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simplify the diagnosis and to include severe reactions that were not classified as anaphylaxis by the previous criteria (Table 1).³

Rapidly progressing reactions may occur even if the onset of symptoms is delayed after allergen exposure, such as reactions caused by alpha-gal and immunotherapy.³

Mastocytosis and mast cell activation syndrome (MCAS)

Mast cell diseases are commonly associated with anaphylaxis. The risk of anaphylaxis in patients with systemic mastocytosis is estimated to be 40%-50% in adults and 10% in children. Currently, there is greater knowledge of the different phenotypes of the disease, more accurate diagnostic methods, and effective treatments for both the prevention and management of anaphylactic conditions. Risk factors for mastocytosis-related anaphylaxis include male sex, serum IgE > 15 kU/L, atopy, and baseline serum tryptase < 42 ng/mL.⁴

Serum tryptase levels should be measured whenever possible during anaphylaxis investigation. However, in cases of suspected systemic mastocytosis, even with normal tryptase levels, a bone marrow biopsy is required for diagnosis. Additionally, it is crucial to

exclude differential diagnoses when tryptase levels are elevated, such as neoplasms, helminth infection, renal failure, hypereosinophilic syndrome, hereditary alpha tryptasemia, and mast cell activation syndrome (MCAS), in addition to systemic mastocytosis itself. Baseline serum tryptase is particularly relevant in cases of anaphylaxis triggered by hymenoptera stings (especially with hypotension independent of urticaria), idiopathic anaphylaxis, and suspected mastocytosis. In these cases, a bone marrow biopsy is recommended, especially when the Spanish Network on Mastocytosis (REMA) prediction score, which establishes clonal mast cell disorders, is ≥2 (Table 2).⁵

The laboratory-defined normal value for serum tryptase is 11.4 ng/mL. An elevation of serum total tryptase level, within 2 hours of the anaphylactic episode, of at least 20% plus 2 ng/mL above the patient's baseline level may provide evidence of MCAS. Furthermore, an elevated baseline level (above 8 ng/mL) may be indicative of hereditary alpha tryptasemia.⁶

In mastocytosis, according to the World Health Organization (WHO) criteria, anaphylaxis can occur spontaneously and, in some cases, be triggered by aerobic exercise. Other potential triggers include food allergies, drug allergies, and pollen-food allergy syndrome.³ While cutaneous mastocytosis

Table 1
Criteria for the diagnosis of anaphylaxis

Anaphylaxis is highly likely when any one of the following 2 criteria are fulfilled:	
1.	Acute onset (minutes to several hours) with involvement of the skin, mucosal tissue, or both (hives, pruritus, swollen lips-tongue-uvula) and at least one of the following:
	a. Respiratory compromise: dyspnea, bronchospasm, stridor, reduced peak expiratory flow, hypoxemia;
	b. Reduced blood pressure or associated symptoms of end-organ dysfunction: hypotonia, syncope, incontinence;
	c. Severe gastrointestinal symptoms: severe crampy abdominal pain, repetitive vomiting.
2.	Acute onset of hypotension or bronchospasm or laryngeal involvement after exposure to a known or highly probable allergen even in the absence of typical skin involvement, defined as one of the following:
	a. Decrease in systemic blood pressure;
	b. Bronchospasm;
	c. Laryngeal involvement.

Source: Cardona V, et al.³.

Table 2
Spanish Network on Mastocytosis (REMA) Score

Sex	Female	-1
	Male	+1
Clinical symptoms	Absence of urticaria and angioedema	+1
	Presence of urticaria and angioedema	-2
	Presyncope or syncope	+3
Baseline tryptase	< 15 ng/mL	-1
	> 15 ng/mL	+2

Source: Alvarez-Twose I, et al.⁵.

and benign mastocytomas can occur in children, they are not usually associated with systemic mastocytosis. Patients with mastocytosis and anaphylaxis after hymenoptera stings should receive lifelong subcutaneous immunotherapy with allergen extracts, starting during pregnancy if necessary. In these cases, the risk of systemic reactions increases with immunotherapy, and caution is required in its administration. The addition of omalizumab may be considered to prevent potential anaphylaxis, especially in rapid desensitization protocols.⁷

MCASs share the characteristic of degranulation of anaphylaxis mast cell mediators. They can be classified into 3 groups: primary/clonal (systemic monoclonal mastocytosis); secondary (IgE-mediated); and idiopathic nonclonal (idiopathic anaphylaxis). Therefore, any patient who does not meet the criteria for anaphylaxis should be evaluated for the following criteria (include all 3)⁸:

- (1) Symptoms in at least 2 different organ systems (cardiovascular, respiratory, naso-ocular, gastrointestinal, and cutaneous);
- (2) Biochemical documentation of the release of anaphylaxis mediators (tryptase, prostaglandin D2, prostaglandin F2-alpha, leukotriene E4, and catecholamines);

(3) Positive response to antimediators, membrane stabilizers, and producers of vasoactive substances (H1 and H2 antihistamines, anti-leukotriene, ketotifen, cromoglycate, omalizumab, and corticosteroids).

Patients with chronic, nonspecific multiorgan symptoms and patients with food and environmental intolerances who do not meet the criteria mentioned above should not be diagnosed with MCAS.

The diagnostic algorithm shows the updated criteria for the investigation of anaphylaxis (Figure 1).

Anaphylaxis in infants and children

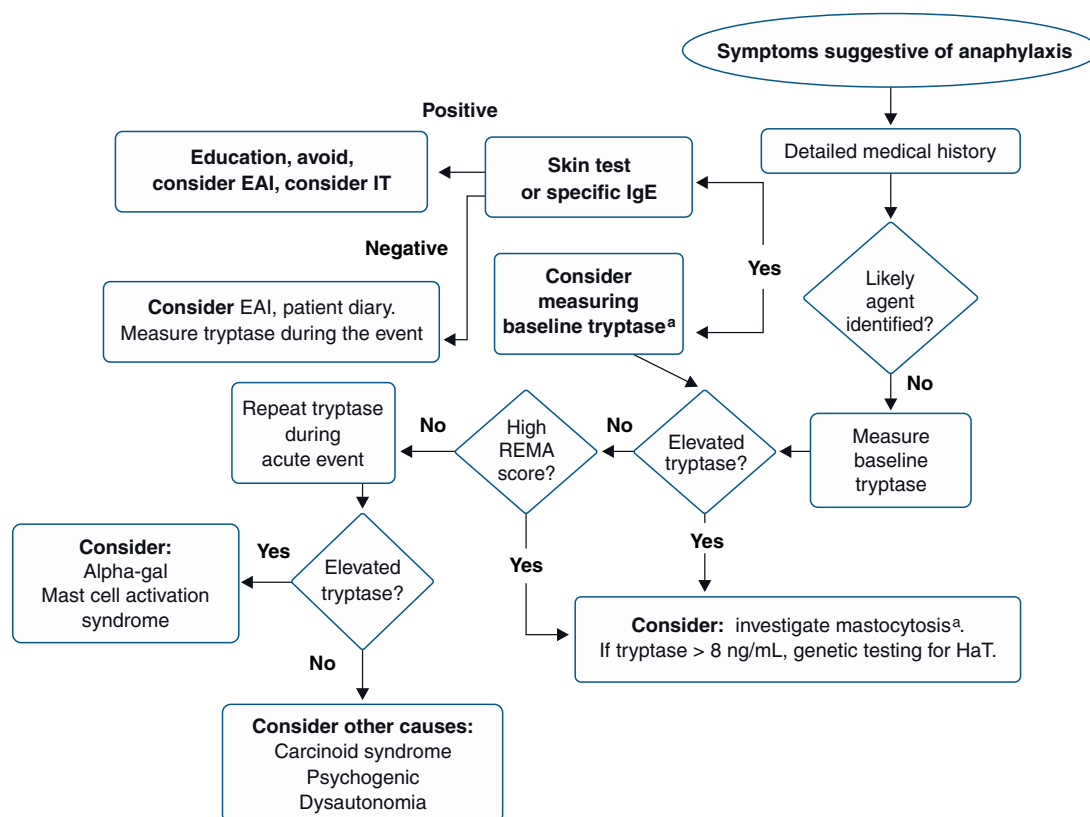
The same anaphylaxis criteria have been applied to both children and adults, despite limited evidence supporting this practice for children, due to a lack of consensus for this age group. In infants and young children, age does not correlate with reaction severity, and anaphylaxis is unlikely as an initial reaction to a food or drug on first exposure. Clinically, infants and young children more often have skin and subjective symptoms, such as pulling and scratching, and less frequently experience respiratory symptoms compared with older children.⁹ Behavioral changes such as withdrawal, inconsolable crying, irritability, or clinging may be observed in infants. While self-

injectable epinephrine in 0.1 mg or 0.15 mg doses may be prescribed for infants/children weighing less than 15 kg, caution is advised as longer needles increase the risk of the needle hitting bone. Further research is needed to determine the true risk of intraosseous injection and its impact on epinephrine effectiveness.¹⁰

Beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) in anaphylaxis

Regarding the use of beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) in anaphylaxis, it is important to consider their previous contraindication in patients at risk of anaphylaxis, since most previous studies focused on non-selective

BBs and did not account for cardiac comorbidities that could independently explain the increased risk of severe anaphylaxis. In addition, discontinuation or change of treatment may pose greater risks than the potential for more severe anaphylaxis. In specific cases, such as a history of anaphylaxis to hymenoptera venom before immunotherapy, venom immunotherapy, and during the maintenance phase of immunotherapy, the continued use of BBs and ACEIs may be justified as long as the need outweighs the risk of more severe anaphylaxis. However, the use of BBs and ACEIs should be discouraged in situations with a significant risk of recurrent or unpredictable anaphylaxis, such as severe food allergies, mastocytosis, MCAS, and exercise-induced anaphylaxis. For planned procedures, such as contrast-enhanced imaging, challenge/desensitization, and infusion, clinicians



EAI = epinephrine auto-injector, HaT = hereditary alpha tryptasemia, IT = immunotherapy.

^a Example: severe reaction to hymenoptera venom, recurrent idiopathic anaphylaxis.

Figure 1

Algorithm for the investigation of anaphylaxis⁴

should engage patients in a shared decision-making process regarding the continuation or discontinuation of BBs and ACEIs. This process should carefully weigh the relative risk of anaphylaxis, the potential for a more severe reaction if the medication is continued, and the risk of discontinuing the medication.¹¹

Perioperative anaphylaxis

Perioperative anaphylaxis (POA) occurs at a rate of 15.3 per 100,000 cases.¹ While there has been a trend toward a decrease in latex-induced anaphylaxis, an increase has been observed in cases due to antimicrobials, particularly cefazolin. Anaphylaxis can be triggered by either immunologic or non-immunologic activation of mast cells. There is sufficient evidence to demonstrate that resuscitation itself cannot account for serum tryptase level elevation. Therefore, increased tryptase levels are directly linked to cases of severe anaphylaxis. Plasma histamine measurement is not recommended due to its rapid degradation and decline in blood levels following anaphylaxis. Interpretation of tryptase levels obtained near death or postmortem may be unreliable due to nonspecific increases during ischemia. While tryptase is estimated to be stable for up to 1 year in a frozen blood sample, the timing of collection is crucial, with an initial peak around 30 minutes followed by a decrease in approximately 120 minutes. If the serum tryptase level is elevated after POA, a repeat measurement should be performed once the patient has recovered to establish a baseline tryptase level.¹²

Immediate hypersensitivity skin testing (percutaneous and intradermal) and/or in vitro specific IgE testing should be performed to all potential pharmacologic and non-pharmacologic culprits used perioperatively. If testing is not feasible, the patient should be referred to another center, or the most effective agents structurally different from the most likely culprit should be used.¹

Neuromuscular blocking agents (NMBAs) are frequently implicated as causes of POA. Therefore, testing should always include the potential culprit NMBA and any alternative NMBA agents to rule out cross-reactivity among chemically related agents, an area that remains poorly documented. Immediate hypersensitivity skin testing to opioids or vancomycin may be unreliable due to high rates of false-positive results, since they are direct mast cell activators. Furthermore, avoidance of drugs with a positive skin test result is the best option when equally effective,

structurally unrelated alternatives are available. Administration of agents with negative test results can proceed safely, suggesting that testing may be helpful in drug selection for subsequent anesthesia. In the case of negative skin test results (eg, latex, lidocaine, chlorhexidine, povidone-iodine), provocative challenges should be performed due to the uncertainty surrounding the sensitivity of these tests. For some agents, such as NMBAs, midazolam, and propofol, it would be appropriate for an anesthesiologist to administer them in a graded dose (ie, “test dose”) of 10% immediately before the planned procedure, followed by full dosing after a period of observation as indicated. Delaying immediate hypersensitivity skin testing for 4 to 6 weeks after anaphylaxis is recommended. If testing or referral to another center are not possible, or the procedure is urgent, the most likely culprits should be avoided, and the most effective structurally different agents should be used.¹³

Regarding penicillin, immediate hypersensitivity skin testing has been validated. If the test result is positive only to the beta-lactam and a challenge for other alternatives is not feasible, all perioperative drugs except for the beta-lactam should be used. In cases of suspected latex allergy where the investigation is still pending, a latex-free environment should be provided.

There is currently no consensus on the use of pretreatment before returning to the operating room in patients with a negative allergy investigation. This decision should be made on a case-by-case basis.

Repeat anesthesia can proceed within the context of shared decision-making, based on the patient's history and the results of the diagnostic evaluation. Studies indicate that the recurrence of POA is 1.7% when the aforementioned measures are adopted.¹⁴

Anaphylaxis in community settings

The literature indicates a higher frequency of anaphylaxis events in younger populations, particularly at home. However, an increase in these events has been observed in schools and restaurants, with 1 in 10 childhood allergic reactions and anaphylaxis cases occurring in childcare centers or schools. Although deaths from anaphylaxis are rare, they can occur in any setting. There is no recommendation to prohibit specific foods in childcare centers or schools. However, implementing allergen-restricted zones (eg, a milk-free table) may be appropriate when there are

children who lack the capacity to self-manage. Other strategies include handwashing before and after eating, avoiding sharing food and drinks with others, and checking ingredient lists for suspected allergens. Adult supervision during meals and snacks, cleaning surfaces where food is prepared or eaten, and taking allergen-avoidance measures when planning classroom activities (eg, parties, crafts, science projects) or field trips are also essential.¹⁵

Clinicians should advise patients that, despite labeling regulations (disclosure of major allergens on the labels of prepackaged foods), restaurants are not required to declare the ingredients. Ideally, restaurant staff should be educated on this, especially for online and takeout orders from Asian restaurants. In this case, restaurants should list allergens (particularly peanuts, tree nuts, and milk) or ingredients on their menus, especially for foods such as sesame, recently added by the Food and Drug Administration (FDA). Most countries do not allow restaurants to purchase self-injectable epinephrine without a prescription.

One study showed that epinephrine was administered in 10% to 15% of inflight allergic reactions, but less than 50% of these cases were reported to airlines. Inflight anaphylaxis is estimated to occur once for every 37,750 flights. While many airlines provide information to passengers with allergies, few offer allergen-free meals or allow priority boarding. In addition, pilots can refuse boarding to passengers who pose a potential risk of flight diversion or danger to themselves.

In parks and other outdoor spaces, anaphylaxis is primarily triggered by insect stings. Food-dependent exercise-induced anaphylaxis is also more common during outdoor dining, while drug reactions are more common at home.¹⁶

Advising individuals at risk of anaphylaxis to wear or carry medical identification (eg, jewelry or wallet card) is considered optional. If it is worn or carried, the wording on medical alert items should be verified for accuracy by a health care professional. The effectiveness of medical alert jewelry or wallet cards in reducing the risk of anaphylaxis or enabling more rapid treatment remains unknown.¹

When to prescribe epinephrine auto-injectors (EAI)s?

While there is no validated guideline that determines when to prescribe epinephrine auto-injectors (EAI)s, expert guidance indicates their prescription in several scenarios (Table 3).¹⁷⁻¹⁹

The omalizumab package insert indicates the use of self-injectable epinephrine, but this practice is not recommended by the FDA based on updated studies. EAI prescription for patients on sublingual immunotherapy is currently indicated only in the United States. Therefore, the indication for EAI)s should be evaluated on a case-by-case basis considering the individual risk of the patient, especially if there is a previous history of anaphylaxis, asthma, or other potential risk factors.^{20,21}

Table 3
Indications for the prescription of epinephrine auto-injectors

History of systemic allergic reaction or anaphylaxis to their food allergen
Idiopathic anaphylaxis
Frequent allergen exposure through occupation or other activities (for venom, latex, drug allergy)
Prior systemic allergic reaction to specific allergen immunotherapy or specific venom immunotherapy
Bee venom allergy with elevated baseline serum tryptase and/or older age and/or cardiovascular disease
Venom-induced anaphylaxis not treated or with incomplete specific venom immunotherapy
Exercise-induced anaphylaxis (all phenotypes)
Cold-induced urticaria

For lower-risk patients, a shared decision-making process is recommended. This approach should consider the patient's risk factors, values, and preferences. While some risk factors can significantly increase the relative risk of anaphylaxis, the absolute risk remains small. A patient's risk of anaphylaxis depends in part on their specific diagnosis, history of previous reactions, ease of avoidance of causative agents or circumstances, presence of cofactors, and completion of specific immunotherapy.¹

It is recommended that factors such as dosage, needle length, cost, access, and patient treatment preferences be considered when prescribing an EAI.²² For example, subcutaneous injection may be preferable to intramuscular injection in patients with obesity due to the needle length, which may be insufficient to reach the muscle. In addition, the fixed dose of EAI may be insufficient or excessive for children. Despite this, EAI remain the safest and most effective option for the vast majority of patients with anaphylaxis, and all patients at risk of future anaphylactic episodes should be encouraged to carry their own EAI. Table 4 provides an overview of the characteristics of the main EAI currently available.

Prescribing 2 EAI devices is justified, even with the increased cost, because less than 10% of anaphylactic reactions require 2 or more doses of epinephrine during a single episode.²³ Additionally, delayed access to medical care is possible, particularly in remote areas or during travel. Prescribing a single device would be more feasible if generic or stock auto-injectors were available in public places such as schools, similar to cardiac defibrillators. However, this practice is not yet common in our context.¹

It is important to highlight that, despite increased awareness of anaphylaxis, the prescription and use of epinephrine by health professionals remain low. Patients and family members, even when properly trained and guided, often feel insecure and afraid about using the auto-injector. We therefore stress the importance of continuous and accessible training for patients and family members, with a focus on early symptom recognition and prompt treatment.^{24,25}

Regarding dose recommendations, the FDA approves 0.3 mg for patients weighing 30 kg or more, 0.15 mg for patients weighing between 15 and 30 kg,

and 0.1 mg (Auvi-Q) for those weighing between 7.5 and 15 kg.²⁶ However, several medical organizations, including the American Academy of Allergy, Asthma, and Immunology (AAAAI), the American Academy of Pediatrics, the Canadian Society of Allergy and Clinical Immunology, and the European Academy of Allergy and Clinical Immunology, support the option of using 0.1 mg (if available in the country) for patients weighing 7.5-13 kg; 0.15 mg for patients weighing 13-25 kg; and 0.3 mg for patients over 25 kg. For patients weighing 45 kg or more, a 0.5 mg dose is recommended, but few manufacturers market auto-injectors with 0.5 mg of epinephrine (Table 5).²⁷

Additionally, when a 0.3 mg dose of epinephrine is administered and repeated doses are needed, the higher 0.5 mg dose should be used. Training on how and when to use epinephrine is also essential and should be part of patient counseling. Early administration of epinephrine in anaphylaxis reduces the risk of biphasic reaction and hospitalization.²⁶

Our review highlights an important update regarding the activation of emergency medical services (EMS) in cases of anaphylaxis.^{28,29} While EMS activation was previously recommended in all situations, recent evidence suggests that it may not be necessary after using an auto-injector if the patient experiences a prompt, complete, and durable response to treatment and is carrying a second EAI. However, EMS activation remains crucial in cases of severe anaphylaxis or when symptoms fail to resolve promptly, fail to resolve almost completely, or return or worsen. The decision to activate EMS should be made through shared-decision making, considering the personal and social limitations of each patient.^{30,31} Table 6 shows the recommendations regarding EMS activation and the administration of a second epinephrine dose.

Patients and caregivers should always remember to replace EAI after the devices have been used or expired. If they forget to replace an expired EAI or cannot do so for other reasons, it is preferable to use the expired device rather than no device at all to treat anaphylaxis. Recent studies have shown that expired EAI retain epinephrine concentrations (80%-90%) well beyond their expiration date.^{32,33} Pediatric doses may degrade more rapidly after expiration than adult doses.^{26,33}

Table 4

General characteristics of the main epinephrine auto-injectors currently available

Brand	Manufacturer	How to store	Concentration	Needle lenght	Excipient
Anapen® 	Owen Mumford Limited	Store below 25 °C	150 µg 300 µg 500 µg	10 mm ± 1.5 mm	Sodium metabisulfite (E223), sodium chloride, hydrochloric acid, and water for injections
Auvi Q® 	Kaleo, Inc.	Store between 20 °C and 25 °C. Do not freeze. DO NOT expose to extreme heat or cold	100 µg 150 µg 300 µg	8.9 mm 14 mm 17.3 mm	Sodium chloride, sodium bisulfite, hydrochloric acid, and water for injections
Emerade® 	Bausch & Lomb U.K. Limited	Store below 25 °C. Do not freeze	150 µg 300 µg 500 µg	16 mm 23 mm 23 mm	Sodium chloride, sodium metabisulfite (E223), disodium edetate hydrochloric acid, and water for injections
EpiPen® 	ALK-Abelló	Store below 25 °C. Do not freeze	150 µg 300 µg	13 mm 15 mm	Sodium chloride, sodium metabisulfite (E223), disodium edetate, hydrochloric acid, and water for injections
Jext® 	ALK-Abelló	Store below 25 °C. Do not freeze	150 µg 300 µg	13 mm 15 mm	Sodium chloride, sodium metabisulfite (E223), hydrochloric acid, and water for injections
Penepin® 	MEFAR ILAÇ SANAYİ A.Ş.	Store at temperature below 25 °C and protected from light	150 µg 300 µg	Information not available	Sodium metabisulfite (E223), sodium chloride

Table 5
Epinephrine dosage recommendations according to weight

EAI 0.15 mg:	recommended for children weighing between 7.5 and 25-30 kg. This device provides a dosage suitable for younger children, ensuring treatment effectiveness while minimizing the risk of overdose.
EAI 0.3 mg:	recommended for children weighing 25-30 kg and also for adolescents and adults. This dosage is adequate for most cases of anaphylaxis in individuals with higher body weight, providing an effective response.
EAI 0.5 mg:	recommended for adolescents and adults weighing ≥ 45 kg. This dosage is used in situations when higher doses are necessary due to body weight (obese) or the severity of the anaphylactic reaction.

EAI = epinephrine auto-injector.

Table 6
Recommendations for activation of emergency medical services and administration of a second dose of epinephrine

Home observation following first dose of epinephrine	Signs and symptoms resolve within minutes of epinephrine administration, without recurrence, or the patient is asymptomatic. Patients with hives or rash (including erythema), even those with newly emerging but isolated hives or erythema without other symptoms occurring after epinephrine administration.
Consider EMS activation and second dose of epinephrine, and home observation may be maintained	Symptoms improve or resolve within minutes of epinephrine administration. For example, persistence of a mild sensation of globus, nausea, coughing, or epigastric pain may be observed at home provided symptoms are improving and do not persist for longer than 10-20 minutes.
Activate EMS immediately, consider second dose of epinephrine, do not observe at home	Symptoms that fail to resolve or worsen, particularly respiratory distress, stridor, altered consciousness, cardiovascular instability, incontinence, episodes of vomiting (> 2), cyanosis, persistent hoarseness, dysphagia, wheezing, or lightheadedness.

EMS = emergency medical services.

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No conflicts of interest declared concerning the publication of this article.

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New diagnostic approach to hereditary angioedema using filter paper

Nova proposta para diagnóstico do angioedema hereditário com papel filtro

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ABSTRACT

Introduction: Hereditary angioedema (HAE) is a rare disease characterized by edema in the subcutaneous tissue, gastrointestinal tract, and upper airways. C1 inhibitor deficiency is caused by a *SERPING1* mutation (HAE-C1-INH) that results in bradykinin accumulation and increased endothelial permeability. HAE may also present with normal C1-INH. Functional assessment of C1-INH allows the detection of both forms of HAE-C1-INH. This study aimed to evaluate patient screening using dried blood spots (DBS) on filter paper compared with the current technique using chromogenic assays. **Methods:** A multicenter prospective study of patients with HAE divided into: G1 – HAE-C1-INH (n = 53; types 1 = 48 and 2 = 5); G2 – HAE with FXII mutation (HAE-FXII) (n = 30); G3 – HAE with unknown mutation (HAE-UNK) (n = 10); and G4 – Control (n = 10). C4 and C1-INH levels were measured (radial immunodiffusion); functional C1-INH levels were assessed using chromogenic assay and DBS. Statistical analysis used GraphPad Prism. The protocol was approved by the Ethics Committee (CAAE:41812720010010082). **Results:** The median C4 and C1-INHq levels were, respectively, 9.14 and 8.9 mg/dL for G1; 33.2 and 34.2 mg/dL for G2; 35.3 and 29.4 mg/dL for G3; and 32.2 and 35.3 mg/dL for G4. The median fC1-INH levels obtained by chromogenic assay and by DBS were, respectively, 35% and 0% for G1; 120% and 81% for G2; 120% and 91% for G3; and

RESUMO

Introdução: O angioedema hereditário (AEH) é raro, caracteriza-se por edema em subcutâneo, trato gastrointestinal e vias aéreas superiores. A deficiência do inibidor de C1 decorre da mutação em *SERPING1* (AEH-C1-INH) que resulta em acúmulo de bradicinina e maior permeabilidade endotelial. O AEH também pode apresentar-se com C1-INH normal. A avaliação funcional do C1-INH permite detectar as duas formas de AEH-C1-INH. O objetivo do estudo foi avaliar a triagem de pacientes usando amostras de gota de sangue seca (DBS - Dried blood spot) em papel filtro comparada à técnica atual por ensaio cromogênico. **Métodos:** Estudo multicêntrico, prospectivo, em pacientes com AEH subdivididos em: G1 - AEH-C1-INH (n = 53; tipos 1 = 48 e 2 = 5); G2-AEH com mutação de FXII (AEH-FXII) (n = 30) e G3-AEH sem mutação conhecida (AEH-UNK) (n = 10) e G4 - Controle (n = 10). Realizadas dosagens de C4 e C1-INH (imunodifusão radial); C1-INH funcional (ensaio cromogênico e DBS). A avaliação estatística utilizou o programa GraphPad Prism. O protocolo foi aprovado pelo Comitê de Ética (CAAE:41812720010010082). **Resultados:** Valores de C4 e C1-INHq resultaram em mediana de 9,14 e 8,9 mg/dL para G1; G2 de 33,2 e 34,2 mg/dL; G3 de 35,3 e 29,4 mg/dL e G4 32,2 mg/dL e 35,3 mg/dL respectivamente. Valores de fC1-INH pelo ensaio cromogênico e por DBS resultaram em mediana de 35% e 0% em G1; G2 de 120% e 81%; G3 de 120% e 91%; e em G4

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This study won the Antônio de Oliveira Lima Prize at the 2023 ASBAI Brazilian Congress of Allergy and Immunology, Maceió, Alagoas, Brazil.

Submitted May 30 2024, accepted Aug 04 2024.

Arq Asma Alerg Imunol. 2024;8(3):235-43.

32.2% and 35.3% for G4. G1 had 42/53 samples (79.2%) and 53/53 (100%) with reduced fC1-INH, respectively. In G2, 30/30 (100%) and 28/30 (93.7%) had fC1-INH above 50%, respectively. In G3 and G4, fC1-INH was normal with both techniques.

Conclusion: The fC1-INH measured in DBS samples allows a more precise identification of patients with HAE-C1-INH than using the chromogenic assay. DBS samples are simple to collect and easy to transport, facilitating the diagnosis of HAE-C1-INH.

Keywords: Hereditary angioedema, C1 inhibitor, factor XII, C1-INH, complement C4, biomarker, diagnosis.

de 32,2% e 35,3%, respectivamente. G1 com 42/53 amostras (79,2%) e 53/53 (100%) com fC1-INH reduzida respectivamente. Em G2 30/30 (100%) e 28/30 (93,7%) com fC1-INH acima de 50% respectivamente. Para G3 e para G4 a fC1-INH estava normal em ambas as técnicas. **Conclusão:** O fC1-INH pela técnica em DBS permite identificar os pacientes com AEH-C1-INH com maior precisão que o ensaio cromogênico. Trata-se de coleta simples, de fácil transporte, facilitando o diagnóstico de AEH-C1-INH.

Descritores: Angioedema hereditário, inibidor de C1, fator XII, C1-INH, Complemento C4, biomarcador, diagnóstico.

Introduction

Hereditary angioedema (HAE) is a term used to describe isolated and/or recurrent episodes of angioedema in subcutaneous and submucosal tissues. It often involves the face, extremities, gastrointestinal tract, genitalia, and upper airways, but is not associated with urticarial-type skin lesions. It often affects multiple family members due to its autosomal dominant inheritance, with 75% of patients having a family history and 25% a *de novo* mutation.¹ There are different types of HAE; the most common subtype is HAE with C1 inhibitor (C1-INH) deficiency (HAE-C1-INH), which is caused by more than 800 mutations affecting the *SERPING1* gene.^{2,3}

Most mutations in *SERPING1* lead to a quantitative deficiency in the synthesis and secretion of C1-INH (HAE-C1-INH type 1), with diagnosis based on low plasma levels of C1-INH (C1-INHq). In approximately 15% of HAE-C1-INH cases, the mutation results in an abnormal protein, detected by functional C1-INH assay (fC1-INH), which is characterized as HAE-C1-INH type 2.⁴ In these patients, quantitative C1-INH levels are normal or high, while C4 levels and functional C1-INH activity are low.^{1,4,5}

C1-INH is a protease inhibitor that inhibits the complement, fibrinolytic, coagulation, and kinin-kallikrein pathways; its deficiency results in uncontrolled release of bradykinin. Bradykinin binds to the B2 receptor on endothelial cells, leading to vasodilation and a release of nitric oxide.^{6,7} However, some patients have normal C1-INH in both value and function (HAE-nC1-INH), which has to date been associated with 8 different mutations. The identified

gene mutations affect coagulation factor XII gene (HAE-FXII)⁸, plasminogen⁹, angiopoietin-1¹⁰, kininogen¹¹, myoferlin¹², heparan sulfate-glucosamine 3-O-sulfotransferase 6¹³, carboxypeptidase N subunit 1¹⁴ and disabled homolog 2-interacting protein^{15,16}. Despite the variety of diagnostic tools, the difficulty lies in accessing the tests and appropriately collecting and handling the samples, given that complement system proteins are thermolabile, i.e., they must be collected quickly and aliquoted at -80 °C for subsequent laboratory assessment.^{1,5,17,18} Moreover, few clinical laboratories in Brazil can determine quantitative and functional C1-INH levels.^{19,20} It is costly to ship samples to distant locations, since they must be packaged in dry ice and delivered quickly. Providing a way to send samples without compromising the functional evaluation of C1-INH would be essential to improving access to HAE-C1-INH diagnosis. In light of the above, the present study aimed to compare functional C1-INH (fC1-INH) levels using filter paper samples (dried blood spot - DBS) to chromogenic assay for HAE-C1-INH diagnosis.

Methods

This multicenter, prospective study included patients > 1 year of age with a confirmed diagnosis of HAE based on clinical presentation, positive family history, and confirmatory biochemical tests for patients with C1-INH deficiency and/or genetic tests for HAE with normal C1 inhibitor. After initial screening, 93 patients were divided into 4 groups: (G1) HAE-C1-INH

(type 1 [n = 48] and type 2 [n = 5]); (G2) HAE-FXII (n = 30); (G3) HAE with normal C1 inhibitor with an unknown mutation (HAE-UNK) (n = 10), because exome sequencing revealed no mutations currently described in the literature; and finally (G4), controls (n = 10). Patients unable to provide informed consent or who were diagnosed with acquired angioedema and/or diseases that could result in complement system dysfunction, such as nephropathies and hepatopathies, were excluded.

The samples were separated by centrifuging freshly collected blood at 3000 rpm for 10 minutes at 4 °C. They were immediately aliquoted and stored at -80 °C to determine plasma levels of C1-INH (C1-INHq), C4, and functional C1-INH (fC1-INH) by the chromogenic method. C4 and C1-INHq were measured by radial immunodiffusion, while fC1-INH was assessed by chromogenic assay and DBS. A commercial Technochrom C1-INH kit was used to determine the functional activity of C1-INH by the chromogenic method. In this technique, synthetic C1 esterase (C1s) substrate is incorporated in the plasma sample to measure the inhibitory activity of C1-INH protein. Through the chromogenic method, fC1-INH is measured by the reaction between C1s and its artificial substrate, Z-Lys-SBzl•HCl, to produce Cbz-Lys and thiomethyl-benzene. Thiomethyl-benzene is measured by chromogenic assay, after derivatization with 5,5'-dithiobis-(2-nitrobenzoic acid). Less intense color indicates greater C1 inhibitor activity due to lower production of thiomethyl-benzene, which is a product of the reaction of C1s and the substrate. Hence, more intense color suggests reduced C1 inhibitor function.

Blood was also collected in EDTA Vacutainer tubes. After collection, the tubes were inverted to resuspend the blood cells, and 60 µL aliquots were placed on the filter paper, which was dried for ≥ 3 hours at room temperature, stored at -20 °C for up to 180 days, and sent to PerkinElmer Genetics for fC1-INH testing via DBS.

Standardized material provided by PerkinElmer Genetics was used for the DBS sampling procedure, in which liquid chromatography/mass spectrometry was used to measure fC1-INH. In this assay, C1-INH is first extracted from the DBS cards and bound to the excess C1s. After that, a reaction is performed with the C1s that was not bound with its substrate in the previous steps. This produces Cbz-Lys and thiomethyl-benzene. The Cbz-Lys product is analyzed directly by liquid chromatography/mass spectrometry. Thus, this

method measures the inhibitory activity of C1s through the C1-INH present in the samples.²¹

We considered normal C4 values to be 16.7-38.5 mg/dL for women and 16.2-44.5 mg/dL for men. Normal C1-INHq values were 19.5-34.5 mg/dL. Normal fC1-INH values were > 69% according to the Technochrom kit and > 62.8% for DBS, according to PerkinElmer Genetics. However, in the literature, values > 50% are used for diagnosis.^{3,17,22}

The study was approved by the Centro Universitário FMABC Research Ethics Committee (decision 41812720010010082). Patients and volunteers provided written informed consent prior to inclusion.

Results

All groups were predominantly female. In G1, the mean age was 40 (SD, 17.7) years for HAE-C1-INH type 1, and 27 (SD, 13.4) years for HAE-C1-INH type 2. In G2, the mean age was 38 (SD, 18.6) years, while in G3 it was 40 (SD, 14.4) years. The majority of patients in all groups were symptomatic at diagnosis, with the mean age at symptom onset ranging from 10 to 26 years (Table 1).

The median serum C4 and C1-INHq levels were 9.14 and 8.9 mg/dL, respectively, in G1; 33.2 and 34.2 mg/dL, respectively, in G2; and 35.3 and 29.4 mg/dL, respectively, in G3 (Table 2). Two patients with HAE-C1-INH type 1 had above normal C4 values (a 4-year-old child and a 27-year-old adult). All patients with HAE-C1-INH type 2 had low C4 values. All values in G2, G3, and G4 were normal (Figure 1).

C1-INHq values were low in 100% of the HAE-C1-INH type 1 patients and high in the 5 patients with HAE-C1-INH type 2, as well as in the G2, G3, and G4 groups (Figure 2).

For fC1-INH by chromogenic assay, the median values were 35% for G1 and 120% for G2 and G3. For fC1-INH by DBS, the median values were 0% for G1 81% for G2, and 91% for G3 (Table 2).

For chromogenic fC1-INH, the G1 values were < 50% in 42 of the 53 patients (79.2%), with 10 HAE-C1-INH type 1 patients and 4 HAE-C1-INH type 2 patients having values > 50%. fC1-INH was > 50% in G2, G3, and G4, (Table 2 and Figure 3). For DBS fC1-INH, the G1 values were < 50% in 100% of the patients. In G2, 2 pregnant women had low values and 28 patients had normal values. In G3 and G4, all values were > 50% (Table 2 and Figure 4).

Table 1

Distribution and characteristics of patients with HAE according to group

	G1		G2	G3	G4
	HAE-C1-INH type 1	HAE-C1-INH type 2	HAE-FXII	HAE-UNK	Control
Distribution	48	5	30	10	10
Women n (%)	35 (72.9%)	4 (80 %)	20 (66.6%)	10 (100%)	4 (40%)
Mean age (years) (SD)	40 ($\pm$ 17.6)	28 ($\pm$ 13.4)	38 ($\pm$ 18.6)	40 ($\pm$ 14.1)	23 ($\pm$ 25.8)
Mean age at symptom onset (years) (SD)	15 ($\pm$ 11.2)	10 ($\pm$ 4.5)	20 ($\pm$ 10.2)	26 ($\pm$ 10.2)	–
Symptomatic	44 (91.6%)	5 (100%)	23 (76.6%)	10 (100%)	–
Asymptomatic	4 (8.4%)	0	7 (23.4%)	0	10 (100%)
Total		53	30	10	10

HAE = hereditary angioedema, FXII = coagulation factor XII mutation, UNK = unknown mutation, C1-INH = C1 esterase inhibitor.

Table 2

Distribution of biochemical values according to group among patients with HAE

	G1		G2	G3	G4
	HAE-C1-INH type 1	HAE-C1-INH type 2	HAE-FXII	HAE-UNK	Control
Median C4 (mg/dL)	9.14		33.2	35.3	32.20
Median C1-INHq (mg/dL)	8.9		34.2	32.25	35.30
Chromogenic fC1-INH n (%)					
$\leq$ 50%	38 (79.1%)	4 (71.5%)	–	–	
$\geq$ 50 %	10 (20.9%)	1 (28.5%)	30 (100%)	–	10 (100%)
Median chromogenic fC1-INH (%)	35		120	120	119.80
DBS fC1-INH n (%)					
$\leq$ 50%	48 (100%)	5 (100%)	2 ^a (6.6%)	–	–
$\geq$ 50 %	–	–	28 (93.4%)	10 (100%)	10 (100%)
Median DBS fC1-INH (%)	0		81.8	109.63	101.20
Total patients	48	5	30	10	10

^a Pregnant.

HAE = hereditary angioedema, FXII = coagulation factor XII mutation, UNK = unknown mutation, C1-INHq = amount of C1 esterase inhibitor, fC1-INH = function of C1 esterase inhibitor.

Discussion

When not diagnosed or properly treated, HAE is potentially fatal, with a mortality rate of 25% to 40% due to glottis edema and asphyxia. (23, 24) An HAE mortality study found a mortality rate of around 17.5%, with only 13% being diagnosed before death.²⁵ This reflects a myriad of factors, such as the ability to recognize the disease, a lack of specialists, and difficulty accessing treatment and diagnostic tests.^{20,26} For example, in Brazil's Unified Health System, only two laboratories are capable of performing all the diagnostic tests²⁷, i.e., C4, C1-INHq, and fC1-INH measurement. When evaluating these components, the blood samples must be processed as quickly as possible in serum and/or EDTA plasma. If the analysis is not performed immediately, the samples must be frozen at -80 °C until they are analyzed or must be shipped in dry ice to specialized laboratories. Another point is that repeated freezing and thawing can lead to in vitro activation of the complement.¹⁸

Currently, to diagnose patients with suspected HAE, the investigation can begin by requesting C4 screening, which several laboratories provide. However, this strategy has low specificity, since C4 can still be normal in 27% of those with HAE-C1-INH.^{28,29} Another relevant test is C1-INHq, which will only be reduced in patients with HAE-C1-INH type 1. Thus, measuring fC1-INH is important for diagnostic purposes due to its potential to diagnose both HAE-C1-INH type 1 and 2.

Given this difficult scenario, in which samples must be shipped to distant locations, it became evident that the collection method and climatic conditions can affect HAE diagnosis. Eleven patients from G1 (HAE-C1-INH) in our study had normal fC1-INH values in the chromogenic assay. With DBS (filter paper), all 53 patients in G1 had C1-INHf values < 50% (HAE-C1-INH), despite sending the samples to another country long after collection. The samples were kept at -20 °C (common freezer) and processed within 180 days (6 months), which did not compromise the results.

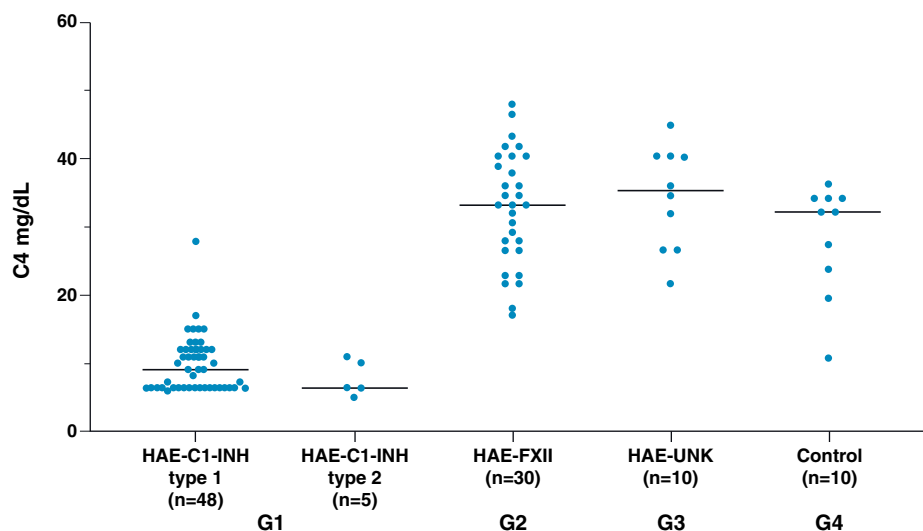


Figure 1

C4 values according to group among patients with HAE

HAE-1 = hereditary angioedema type 1, HAE-2 = hereditary angioedema type 2, HAE-FXII = hereditary angioedema with coagulation factor XII mutation, UNK = hereditary angioedema with unknown mutation.

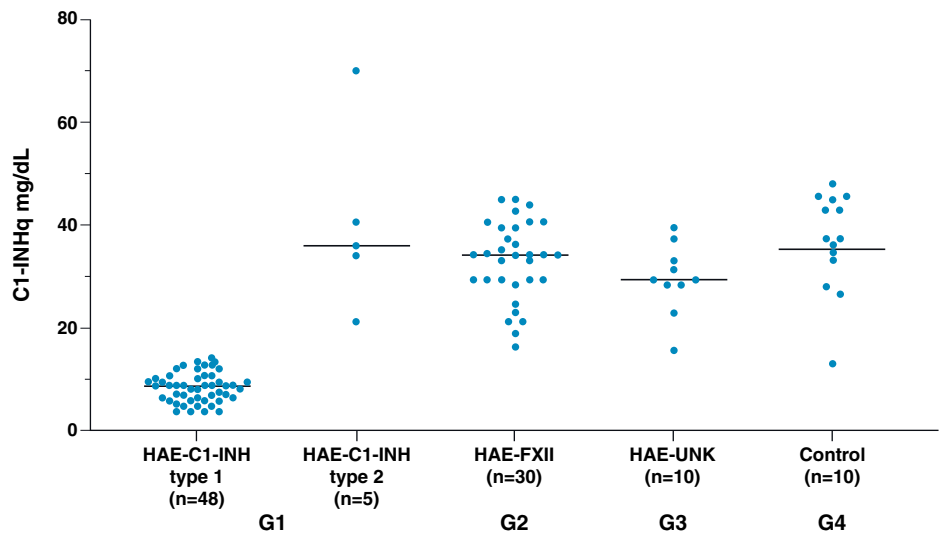


Figure 2
C1-INH values according to group among patients with hypertension
HAE-C1-INH type 1 = hereditary angioedema type I, HAE-C1-INH type 2 = hereditary angioedema type 2, HAE-FXII = hereditary angioedema with coagulation factor XII mutation, UNK = hereditary angioedema with unknown mutation, fC1-INH = amount of C1 esterase inhibitor.

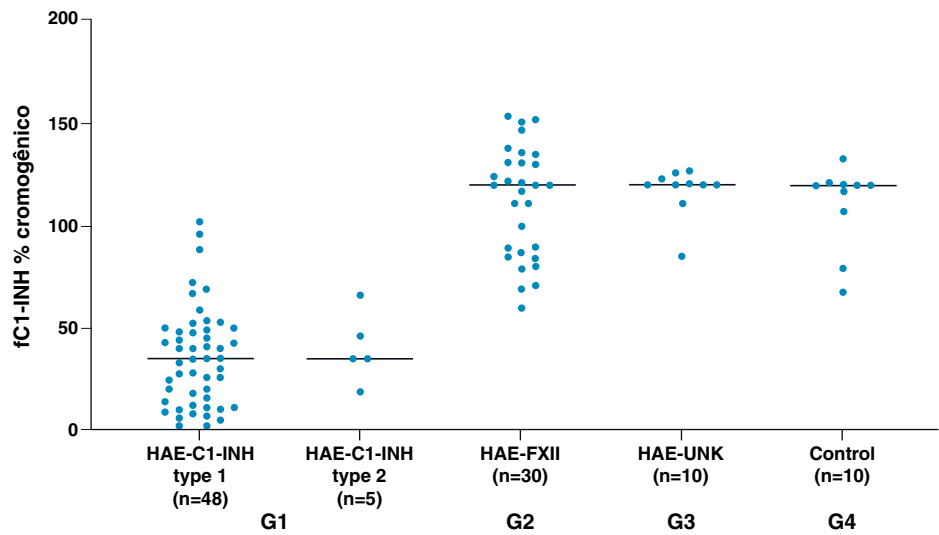
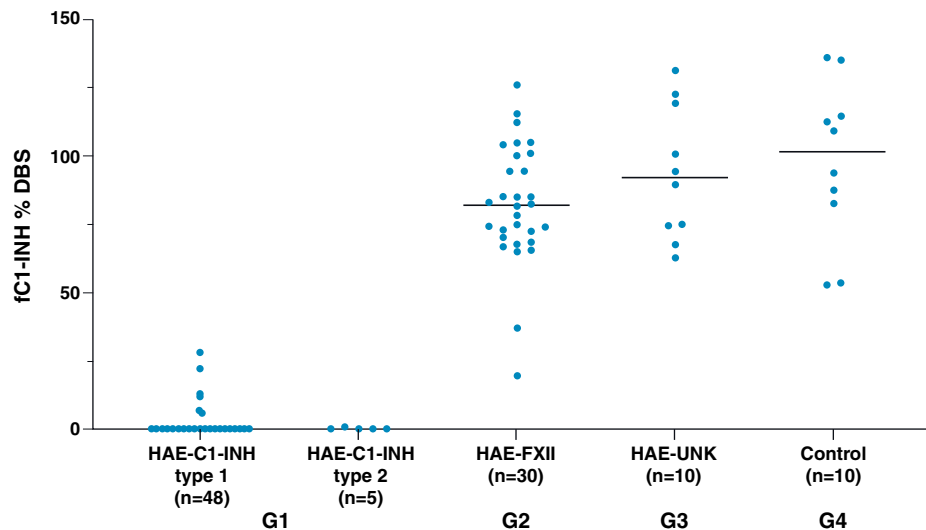


Figure 3
C1-INH function values in patients with HAE according to chromogenic assay
HAE-C1-INH type 1 = hereditary angioedema type I, HAE-C1-INH type 2 = hereditary angioedema type 2, HAE-FXII = hereditary angioedema with coagulation factor XII mutation, UNK = hereditary angioedema with unknown mutation, fC1-INH = C1 esterase inhibitor function.

**Figure 4**

C1-INH function values in patients with HAE according to DBS assay

HAE-C1-INH type 1 = hereditary angioedema type I, HAE-C1-INH type 2 = hereditary angioedema type 2, HAE-FXII = hereditary angioedema with coagulation factor XII mutation, UNK = hereditary angioedema with unknown mutation, fC1-INH = C1 esterase inhibitor function.

From a methodological point of view, the chromogenic assay is based on 2 reaction steps, while the liquid chromatography/mass spectrometry assay measures the direct product of the C1s reaction, i.e., the assay variation may be smaller.²¹

Two patients with HAE-C1-INH type 1 had above-normal C4 values, i.e., 4% of patients with HAE-C1-INH type 1 could remain undiagnosed if only this screening method were used. It is worth noting that after DBS sample standardization, fC1-INH in whole blood remained stable for 7 days at 4 °C, for up to 3 days at 45 °C, and for 134 days when stored at room temperature²¹, which could facilitate the testing process by reducing shipping costs.

It is also worth mentioning that the DBS technique was applied to patients with normal C1 inhibitor levels, since its validation study only involved patients with

C1-INH deficit. Interestingly, in the DBS results for the group with HAE-nC1-INH and FXII mutation, pregnant women had reduced (< 50%) fC1-INH.

Conclusions

The study demonstrated that, in comparison with the chromogenic test, assessing fC1-INH with the DBS technique is a reliable method of HAE-C1-INH diagnosis. It has superior reproducibility and greater diagnostic accuracy due to its simple, easy-to-transport, and thermostable samples.

Acknowledgements

The authors would like to thank Takeda for the financial and infrastructure support, the participating centers, and the FMABC team.

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Financing: Maine L. D. Bardou received a LASID researcher initiative grant in 2022-2023 (Takeda Scholarships). Anete S. Grumach is a CNPq productivity fellow (309824/2021-4) and holds a Shire/Takeda researcher initiative grant.

Conflict of interests: Maine L. D. Bardou and Ana Júlia Ribeiro Teixeira declare no conflicts of interest. Anete S. Grumach is a speaker and/or consultant for Takeda, CSL Behring, Pharvaris, Kalvista, Exeltis, Pint-Pharma, Biomarin, Binding site, and

Multicare. She holds a CNPq productivity grant and a grant from Shire/Takeda to support investigator-initiated research. Maria Luisa O. Alonso, Pedro Giavina-Bianchi, Solange O. R. Valle and Eli Mansour have received financial support and/or honoraria from Takeda and CSL Behring.

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Prurigo nodularis: what do patients and their skin have to tell us?

Prurigo nodular: o que o paciente e a sua pele têm a nos dizer?

Bruno Emanuel Carvalho Oliveira¹

ABSTRACT

Prurigo nodularis (PN) is a chronic skin disease characterized by pruritic lesions that can severely affect quality of life, impacting daily activities, sleep, mental health, and social relationships. Its pathogenesis involves a complex neuroimmune feedback loop. The case of a young patient illustrates the suffering caused by PN, which led to school dropout, social isolation, and depressive symptoms. After failure of treatment with corticosteroids and methotrexate, dupilumab treatment and psychological and psychiatric support were initiated. The management of PN requires humanized care and personalized strategies to minimize the impact of the disease and improve quality of life.

Keywords: Pruritus, quality of life, chronic disease.

RESUMO

O Prurigo Nodular (PN) é uma doença crônica da pele caracterizada por lesões pruriginosas que afetam gravemente a qualidade de vida, com impacto em atividades diárias, sono, saúde mental e relações sociais. Sua patogênese envolve um ciclo neuroimune complexo. O caso de uma jovem paciente ilustra o sofrimento causado pelo PN, que levou ao abandono escolar, isolamento social e sintomas depressivos. Após falhas terapêuticas com corticoides e metotrexato, iniciou tratamento com dupilumabe e suporte psicológico e psiquiátrico. O manejo do PN exige cuidado humanizado e estratégias personalizadas para minimizar o impacto da doença e melhorar a qualidade de vida.

Descritores: Prurigo, qualidade de vida, doença crônica.

Introduction

The term “prurigo” derives from the Latin “pruire,” which means “itching,” and was coined by Ferdinand von Hebra in 1850, in Vienna, when describing papules and nodules accompanied by intense pruritus. However, some authors attribute to Robert Willan, more than 200 years ago, the first description of pruritic papules under the term “prurigo.”

Prurigo is a reactive hyperplastic skin condition that manifests clinically as isolated or multiple papules, plaques, and/or nodules with intense pruritus. Some authors classify prurigo based on different criteria,

such as type (acute, subacute, or chronic), clinical form, or causative agent/associated disease.¹

All information and concepts are widely available in the main studies and literature reviews on prurigo. However, it is crucial that we focus on the particularities of each patient and the major impact that the disease has on their lives. For this reason, we chose not to present a traditional case report from the physician's perspective, but rather to share the patient's own perspective. This case, full of particularities, suffering, and pain, illustrates the reality that we can encounter in

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Submitted July 10 2024, accepted Aug 05 2024.

Arq Asma Alerg Imunol. 2024;8(3):244-9.

our daily practice as allergists and immunologists. Our objective is to encourage deep and comprehensive reflection that will inspire others to search for all the necessary tools to offer the best support to patients.

Case report from the patient's perspective

"Doctor, I am 17 years old and have suffered from recurring wounds on my body since I was a child. Although treated with dermatological ointments, the wounds always returned, marking my childhood with trips to the doctor's office. Starting in 2021, the frequency and severity of the wounds increased, even with the continued use of ointments. In 2023, the boils on my leg and lesions became so severe that I was unable to wear a bra due to a lesion on my back. I saw a dermatologist and was diagnosed with atopic dermatitis. The initial treatment lost its effectiveness over time, and the lesions began to affect my social and personal life to the point that I could not get dressed for school. The shame of my body, intensified by the bullying I suffered at school, being called 'scabby' and 'mangy,' led me to drop out of school, something I had always loved. There were days when I could not wash my hair because of the painful wounds on my arm. I needed my aunt's help for simple everyday tasks. Taking a shower was a pain because my body ached from the water and the prescribed soaps. The search for medical help, with visits to several specialists and the use of different medications, was unsuccessful. The disease prevents me from doing the things I love, because I feel ashamed of my body and fear judgment from others. I avoid wearing clothes that expose my wounds, which leads me to isolate myself at home. Even when I go out, I wear clothes that hide me. I would like to go back to playing volleyball and attending school normally. My romantic relationships are also affected. Last year, I had an online relationship that I ended by putting off meeting in person for fear of being judged. I believe my condition contributed to the end of the relationship. Recently, the disease has worsened, with the appearance of nodules and lesions on my face and flaking on my scalp. This has made me extremely sad. At the beginning of the year, I sought help from a family member and, since then, my mother has been providing me with psychological support. I feel like I lost half of my teenage years because of the pain and lack of motivation caused by the disease. I wish I could go back to living the way I used to, but the pain and wounds prevent me from doing so. I really need your help."

Prurigo nodularis (PN) is a chronic skin disease, present for more than 6 weeks, characterized by history and/or signs of repeated pruritus and the presence of multiple pruritic lesions of the nodular type, which may be localized or generalized (see diagnostic criteria in Table 1). A Japanese consensus² classified the types of prurigo according to the underlying cause, as shown in Table 2.

Prurigo in general, and PN in particular, can be extremely debilitating for patients. Indeed, prurigo represents a significant public health burden, contributing to a large number of years lived with disability. It is a major source of morbidity globally,



Figure 1

Numerous infiltrated and excoriated hyperkeratotic nodules on the right arm and abdomen

compared even with other chronic diseases such as anxiety disorders and diabetes mellitus. PN has a profound impact on individual health, affecting sleep, resulting in school and/or work absenteeism, compromising mental health and quality of life, and increasing the need for care. Substantial impacts on quality of life have been demonstrated in other pruritic skin conditions, such as atopic dermatitis (AD) and chronic urticaria.³ However, there are conflicting data on the specific impact of PN on quality of life. In a systematic review and meta-analysis of studies that assessed symptom and quality-of-life burden in patients with PN, Janmohamed et al. evaluated 13

studies and concluded that quality of life is negatively impacted in PN.⁴ They recommend that clinicians be aware of the burden of disease on their patients, monitor their quality of life, and incorporate this information into treatment decision-making.⁵

The pathogenesis of PN is associated with a self-sustained itch-scratch vicious cycle. Although recent research has partially elucidated the complex interactions of the cutaneous neuroimmune network, the underlying mechanism is still not fully understood.

Several mediators play a crucial role in pruritus amplification in PN. These include a number of pro-inflammatory and pruritogenic mediators, such as cytokines (IL-4, IL-13, IL-31, oncostatin M, IL-17, IL-22, and TSLP), neuropeptides (substance P, calcitonin gene-related peptide [CGRP], cortistatin), neurophins (nerve growth factor [NGF]), extracellular matrix proteins (periostin), vasculogenic substances (vascular endothelial growth factor [VEGF], endothelin-1 [ET-1]), ion channels, and intracellular signaling pathways

Table 1
Diagnostic criteria for chronic prurigo

Major criteria
i. Chronic pruritus (≥ 6 weeks) ii. History and/or signs of repeated pruritus iii. Presence of multiple localized or generalized pruritic lesions^a
Associated criteria
i. Signs: Pruritic lesions: symmetrically distributed, rarely affecting the face and palms Signs of scratching: excoriation, scars, lichenification ii. Diversity of clinical manifestations Papular type Nodular type Plaque type Umbilicated type Linear type iii. Symptoms Usually pruritic lesions develop after the onset of pruritus Quality: pruritus, burning, pain, or stinging Signs of chronicity: great intensity of pruritus, allokinesis, hyperkinesia, continuous increase in the number of lesions Impaired quality of life, loss of sleep, days of absenteeism from work, and/or obsessive-compulsive behavior iv. Emotions Depression Anxiety Anger Disgust Shame Hopelessness

^a Definition of pruritic lesions: excoriated papules and/or nodules and/or desquamative and crusted plaques, often with a whitish or pink center and hyper-pigmented border.

Adapted from Satoh T. et al.¹

Table 2
Classification of chronic prurigo according to the underlying cause

Symptomatic prurigo (associated with underlying systemic or cutaneous conditions)
Prurigo in atopic dermatitis
Prurigo in diabetes mellitus
Prurigo in renal failure
Prurigo in liver failure
Prurigo in internal malignancy
Prurigo in hematological malignancy
Prurigo associated with eczematous diseases
Prurigo in HIV infection/pruritic-papular eruption of HIV (prevalence of 24% to 36%)
Prurigo in pregnancy/Prurigo gestationis (special form: polymorphic eruption of pregnancy)
Prurigo in allergy to drugs
Prurigo in allergy to metals
Prurigo in psychiatric diseases
Idiopathic prurigo (undetermined cause)

Insect bite reaction

Adapted from Satoh T. et al.¹.

(members of the Janus kinase [JAK] family: JAK1, JAK2, JAK3, and TYK2). A deeper understanding of the mechanism of action of these mediators will be critical for the development of new targeted antipruritic agents.

Approximately half of patients with PN also have AD or atopic predisposition, suggesting a possible overlap in the pathogenesis of the two diseases. Although both diseases feature type 2 inflammation, recent transcriptomic studies have clearly differentiated PN from AD. PN does not exhibit the strong type 2 response pattern that is typically found in AD, but it is characterized by stromal remodeling and neurovascular dysregulation.^{5,6}

The therapeutic approach to PN is currently based on case series and clinical experience. Treatment can be challenging due to recurrence of lesions, often associated with underlying diseases, or the limitation of the use of systemic medications in patients susceptible to adverse effects. Table 3 lists a series of approaches reported in the literature, both pharmacological and non-pharmacological. However, treatment success relies heavily on the correct diagnostic classification and identification of underlying conditions.⁷



Figure 2
Numerous infiltrated and excoriated hyperkeratotic nodules on the lateral portion of the right thigh and buttock

After analyzing the patient’s report, the impact of the disease on several areas of her life is enormous, including daily activities, school performance, interpersonal relationships, and social and leisure activities, as is the number of years lived with disability. The Dermatology Life Quality Index (DLQI) showed a score of 30, indicating an extreme effect on the patient’s quality of life. In addition to PN, the patient has a diagnosis of AD, allergic rhinitis, and asthma, comorbidities that also contribute to the impairment of her quality of life. The patient’s treatment history includes multiple cycles of oral corticosteroids, with negative consequences for her health, and methotrexate for 3 months, discontinued due to adverse gastrointestinal effects. Treatment with dupilumab was initiated 1 month ago, and the patient

was referred for psychiatric support due to depressive symptoms and advised to continue psychological therapy. Monthly follow-up was suggested to monitor and evaluate the effectiveness of the proposed therapies.

In conclusion, PN exerts a negative impact on the personal, professional, and social life of patients. Providing a space for these patients to express their feelings regarding the disease is the first step in the treatment process. Therefore, it is essential to raise this issue, seeking a global assessment of these individuals to establish a more comprehensive, effective, and personalized therapy. As the physician, professor, researcher, and writer from Minas Gerais, Celmo Celeno Porto, wisely expressed: *“We must have compassion for our patients. Compassion is*

Table 3
Treatments indicated for prurigo

Topical treatments
Emollients
Topical corticosteroids ^a
Calcineurin inhibitors (tacrolimus/pimecrolimus)
Intralesional corticosteroids ^a
Topical capsaicin ^a
Systemic treatments
UV phototherapy (narrow band UVB)
H1 antihistamines
Gabapentin, pregabalin ^a
Antidepressants (e.g., mirtazapine) ^a
Cannabinoids
Immunosuppressants (methotrexate, cyclosporine A) ^a
Thalidomide ^a
Neurokinin 1 antagonist (NK1 - aprepitant) ^a
μ-opioid receptor antagonist (naloxone, naltrexone) ^a
JAK inhibitors (abrocitinib, tofacitinib, upadacitinib) ^a
Anti-IL-4/13: dupilumab ^a
Anti-IL-31: nemolizumab ^a
Anti-oncostatin anti-receptor (OSMRb/IL-13): vixarelimab ^a
KIT anti-receptors (CDX-0159) ^a

^a Indicated in chronic prurigo.
Adapted from Satoh T. et al.¹.

understanding the patient's suffering, whatever it may be, not just the pain, and doing everything in your power to eliminate or reduce it."

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No conflicts of interest declared concerning the publication of this article.

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Rapid idursulfase desensitization tailored to a patient with mucopolysaccharidosis type II

Dessensibilização rápida à idursulfase adaptada para um paciente com Mucopolissacaridose tipo II

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ABSTRACT

Mucopolysaccharidosis type II (MPS II), or Hunter syndrome, is a rare X-linked disease characterized by the accumulation of glycosaminoglycans (GAGs) due to deficiency of the enzyme iduronate-2-sulfatase. Standard treatment is enzyme replacement therapy (ERT) with idursulfase, which, although effective, can cause serious adverse reactions, including anaphylaxis. Desensitization is an option in cases of severe allergic reactions when no viable alternative treatment is available. We report the case of a 9-year-old boy with MPS II who, after 2 years and 9 months of idursulfase use, developed severe allergic reactions during infusion. Skin testing indicated a possible IgE-mediated hypersensitivity reaction. After several attempts to adjust the infusion rate and to use premedication, we decided to perform desensitization using a protocol based on that described by Professor Castells. The first attempt was unsuccessful. However, after adjustments to the infusion rate and use of additional premedication, the patient began to tolerate the full dose of idursulfase weekly. Immediate hypersensitivity reactions to idursulfase are common, and skin testing is useful to identify IgE-mediated reactions. Desensitization was effective in this case, avoiding treatment discontinuation. The adjustments were tailored to the patient's response, highlighting the importance of an individualized approach. Idursulfase desensitization is a safe and effective option for patients with MPS II who experience severe immediate hypersensitivity reactions to ERT. This case contributes to the understanding of the management of allergic reactions during treatment with idursulfase, encouraging future studies to improve the technique.

Keywords: Idursulfase, mucopolysaccharidosis type II, Hunter disease, desensitization.

RESUMO

A Mucopolissacaridose tipo II (MPS II), ou Síndrome de Hunter, é uma doença genética rara ligada ao cromossomo X, caracterizada pelo acúmulo de glicosaminoglicanos (GAGs) devido à deficiência da enzima iduronato-2-sulfatase. O tratamento padrão é a terapia de reposição enzimática (TRE) com idursulfase, que, apesar de eficaz, pode provocar reações adversas graves, incluindo anafilaxia. A dessensibilização é uma opção em casos de reações alérgicas graves quando não há terapias substitutas viáveis. Relatamos o caso de menino de 9 anos, com MPS II, que após 2 anos e 9 meses de uso de idursulfase desenvolveu reações alérgicas graves durante as infusões. Testes cutâneos indicaram uma possível reação de hipersensibilidade mediada por IgE. Após várias tentativas de ajuste da infusão e uso de pré-medicações, optou-se pela dessensibilização, utilizando protocolo baseado no descrito pela Profa. Castells. A primeira tentativa foi malsucedida, porém, após modificações no tempo de infusão e uso de pré-medicação adicional, o paciente passou a tolerar a dose completa de idursulfase semanalmente. Reações de hipersensibilidade imediata à idursulfase são comuns, e os testes cutâneos são úteis na identificação de reações mediadas por IgE. A dessensibilização demonstrou ser eficaz neste caso, evitando a suspensão do tratamento. O protocolo foi ajustado conforme a resposta do paciente, destacando a importância de abordagens individualizadas. A dessensibilização à idursulfase é uma alternativa segura e eficaz para pacientes com MPS II que apresentam reações de hipersensibilidade imediata graves à TRE. Este caso contribui para a compreensão da gestão de reações alérgicas no tratamento com idursulfase, incentivando estudos futuros para aprimorar a técnica.

Descritores: Idursulfase, mucopolissacaridose tipo II, Doença de Hunter, dessensibilização.

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Introduction

Mucopolysaccharidoses (MPS) are rare, heterogeneous genetic diseases characterized by an accumulation of glycosaminoglycans in tissue lysosomes, leading to various systemic manifestations over time.^{1,2} Mucopolysaccharidosis type II (MPS II), or Hunter Syndrome, is a recessive disease linked to the X chromosome, which thus primarily affects males.^{3,4} The disease's prevalence ranges from 0.38 to 1.07 per 100,000 live births⁵, and it was first described by Charles Hunter in 1917 after observing 2 brothers.⁶

In this disease, a genetic alteration occurs in chromosome Xq28, which leads to insufficient levels of the enzyme iduronate-2-sulfase, which is encoded by the IDS gene and is responsible for the degradation of glycosaminoglycans. The lack of this enzyme leads to an accumulation of lysosomal glycosaminoglycans, which results in organomegaly and dysfunction in a number of systems, such as the ocular, central nervous, skeletal, respiratory, cardiac, and gastrointestinal systems. This dysfunction can range from mild (often without cognitive deficit) to severe (with significant cognitive deficit and possible organ failure, especially in the heart).⁷⁻¹⁰

For many years, treatment was limited to supportive and palliative measures. However, this has changed since the genetic and pathophysiological bases of the disease were discovered: bone marrow and hematopoietic cell transplants were introduced in 1980 and enzyme replacement therapy, which remains the most widely used treatment, was introduced in 2006.¹¹⁻¹³

Idursulfase (brand name Elaprase) provides the deficient enzyme to MPS II patients, resulting in the breakdown of accumulated glycosaminoglycans, which is essential for treatment.¹⁴ This drug is indicated for all symptomatic patients with a confirmed diagnosis of MPS II, although there are still some questions about its long-term benefits.^{11,15,16} The major problem with intravenous enzyme replacement therapy is that it does not reach all affected organs, especially the central nervous system, because it does not cross the blood-brain barrier. Thus, it does not reduce cognitive impairment and results in a high rate of adverse reactions during infusion, which affect up to two thirds of patients, especially in the first three months.^{11,17}

Most adverse infusion reactions are mild to moderate, such as the appearance of rash,

headache, fever, dyspepsia, urticaria, angioedema, abdominal pain, rhinitis and, in some cases, bronchoconstriction.^{17,18} These reactions are usually treated or prevented through premedications, such as antihistamines, antipyretics, or corticosteroids, in addition to changes in the infusion speed and interrupting the infusion.^{15,17,19} However, anaphylaxis has been reported in the literature, although extreme caution should be used when administering adrenaline in these patients due to the increased risk of coronary disease.^{15,20}

Adverse infusion reactions can involve hypersensitivity through IgE- and non-IgE-mediated mechanisms. Although IgG and IgM and IgE anti-idursulfase formation, triggering the complement cascade, cytokine release, direct mast cell activation, immune complex deposition, and T cell stimulation are all possible mechanisms, the exact cause is not yet fully understood.^{11,19-24} Desensitization is indicated for severe or recurrent immediate hypersensitivity reactions or when premedication fails to prevent them.¹⁹

Rapid drug desensitization is used to induce a state of hyporesponsiveness to specific allergens. This treatment involves the gradual controlled administration of the allergen to modify the patient's immune response and inhibit an immediate hypersensitivity reaction. It is indicated when patients have an immediate hypersensitivity reaction to a necessary drug and no viable alternatives are available.^{25,26}

Here we report the first description, to our knowledge, of a Brazilian case of desensitization to idursulfase.

Case report

A 9-year-old boy, born and raised in Umuarama, Paraná, weighing 37 kg, was diagnosed with MPS II at 5 years of age. He had been taking idursulfase at a weekly dose of 0.5 mg/kg since the age of 5 years, 4 months. Two years, 9 months after beginning weekly infusions (September 2022), he developed erythema and itching at the application site, minutes after the end of the infusion. At that point, premedication was begun prior to infusion (first-generation antihistamines, intravenous corticosteroids, and nonsteroidal anti-inflammatory drugs), which resolved the reactions.

In December 2022, the patient began reacting again, this time 1 h after the infusion began, resulting in erythema on the face, arms, and trunk, associated

with local itching and extreme irritation. The medication was immediately suspended and the skin symptoms abated without the further medications; the infusion was postponed until the following week. Again the following week, the skin reaction recurred 1 h after the idursulfase infusion began, but it spontaneously improved after the infusion was suspended. The patient received no other medications (Figure 1).

Since then, several infusion attempts have been made, including premedication before and during the procedure and reducing the infusion rate to a maximum of 50 mL/h, although reactions always occurred, causing considerable discomfort for the patient and family. In addition, the required dose of 18 g of medication was not being administered, reaching a maximum weekly tolerated limit of 6 g before infusions were indefinitely suspended.

In April 2023, our team was called to evaluate the case. First, skin tests were performed in a controlled environment to determine whether a specific IgE-mediated immediate hypersensitivity reaction was involved. A skin prick test with idursulfase was applied at a concentration of 2 mg/mL (undiluted), in addition to a negative control (saline solution) and a positive control (histamine). After 15 min the results were negative for idursulfase and the negative control and positive for histamine (3x3 mm). An intradermal test with idursulfase was then performed at dilutions of 1:1000 (0.002 mg/mL), 1:100 (0.02 mg/mL) and 1:10 (0.2 mg/mL), with readings 20 min after each dilution. Only the 1:10 test (0.2 mg/mL) was positive, with the initial papule increasing by 3 mm (3x3 mm to 6x6 mm).

Given that a probable IgE-mediated or mixed-mechanism reaction was observed, it was decided to perform the desensitization procedure. Since the patient had already reacted to a slow infusion at a fixed rate of 50 mL/h, this was set as the maximum achievable value.

The desensitization protocol was based on Castells et al.²⁷, in which the medication was diluted in 3 100 mL bags of 0.9% saline solution to reach a total final dose of 18 mg (0.5 mg/kg, according to the manufacturer's instructions). Concentration and infusion speed were progressively increased and vital signs were measured between stages (every 15 min) until the final stage was reached: the final speed of bag 3 was 50 mL/h, which was kept constant until the bag was completely drained, as shown in Table 1.

After the first desensitization attempt, which was preceded by premedication (oral H1-antagonist and oral corticosteroid), the patient reacted to a rate of 25 mL/h during the third bag (step 11) and the infusion had to be interrupted. In the second attempt the following week, the protocol was changed, extending step 10 (12.5 mL/h during the third bag) to



Figure 1
Skin reactions after beginning the idursulfase infusion

30 min and premedicating again after this step. Step 11 (at 25 mL/h) was also extended to 30 min. After these adjustments, the patient no longer reacted to the infusions, and these changes were maintained, subsequently allowing him to receive 18 mg of idursulfase weekly.

Discussion

If an IgE-mediated hypersensitivity reaction is suspected, the first step in the investigation is an allergy skin test involving the medication in question. For idursulfase, positivity appears to correlate well with IgE-mediated reactions. According to Kim et al., a skin prick test with idursulfase had a sensitivity of 66.7% and a specificity of 100% for IgE-mediated symptoms. Of the 34 patients who received the medication, 3 had anaphylactic reactions (8.8%) during the infusions, while the prick test for idursulfase was positive for 4

patients, including all of those who had anaphylaxis (100%). This same study found that ELISA could reveal the presence of anti-idursulfase IgE, with results > 2 SD from the mean of healthy controls in 7 patients with hypersensitivity reactions.²⁰

It has been postulated that de novo sensitization occurs due to the high purity of the medication, the dissimilarity of idursulfase's amino acid sequence to other known allergens, and the time required for reactions to begin – several infusions after initiation, as was also observed in our report.²⁰

We chose to desensitize the patient to the drug because we considered the benefits of avoiding discontinuation to outweigh the risks, since no other drug with the same function could replace it. The desensitization protocol can vary, depending on the allergen in question, the severity of the immediate hypersensitivity reaction, and patient characteristics.²⁵⁻²⁷

Table 1

Total target dose of 18 mg. The concentration in bag 1 was 0.0018 mg/mL: 0.09 mL of idursulfase (2 mg/mL) in 99.91 mL of 0.9% saline. The concentration in bag 2 was 0.018 mg/mL: 0.9 mL of idursulfase (2 mg/mL) in 99.1 mL of 0.9% saline. The concentration in bag 3 was 0.178 mg/mL: 8.9 mL of idursulfase (2 mg/mL) in 91.1 mL of 0.9% saline

Stage	Bag	Rate (mL/h)	Time (min)	Dose administered at this stage (mg)	Cumulative dose (mg)	Concentration in the bag (mg/mL)
1	1	1.3	15	0.0006	0.00	0.0018
2	1	3.1	15	0.0014	0.00	0.0018
3	1	6.3	15	0.0028	0.00	0.0018
4	1	12.5	15	0.0056	0.01	0.0018
5	2	3.1	15	0.0141	0.02	0.018
6	2	6.3	15	0.0281	0.05	0.018
7	2	12.5	15	0.0563	0.11	0.018
8	2	25.0	15	0.1125	0.22	0.018
9	3	6.3	15	0.2778	0.50	0.178
10	3	12.5	15	0.5556	1.05	0.178
11	3	25.0	15	1.1112	2.17	0.178
12	3	50.0	106.875	15.8341	18.00	0.178

Total infusion time = 271.875

Serrano reported the first desensitization to idursulfase in 2011. In this case, urticaria began after the sixth infusion. Because the skin tests were negative, it was considered a non-IgE mediated reaction, and an alternative 8-h desensitization protocol was successful.²⁸

Bustamante et al. reported that 3 years after starting idursulfase treatment, the patient presented anaphylaxis. Skin tests were performed at the same concentrations we tested, with a concentration of 1:10 (0.2 mg/mL) being positive, which also indicated that it could be an IgE-mediated reaction. In this study, 5 healthy controls were tested with all concentrations of idursulfase to rule out an irritant reaction, and all were negative. Desensitization was performed in 12 steps, as in our report, and occurred without complications.²⁹

A patient of Emeksiz et al. had an anaphylactic reaction after 12 years of weekly infusions. Since skin tests were negative, it was considered a non-IgE-mediated reaction and a 16-step desensitization procedure was used for the next infusion. The patient suffered no further reactions during the procedure, and it was repeated for subsequent infusions.³⁰

Gragnaniello et al. also desensitized a patient who had a negative skin test, but in this case the symptoms, including fever and vomiting, began 18 h after the first infusion and recurred during the eighth infusion when, 1 h after the infusion began, the patient developed a bilateral malar rash, and it was decided to perform a 7-h, 3-bag desensitization protocol. However, fever and bronchospasm occurred 4 h after desensitization began. The authors were unable to differentiate whether this reaction was due to an infectious process or to a reaction to the medication, although they subsequently collected a positive rhinovirus swab.²⁴

In any case, reactions can occur during the desensitization process, and the methods of addressing them vary considerably, depending on the team monitoring the case, since there is no defined consensus on the subject. The protocol can be maintained and the reactions treated, the protocol can be suspended and then modified, or the protocol can be resumed at a lower concentration or speed in a step prior to the reaction, all of which are valid options.²⁵⁻²⁷

Gragnaniello et al. decided to reduce the total dose to 50% of that required in subsequent infusions, following the same 3-bag desensitization process

as before and increasing the maximum tolerated dose with every 2 successive infusions, reaching the desired target dose in 1.5 months. The concentration was also progressively increased and the infusion time was reduced to 3.5 h, with no further reactions after 3 months.²⁴ However, in the present case we modified the protocol by increasing the infusion time during the final steps, in addition to repeating premedication before the step that triggered the reaction in the previous procedure.

Finally, Spataro et al. introduced a new approach to the idursulfase desensitization process. In their report, two patients with MPS II began showing symptoms of an immediate hypersensitivity reaction (hives) 1 year after the start of weekly infusions (first case) and 3 years after the start of infusions (second case). In both patients, the skin test was positive at a concentration of 1:100 and, thus, the reactions were considered to be IgE-mediated. It was decided to perform a 12-step desensitization protocol based on Casells et al. and, as in our case, the patients reacted during the procedure. The first patient reacted during step 12 of the initial desensitization at a rate of 150 mL/h, which was treated with an H1-antagonist and an intravenous corticosteroid. By reducing the infusion rate to 40 mL/h for 60 min, they were then able to resume a rate of 150 mL/h with no further reactions.³¹

The second patient, a 9-year-old boy, was very similar to our case: an initial attempt was made to increase the infusion time and decrease the total dose for several months, but the patient could only tolerate 4 mg of the total required daily dose. When desensitized with a 12-step protocol, with premedication before and between steps 8 and 9, the patient reacted during step 12 with generalized urticaria, being medicated again with an H1-antagonist and an intravenous corticosteroid. The final rate was resumed after the reaction was resolved, with no further complications.³¹

In both patients, after reactions during desensitization, an immunotherapy protocol similar to that for hymenoptera venom was implemented, which was associated with traditional desensitization. The protocol consisted of subcutaneous injections of idursulfase (3 or 4 in each session), intradermal injections spaced 20 min apart every 2 days, with increasing concentrations and volume as the steps progressed for a total duration of 3 weeks. No further reactions occurred in the first patient, so the infusion time was reduced to 3 h and premedication consisted

of oral H1-antagonist alone. It was unnecessary to continue intradermal injections in this patient after the initial 3 months. The second patient, however, continued to react for 2 further desensitization sessions. When the procedure was increased to 4 bags and 20 steps, the patient no longer reacted. Over the following weeks, the immunotherapy protocol was reduced to just 6 steps, 1 bag, and approximately 2 h.³¹

These cases, like ours, show that there are many possibilities for desensitization and that performing the procedure does guarantee a lack of reaction. Our patient no longer experiences reactions with our modified protocol, which is maintained weekly. As a next step, we intend to simplify and shorten our desensitization protocol.

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No conflicts of interest declared concerning the publication of this article.

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Intravaginal desensitization in a woman with IgE-mediated allergy to seminal fluid: a case report

Dessensibilização intravaginal em uma mulher com alergia mediada por IgE ao fluido seminal: um relato de caso

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ABSTRACT

Semen allergy is an IgE-mediated disease in which patients develop several clinical symptoms, whether local or systemic, subsequent to contact with the components of their partner's seminal fluid. Although uncommon, this allergy can have a major psychological impact on the lives of patients and their partners, which should be considered in the treatment decision-making. Treatment options include actions aimed at preventing the patient's contact with semen or interventions with specific desensitization using the sexual partner's seminal fluid. We report the case of a patient with a diagnosis of semen allergy who was treated with an intravaginal desensitization protocol to her partner's seminal fluid. This treatment allowed her to have an active sexual life, without the need for a barrier method, with the possibility of pregnancy if desired.

Keywords: Semen, hypersensitivity, immunologic desensitization.

RESUMO

A alergia ao sêmen é uma doença mediada por IgE, na qual a paciente apresenta diversos sintomas clínicos, localizados ou sistêmicos, após contato com os componentes do líquido seminal do parceiro. Apesar de não ser comum, esta alergia pode gerar um grande impacto psicológico na vida da paciente e de seu parceiro, o que deve ser considerado no momento da escolha do tratamento. As opções terapêuticas englobam, além das ações que visam prevenir o contato da paciente com o sêmen, a possibilidade de intervenção com a dessensibilização específica utilizando o fluido seminal do parceiro sexual. No presente relato, descrevemos o caso de uma paciente com diagnóstico de alergia ao sêmen, tratada com um protocolo de dessensibilização intravaginal ao líquido seminal de seu parceiro. Este tratamento possibilitou a ela ter uma vida sexual ativa, sem necessidade de uso de método de barreira, além da possibilidade de gestação.

Descritores: Sêmen, hipersensibilidade, dessensibilização imunológica.

Introduction

Semen allergy, also known as seminal plasma hypersensitivity, is a disease with uncertain incidence, manifesting with diverse clinical symptoms after contact with protein components present in the seminal fluid of a sexual partner. It is estimated that the incidence of this condition is higher than reported, and

it is an underdiagnosed and underreported disease. Its prevalence is estimated at around 40,000 women in the USA.¹⁻³

Semen allergy is mediated by IgE to specific proteins present in seminal plasma, not to sperm, and can occur at the first sexual intercourse or throughout

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Submitted Aug 15 2024, accepted Oct 12 2024.

Arq Asma Alerg Imunol. 2024;8(3):257-62.

sexual life.^{1,2,4} Women with semen allergies may present with signs and symptoms ranging from localized to systemic. Local manifestations are often underdiagnosed, manifesting as burning and pain, angioedema, erythema and hives, as well as vaginal discharge and vulvar and vaginal itching.^{1,3,5}

Systemic respiratory tract symptoms range from rhinorrhea and nasal obstruction to dyspnea and/or wheezing. Other possible symptoms in the gastrointestinal tract include vomiting or diarrhea, while pruritus and/or generalized hives can occur on the skin. Pelvic pain and malaise can also be observed. Some cases progress to severe anaphylaxis, with circulatory shock and loss of consciousness. Most reactions occur < 1 h after unprotected sexual intercourse. Some authors report a higher incidence of systemic than local manifestations. Symptoms proportionally increase in severity with recurrent exposure, and the interval between contact and symptom onset may gradually shorten.^{1,3}

The mechanism of sensitization is not yet completely clear, but it is believed that IgE-mediated allergy occurs after exposure to proteins present in seminal fluid. Other rare cases, compatible with type III and IV hypersensitivity, have also been reported. Seminal plasma is rich in minerals, spermine, free amino acids, prostaglandins and enzymes. The prostate is the main source of seminal fluid proteins, and a prostate-specific antigen, 33-34 kD glycoprotein, is the most relevant sensitizer. Other proteins, not yet as well characterized, may also be involved. Reports of vasectomized men who induced reactions reinforce the findings implicating seminal plasma proteins in hypersensitivity reactions. However, in rare cases, spermatozoa have been identified as inducers of a cell-mediated reaction.^{2,3,6}

Diagnosis is based on clinical history associated with IgE sensitization to seminal proteins, i.e. a reproducible immediate reaction after direct contact with semen during unprotected sexual intercourse. Elements that corroborate clinical suspicion include a lack of reaction during condom-protected intercourse and recurrent reaction after a ruptured condom. Sensitization to seminal fluid proteins is proven through in vivo or in vitro immunological tests, such as specific IgE to seminal plasma antigens or immediate skin tests, such as a prick test or an intradermal test.⁵ Differential diagnoses include other coital-related disorders, such as IgE-mediated allergy to latex, contact dermatitis to latex-based condoms, spermicidal lotions or lubricants, exogenous allergens

(such as foods or drugs) the partner has ingested, and even infectious conditions such as infectious vulvovaginitis and sexually transmitted diseases.^{1,3}

Treatment may be preventive or interventional and must also consider psychological aspects. The couple should be advised to prevent exposure to the allergen by using barrier methods, such as condoms, and/or abstaining from intercourse. Coitus interruptus is not very safe and should not be recommended. Some patients (e.g., those considering pregnancy) may be considered for desensitization treatment.⁵ The patient and her partner should also be advised about emergency measures after accidental exposure to semen, including self-injectable epinephrine for anaphylaxis.⁵ Using antihistamines before sexual intercourse may help prevent mild, local post-coital reactions.⁶

An interesting therapeutic option for patients with IgE-mediated hypersensitivity to semen is specific desensitization using the seminal fluid of their sexual partner. There are several desensitization protocols in the literature, either subcutaneously or intravaginally.² The advantages of intravaginal desensitization over the subcutaneous route include greater ease, less complexity in processing the material, and the possibility of performing the procedure in a single day.⁶

In this report, we describe the case of a patient diagnosed with IgE-mediated hypersensitivity to her partner's semen, who underwent intravaginal desensitization.

Case report

A 29-year-old patient had a history suggestive of immediate reaction after unprotected vaginal intercourse, although skin contact was tolerated. She had been with a sole partner for 5 years, but reported no signs or symptoms during or after sexual intercourse in the first 3 years. In the last 2 years, on average 5 min after unprotected sexual intercourse, she began to experience reactions. Initially, they were mild, such as a runny nose, itching and nasal congestion, with spontaneous improvement after a few hours. However, the severity progressively increased, culminating in anaphylaxis, which manifested as dyspnea, wheezing, bilateral eyelid angioedema, and widespread hives. On this occasion, the patient did not seek emergency care, but self-medicated with fexofenadine 180 mg and albuterol spray 100 µg, which resulted in considerable

improvement, except for the eyelid edema, which lasted until the following day.

After anaphylaxis, the patient used the withdrawal method for almost 2 years, during which some episodes of sneezing and mild nasal itching occurred, although they improved in less than 1 h after using oral antihistamines. She was then advised to have intercourse only using condoms and was referred for desensitization assessment.

Prior to the investigation of IgE-mediated allergy to seminal plasma, some additional tests were requested for the patient and her partner to prevent transmissible diseases (Table 1). The patient was instructed to avoid contact with semen by using a condom during sexual intercourse.

To confirm the allergy, the partner's semen was used to perform a titrated prick test, as described previously.⁷ The collected semen was centrifuged at room temperature for 10 min at 4000 rpm to separate the seminal plasma from the sperm. After centrifugation, the sperm were discarded and the seminal plasma was used for the prick test and subsequent desensitization. The prick test was performed using the seminal plasma titrated in decimal dilutions. The results, shown in Table 2, were positive for seminal plasma at dilutions of 1:10 and pure.

Desensitization followed the same protocol, using previously frozen seminal plasma.⁷ On the day of desensitization, the seminal plasma was thawed at room temperature, and decimal dilutions were prepared with 0.9% saline solution, from 1:10 to

1:1,000,000. The patient was placed on a stretcher in the lithotomy position, with a pillow under the buttocks, tilting the pelvis to prevent leakage of the injected liquid during the procedure.

According to protocol⁷, a plastic syringe without a needle or lubrication was used to administer 3 mL of each dilution intravaginally at 15-min intervals. The 1:1,000,000 solution was used first, without incident; approximately 5 min later, the 1:100,000 dilution was applied and the patient developed mild nasal itching, which resolved spontaneously in approximately 10 min. Again, approximately 5 min after the 1:10,000 dilution was applied, the patient developed wheals on her trunk and she was medicated with oral bilastine 40 mg. Since the reaction was mild, the applications were continued as planned. Complete remission of the wheals occurred approximately 20 min after antihistamine treatment. The remaining dilutions, 1:1000, 1:10, and pure semen, were administered at 15-min intervals and were uneventful, even during the subsequent 90 min observation period. The patient was then discharged, instructed to have unprotected sexual intercourse 2 to 3 times a week, and was given an action plan for possible reactions. If this schedule was interrupted, such as during travel, the patient was instructed to freeze a sufficient quantity of semen and apply it intravaginally 2 to 3 times a week.⁶

Seven months after desensitization, the patient continued having unprotected intercourse twice a week, with rare episodes of sneezing and nasal itching occurring approximately 5 minutes after intercourse, which spontaneously improved in less than 1 h.

Table 1
Complementary examinations

Patient	Partner
HBsAg: 0,54 (VR - reag > 1)	HBsAg: 0,76 (VR - reag > 1)
HBeAg: NR	
Anti-HBe: NR	
Anti-HBs: 14,19 (VR - reag > 10)	Anti-HBs: 845,6 (VR - reag > 10)
Anti-HCV: NR	Anti-HCV: 0,04
Anti-HIV 1 e 2: NR	Anti-HIV 1 e 2: NR
HTLV 1 e 2: NR	

Table 2
Titrated prick test

Material	Result
Seminal plasma 1:10.000	0
Seminal plasma 1:1000	0
Seminal plasma 1:100	0
Seminal plasma 1:10	3x3 mm
Pure seminal plasma	4x4 mm
Positive control (histamine)	7x7 mm
Negative control	0

However, one episode of dyspnea and wheezing occurred immediately after intercourse, for which the patient used fexofenadine 180 mg and albuterol spray, resulting in rapid improvement. Currently, and unlike the original treatment plan⁶, the patient has sexual intercourse every 7 to 10 days, with no further episodes of systemic allergic reactions. On rare occasions, the patient experiences sneezing and mild nasal itching immediately after intercourse, treated with antihistamines, resulting in rapid and complete remission.

Discussion

The patient in this case suffered from an immediate type allergy after unprotected sexual intercourse, which began after 3 years of her relationship with the same partner, with no previous history of similar symptoms with other partners. According to the literature, in around 41% of cases the reaction occurs immediately upon first exposure, suggesting that these patients may be sensitized prior to first contact with human semen. However, in other reports, patients developed the allergy after varying periods of intercourse with the same partner or when they changed sexual partners.^{6,8-10}

One as yet unproven explanation for first-contact reaction is cross-reactivity with some common protein

structurally similar to prostate-specific antigens. Prostatic kallikrein isolated from dog urine has been reported to have about 80% structural homology to human prostate-specific antigens. Thus, sensitization may occur through previous exposure to dog urine.²

It is likely that, once a semen allergy has developed, it will occur with different partners. However, as in this case, a comparison could not be established since the patient has had a relationship with only one partner and there are ethical impediments to performing a skin test using seminal material from other men, in addition to the fact that specific IgE tests for seminal fluid have not been clinically validated and their negative and positive predictive values are unknown.⁶

Although effective, avoiding contact with the proteins in seminal fluid through condom use and sexual abstinence can present an obstacle for patients who wish to conceive and it can interfere in the relationship between partners. Thus, for patients who wish to become pregnant, desensitization is a relevant therapeutic alternative.^{2,3} Another option would be artificial insemination.¹¹

Semen desensitization can be performed either subcutaneously or intravaginally. However, subcutaneous desensitization requires more complex sample processing, limiting its use. Observational studies have shown good results from rapid vaginal semen desensitization, with a reduction in local and

systemic reactions. For this reason, patients who are unable to become pregnant after completing desensitization should be investigated for infertility.⁶ For the patient described in this report, we chose to perform intravaginal desensitization due to its greater ease as an outpatient treatment, our familiarity with the protocols, and to reduce the risk of systemic reactions.

A number of intravaginal desensitization protocols have been published, many of which use 2 mL of seminal fluid administered intravaginally every 15 to 20 minutes, starting at a dilution of 1:1000, progressing to 1:100, to 1:10, and then to the undiluted material. For patients who have had more severe reactions, other protocols begin with higher dilutions of 1:10,000, 1:100,000, or 1:1,000,000. In the present case, we began with a dilution of 1:1,000,000 due to the patient's history of systemic reactions, including anaphylaxis. There are also intravaginal desensitization protocols involving fractionation of semen components, in which high molecular weight proteins are eliminated. The fractionation procedure is the same as that of subcutaneous desensitization.¹² The literature suggests that the high molecular weight components of seminal fluid may have immunosuppressive action and could attenuate the efficacy of immunotherapy with unprocessed semen.⁷

In interventional therapy, such as semen desensitization, whether subcutaneous or intravaginal, the couple must be advised of the possible risks, which could range from local to systemic symptoms due to an IgE-mediated response. Thus, the couple is to be provided guidance on emergency measures in case of a reaction.⁵

After the desensitization procedure, the patient should be advised to have unprotected intercourse regularly (every 72 h) to promote immunological tolerance and avoid the recurrence of previous symptoms. Intravaginal application of semen samples may be considered when the partner is absent for more than 72 h.¹² Non-barrier contraceptive methods, such as oral contraceptives or intrauterine devices, should be used in patients who do not desire pregnancy.

Although the patient was instructed to have unprotected sexual intercourse every 2 or 3 days to maintain desensitization, as previously described⁷, this frequency was only followed in the first 2 months. Soon afterwards, the interval was extended to once every 7 to 10 days. Despite recommendations to the contrary, decreasing the frequency of sexual intercourse in the present case did not result in serious

systemic events after intercourse. Although tolerated by the patient, longer intervals are not recommended. According to the literature, intervals longer than 72 h between unprotected episodes of sexual intercourse could result in decreased or lost immunological tolerance and, consequently, a return of local and/or systemic symptoms.⁶ Additionally, cofactors, such as infections, might lead to a lower tolerance threshold and an increased risk of severe reaction. Therefore, patients and their partners should be provided with an emergency action plan, including instruction on the use of self-injectable epinephrine in cases of anaphylaxis.¹¹

Conclusions

IgE-mediated semen allergy, although uncommon, can have a major impact on patients and their partners due to the risk of serious symptoms from accidental exposure and the impossibility of pregnancy. Therefore, in addition to being considered a safe and effective method, specific desensitization to seminal fluid can reduce the psychological impact of the disease on the couple's life.

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No conflicts of interest declared concerning the publication of this article.

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Erythema multiforme: diagnosis and treatment

Eritema multiforme: diagnóstico e tratamento

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ABSTRACT

The recognition and adequate treatment of erythema multiforme (EM) are challenging. In this review, we summarize the main aspects of the etiology, diagnosis, and treatment of EM. EM is an acute self-limited immune-mediated disease characterized by typically erythematous target lesions on the skin, although the mucous membranes may also be affected. It occurs predominantly in young female adults. The etiology varies, but the main causative agent is herpes simplex virus (HSV). Diagnosis is clinical, based on medical history and through skin examination. A skin biopsy may be performed in cases of doubtful diagnosis, and an analytical study may show nonspecific changes. Urticaria appears as a differential diagnosis in EM. This review addresses two clinical cases referred from primary care to the immunoallergy department. In acute episodes of EM, management is based on removal or treatment of the causative factor. Most episodes resolve spontaneously within a few weeks. However, in some cases, treatment for symptom relief may be necessary using oral antihistamines or topical and systemic corticosteroids in more severe cases. When HSV is identified as the causative factor in multiple EM recurrences, antiviral prophylaxis is indicated.

Keywords: Erythema multiforme, herpes simplex, diagnosis, differential diagnosis.

RESUMO

O reconhecimento e tratamento adequado do Eritema Multiforme (EM) é um desafio. Nesta revisão, resumiram-se os principais aspectos da etiologia, diagnóstico e tratamento do EM. O EM é uma doença imunomediada aguda e autolimitada, caracterizada por lesões cutâneas eritematosas tipicamente em forma de alvo, podendo as mucosas estar também afetadas. O EM acomete maioritariamente adultos jovens, do gênero feminino. A sua etiologia é variada, sendo o principal agente causal o Vírus Herpes Simplex (VHS). O diagnóstico de EM é clínico, baseado numa história clínica e exame objetivo cutâneo pormenorizado. A biópsia cutânea poderá ser realizada em caso de dúvidas no diagnóstico e o estudo analítico poderá apresentar alterações inespecíficas. A urticária surge como diagnóstico diferencial mais comum no EM. Nesta revisão abordam-se dois casos clínicos enviados pelos cuidados primários à consulta de Imunoalergologia. Quando perante um episódio agudo de EM, o tratamento consiste na remoção ou tratamento do fator causal. A maioria dos episódios resolve-se espontaneamente em poucas semanas. Todavia, em alguns casos, poderá ser necessário tratamento de alívio sintomático, nomeadamente, anti-histamínicos orais e corticoides tópicos ou sistêmicos nos casos mais graves. Quando o VHS é identificado como fator causal das várias recorrências de EM está indicada a profilaxia antiviral.

Descritores: Eritema multiforme, herpes simples, diagnóstico, diagnóstico diferencial.

Introduction

This article reviews the etiology, diagnosis, and treatment of erythema multiforme (EM), discussing two clinical cases referred by primary health care to our immunoallergy department.

EM is an acute, self-limiting, immune-mediated disease characterized by erythematous, typically target-shaped, skin lesions that affect less than 10% of the body surface area.¹ Its distribution is centripetal

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Submitted May 15 2024, accepted May 23 2024.

Arq Asma Alerg Imunol. 2024;8(3):263-8.

and symmetrical, initially affecting the limbs and then the trunk. The lesions develop over a few days and generally resolve within 3 to 5 weeks.²

In some cases, the mucous membranes may be affected by ulcers and blisters, and systemic symptoms, such as fever and arthralgia, may occur, which classifies these cases as major EM. Cases that do not involve the mucous membranes or systemic symptoms are classified as minor EM.³

Cases involving multiple acute episodes (> 6 per year) are known as recurrent EM. Cases of persistent EM are rare and involve continuous episodes throughout the year, with widespread typically necrotic bullous papular lesions.³

Although EM prevalence data are limited, they indicate that it affects < 1% of the population, with the majority of cases occurring in young adults (20-40 years of age). It is slightly more predominant among women (1.5:1).⁴

Etiology

EM can be triggered by several factors. In about 90% of cases, the etiological factor is viral, bacterial, or fungal infection. The most frequent infectious agent is the herpes simplex virus (HSV), which accounts for approximately 80% of EM cases due to infection.⁴ The second most common infectious agent is *Mycoplasma pneumoniae*, which mainly affects children.⁵

Drugs are the second most common etiological factor (approximately 10% of cases), the most frequent of which are non-steroidal anti-inflammatory drugs, sulfonamides, and antiepileptics.⁴ In a minority of patients, EM can also be triggered by autoimmune diseases, neoplasms, or radiation.⁵

Cases with an undetermined etiological factor are called idiopathic EM, although studies have detected HSV DNA in approximately 44% of patients diagnosed with idiopathic EM.⁶ According to some studies, the HLA 36 and HLA 35 phenotypes have a greater predisposition to EM.^{3,4}

Pathogenesis

The mechanism by which the typical clinical manifestations of EM are triggered is thought to vary slightly depending on the precipitating factor. The pathogenesis of EM is most easily studied in cases where HSV is the triggering factor.⁶ EM secondary to HSV infection appears to be due to the deposition of immune complexes, which leads to skin lesions.⁴ Upon reactivation of the HSV infection,

the virus is released into the bloodstream and is subsequently phagocytosed by CD34+ Langerhans cells, from which it is transferred to keratinocytes in the epidermis. The expression of HSV in epidermal cells leads to increased expression of E-cadherin in the epidermal cell membrane and the recruitment of CD4+ Th1 cells. These initiate an inflammatory cascade through the production of IFN-gamma, with lysis of infected keratinocytes and the recruitment of new T cells. These events lead to changes in the skin barrier that are characterized by visible target lesions approximately 7 to 21 days after HSV infection. In individuals with a history of HSV infection, EM does not necessarily accompany recurrent cold sores.^{1,3}

Clinical manifestations

EM is characterized by target-shaped skin lesions with a central zone of necrosis, followed by two erythematous rings separated by a paler edematous zone. These lesions are usually < 3 cm and have a symmetrical acral distribution, mainly affecting the extensor surfaces of the limbs and expanding centripetally.³ Although many of these lesions are accompanied by itching or a burning sensation, most are asymptomatic.⁴

The skin lesions appear over 3 to 5 days, lasting between 1 and 4 weeks, and may leave a residual post-inflammatory hyperpigmented papule that can persist for months.³

Mucous membranes may be affected, with typical lesions including erythema, erosions, and blisters.⁴ Prodromal symptoms, such as fever and myalgia, rarely occur, but when they do, they precede the skin and/or mucous membrane lesions by 7 to 14 days.³

Diagnosis

The diagnosis of EM is clinical, based on clinical history and physical examination. In the anamnesis, it is important to ask about the onset, characteristics, location, and evolution (acute, self-limited, or episodic) of the lesions. It is important to determine the impact on daily activities and any triggering factors, namely a recent history of HSV, respiratory symptoms suggestive of *Mycoplasma pneumoniae* infection, or recent medication use. It is also important to ask about the presence of lesions in the mucous membranes.³

After careful anamnesis and a complete and detailed examination of the skin, it is essential to characterize the lesions and their distribution. It is important to examine all mucous membranes (oral, ocular, and genital).⁷

In cases of diagnostic uncertainty, a skin biopsy may be useful. Histological findings include the destruction of basal cells, keratinocyte necrosis, and lymphocytic infiltration around blood vessels and at the dermoepidermal junction. Papillary edema and extravasation of red blood cells may also be visible in the early stages of the lesions. In biopsies of mucosal lesions, histological evaluation is similar to that of skin lesions. Immunofluorescence microscopy findings are usually nonspecific.⁴

In the most severe cases, laboratory assessment may show an increased sedimentation rate, leukocytosis, and liver dysfunction. However, in the vast majority of cases no changes are observed.³

Testing for HSV antibodies in the blood may be useful if the patient is not immune, since it excludes diagnosis of EM secondary to HSV infection. If immunity to HSV is found, this indicates the possibility of, but does not confirm, HSV as a causal factor.⁶

Differential diagnosis

The target skin lesions characteristic of EM are also present in other skin pathologies, the most common of which are listed below.

- *Urticaria* is often accompanied by target lesions similar to EM, but the central area of the lesion is generally unchanged or slightly erythematous, unlike EM, in which the central portion is necrotic; however, urticaria lesions are transient, lasting < 24 hours and accompanied by intense itching, which does not occur in EM.^{8,9}
- *Steven-Johnson syndrome* was formerly considered a more severe form of EM, but it has recently been considered a distinct pathology. Steven-Johnson syndrome may show more extensive epidermal necrosis, and rapid diagnosis is essential due to the possibility of life-threatening complications. Target skin lesions are macules rather than papules, which are more characteristic of EM. Furthermore, the distribution of these lesions in Steven-Johnson syndrome is centrifugal, i.e., typically more prominent on the trunk and expanding to the limbs.¹⁰
- *Fixed erythema* presents with lesions very similar to EM, but these lesions are fewer in number and are typically preceded by medication use. Histologically, it involves deeper extension of the inflammatory infiltrate with fewer neutrophils.³
- *Bullous pemphigoid* is an autoimmune pathology that, in addition to being accompanied by lesions

similar to urticaria, is also accompanied by blisters. Histologically, an eosinophilic spongiotic infiltrate is visible. On closer investigation, IgG and C3 deposits are found in the basement membrane, and BP180 and BP230 antibodies are present.³

- *Polymorphous light eruption* is characterized by skin lesions similar to EM, although they occur after exposure to ultraviolet radiation and in exposed areas, sparing the face and back of the hands in the vast majority of cases.³

Treatment

For acute episodes of EM, treatment consists of removing or treating the causal factor.^{1,3} However, for HSV infection, antiviral treatment does not alter the development or progression of EM.³

Most episodes resolve spontaneously within a few weeks. If EM lesions cause symptoms that negatively impact the patient's quality of life, symptomatic treatment is necessary. In particular, antihistamines can be used to relieve itching, topical cutaneous corticosteroids and/or oral gel can be used to reduce inflammation and accelerate the healing process, and oral antiseptics including lidocaine and diphenhydramine can be used to hinder the penetration of pathogens into mucosal lesions and reduce pain.⁴

In severe cases where topical treatment is insufficient, oral corticosteroids (prednisolone 40-60 mg/day) may be administered for 2 to 4 weeks. If there is ocular involvement, the patient must be referred to an ophthalmologist as soon as possible to assess long-term complications, namely conjunctival scarring or vision changes.³

For recurrent episodes of EM, the causal factor must be removed and symptom relief must be provided in acute episodes. When HSV is confirmed as the causal factor for recurrent EM, antiviral prophylaxis is indicated for 6 months to 1-2 years, depending on the response. The antiviral can be acyclovir (400 mg twice a day - 20 mg/kg/day for children), valacyclovir (500 mg twice a day), or acyclovir (250 mg twice a day). If no response occurs, these doses may be doubled. If there is still no clinical response and the symptoms have a significant impact on quality of life, other drugs may be administered, such as mycophenolate mofetil (1000-1500 mg twice a day), dapsone (100-200 mg per day), and azathioprine (100-150 mg per day).³

All cases can be treated on an outpatient basis, with hospitalization reserved for patients unable to

feed themselves due to extensive lesions of the oral mucosa. Mucosa lesions that can be treated on an outpatient basis must be reassessed in 2 weeks.⁷

Clinical cases

Clinical case 1

A 38-year-old woman was referred to the immunoallergology department for “recurrent urticaria with lesions on the face, knees, hands, and feet”. During the consultation, the patient reported recurrent episodes, beginning in adolescence, of scattered maculopapular target-shaped skin

lesions, more concentrated on the face and limbs, associated with some pruritus. The patient could not identify a triggering factor and reported that each episode lasted approximately 3 weeks, totaling approximately 3 episodes per year. After medication with antihistamines and oral corticosteroids, the symptoms improved slightly. There was no relevant information in her medical history, and she was not taking any medications regularly. The physical examination revealed maculopapular target-shaped skin lesions with a scaly center scattered across the limbs, face, and neck. The mucous membranes were



Figure 1

Target maculopapular lesions with a scaly center on the face



Figure 2

Target maculopapular lesions with a scaly center on the back of the hands

not affected (Figures 1 and 2). She later reported episodes of labial herpes approximately 2 weeks prior to the appearance of the skin lesions and had positive serology results for HSV type 1 IgG. Thus, she was diagnosed with EM triggered by HSV infection, and treatment with valacyclovir 500 mg twice daily was initiated. Since then, no new episodes of labial herpes or EM skin lesions have occurred, and the patient has completed 1 year of antiviral therapy.

Clinical case 2

A male adolescent was referred to the immunoallergology department due to “recurrent episodes of urticaria” for the last 3 years, with approximately 6 episodes per year. At the consultation, he reported recurrent episodes of target-shaped, pruritic maculopapular lesions that affected his face and arms, reporting heat as a possible triggering/aggravating factor. Antihistamines and oral corticosteroids had been prescribed several times and initially led to a response, but had no effect in recent episodes. He reported a significant impact on his quality of life, with school absenteeism during outbreaks that lasted approximately 1 week, although the lesions only completely resolved after 3 weeks. There was nothing significant in his medical history, and he was not taking any regular medications. Physical examination revealed numerous target-shaped skin lesions, some with a crusty center and others with violaceous centers on the face and arms, as well as lesser quantities on the legs, in addition to erythematous lesions and erosions on the labial mucosa. Other mucous membranes were not affected. He later reported episodes of labial herpes approximately 2 weeks before the appearance of the skin lesions and had positive serology results for HSV type 1 IgG. Thus, he was diagnosed with EM triggered by HSV infection, and treatment with valacyclovir (500 mg twice a day), in addition to antihistamines and oral corticosteroids, was initiated. No new episodes had occurred after 3 months.

Discussion

The cases described above were referred for an immunoallergology consultation based on a diagnosis of urticaria. In fact, urticaria can also present with maculopapular target lesions. However, these lesions are transient and migratory, generally responding well to antihistamine and corticosteroid therapy, unlike EM.

The primary etiological factor is HSV, with recurrent episodes in most cases. However, the association between HSV infection and EM is not always clear, given that cold sores are relatively common and generally not concerning to patients, not all HSV recurrences trigger EM, and there is typically a two-week interval between herpes infection and the appearance of EM lesions.

The initial treatment was symptomatic, but after determining the etiological factor and several recurrences, targeted antiviral treatment was administered, resulting in the disappearance of the lesions, with no recurrence to date.

Conclusions

EM is a self-limiting disease characterized by target-shaped skin lesions. In 90% of cases, the etiological factor is infectious, of which the most common is HSV. Its pathogenesis, although not yet fully understood, is due to the deposition of immune complexes in the skin barrier. Diagnosis is clinical and skin biopsy is rarely used.

Treatment involves removing or controlling the causative factor (HSV), which may be accompanied by corticosteroids and antihistamines for symptomatic relief. In more severe cases, immunosuppressive treatment may be necessary, but differential diagnoses must always be considered.

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No conflicts of interest declared concerning the publication of this article.

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Recurrent sepsis in secondary immunodeficiency induced by nasal steroid misuse

Sepse de repetição na imunodeficiência secundária por uso abusivo de corticoide nasal

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ABSTRACT

Nasal corticosteroids are recommended as first-line therapy for patients with moderate-to-severe allergic rhinitis. We report a case of a patient who presented with recurrent sepsis and was found to have secondary immunodeficiency induced by inappropriate use of nasal corticosteroids, highlighting the risks associated with the misuse of this medication.

Keywords: Secondary immunodeficiency, nasal steroids, septicemia, Cushing's syndrome, corticosteroids.

RESUMO

Recomenda-se o uso de corticoides nasais como tratamento de primeira linha na rinite alérgica moderada a grave. Relatamos o caso clínico de um paciente com sepse de repetição no contexto de imunodeficiência secundária ao uso inadequado de corticoide nasal, destacando-se os riscos associados ao uso abusivo de tais medicamentos.

Descritores: Imunodeficiência secundária, corticoides nasais, septicemia, síndrome de Cushing, corticosteroides.

Sepsis is a clinical syndrome defined as life-threatening organ dysfunction caused by a dysregulated or aberrant host response to infection¹. When recurrent, it is usually attributable to anatomic lesions, functional disorders, or primary or secondary immunosuppression. Secondary immunodeficiencies are far more prevalent than primary immunodeficiencies and should be considered in the presence of underlying diseases such as diabetes mellitus, human immunodeficiency virus (HIV) infection, nephrotic syndrome, chronic renal failure, or administration of immunosuppressive drugs such as chemotherapeutic agents and corticosteroids¹.

We report the case of a 39-year-old male who was admitted to the Intensive Care Unit with a one-day history of progressive fever, malaise, cough,

dyspnea, and hemodynamic instability. He has already experienced three prior hospitalizations: one for pneumonia at the age of seven, another for pulmonary thromboembolism of undetermined cause eight years ago, and a previous episode of sepsis secondary to pneumonia three years ago. Comorbidities included hypertension, hypercholesterolemia, depression, increased intraocular pressure, and a rib fracture not associated with any known trauma. The patient also reported a remote history of allergic rhinitis and asthma, which were in remission without any maintenance therapy. He had intermittently used a low-dose inhaled combination of corticosteroids and long-acting bronchodilator in the past but had not taken any medication for his asthma in the past five years. He likewise denied taking systemic corticosteroids for any reason during this period.

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Submitted: Nov 07 2024, accepted Nov 14 2024.

Arq Asma Alerg Imunol. 2024;8(3):269-73.

Broad-spectrum antibiotics were started immediately upon admission. Due to progressive respiratory failure, the patient was placed on mechanical ventilation. Cardiocirculatory instability necessitated administration of vasopressors. The patient's condition continued to deteriorate; less than 24 hours after admission, extracorporeal membrane oxygenation (ECMO) was started. Multiple tests for COVID-19 were performed, all negative.

Blood cultures were positive for multisensitive *Streptococcus pneumoniae*. The patient improved on appropriate antibiotic therapy and systemic corticosteroids (methylprednisolone 0.75 mg/kg); ECMO was discontinued after 3 days, and he was extubated on the sixth hospital day. Thirteen days later, the patient had a recurrence of dyspnea. A saddle pulmonary embolism was promptly diagnosed and surgically removed. After 28 days of hospitalization, the patient was discharged to outpatient follow-up with an immunologist for etiological investigation of recurrent sepsis.

Laboratory results on the day of hospital admission were notable for an immunoglobulin G (IgG) of 601 mg/dL (reference value: 600-1500 mg/dL), which increased progressively throughout his hospital course. Other immunoglobulins were within normal range (Table 1). HIV serology was negative. The patient denied diabetes or any other cause of secondary immunodeficiency. There was no family history of consanguinity, adrenal insufficiency, recurrent infection, or inborn errors of immunity.

A review of the patient's medical records revealed that his serum cortisol and adrenocorticotrophic hormone levels were below reference range 2 years earlier (Table 2). Regrettably, the patient was unaware of the purpose of these tests when performed, and no subsequent action was taken in response to their results. Osteoporosis was diagnosed through bone densitometry (lumbar spine T-score: -2.6 SD). Low serum levels of cortisol and aldosterone persisted (Table 2). When asked about exogenous use of corticosteroids, the patient finally reported self-administration of Decadron Nasal®, an over-the-counter fixed-dose combination of dexamethasone disodium phosphate 0.5mg/ml, neomycin sulfate 3.5mg/ml, and phenylephrine hydrochloride 5.0mg/ml for topical nasal administration. He had been using approximately 1ml per day, every day, for the past 21 years. The patient said he did not consider this product to be a "real medication"; he had originally borrowed it from his father to self-manage his rhinitis, and found

it worked so well for his symptoms that he became dependent.

New measurements of immunoglobulin and its subclasses, lymphocyte immunophenotyping, complement system testing, and assessment of the response to pneumococcal vaccine were obtained and found to be unremarkable (Table 1). The patient had received the pneumococcal conjugate vaccine after his first two episodes of sepsis and before presenting to our facility; consequently, we were only able to measure post-vaccination antibody titers.

The patient was diagnosed with sepsis, secondary immunodeficiency due to nasal corticosteroid misuse, Cushing's syndrome, and adrenocortical insufficiency. He made good progress on daily replacement doses of hydrocortisone until complete recovery of adrenal gland function. Four years after his initial presentation, the patient is no longer dependent on continuous exogenous systemic steroid therapy and has not experienced any new manifestations of immunodeficiency or adrenal insufficiency. However, during infections and other stressful situations, he still receives stress doses of systemic corticosteroids.

Corticosteroids are essential hormones for life, as they regulate several physiological and developmental processes. The human endogenous glucocorticosteroid, cortisol, is synthesized in the adrenal cortex under the control of hypothalamic corticotropin-releasing hormone (CRH) and pituitary adrenocorticotrophic hormone (ACTH), constituting the hypothalamic–pituitary–adrenal (HPA) axis. Through a negative feedback loop, cortisol inhibits CRH and ACTH release. Exogenous corticosteroids are likewise able to inhibit HPA axis function; if this stimulus is persistent, the reduction of endogenous ACTH secretion can lead to adrenocortical insufficiency and adrenal hypoplasia or atrophy^{2,3}.

Adrenocortical insufficiency (AI) may occur even with physiologic doses of exogenous corticosteroids but is more commonly observed with higher supraphysiologic dosages and long-term use. A higher risk of developing AI also has been linked with specific aspects of the treatment regimen, such as split daily doses and night-time administration, as well as with pharmacokinetic/pharmacodynamic properties of the involved corticosteroid and its route of administration. The risk of AI with intranasal corticosteroids should not be disregarded³. We hypothesize that the initial drop in blood pressure observed in our patient at the onset of hospitalization could be attributed not only to septic shock but also to adrenal insufficiency.

Table 1

Patient's immune parameters during and after hospitalization

Test	Day of admission	21st day of hospitalization	2 weeks after hospital discharge	18 months after hospital discharge	Reference values
Leukocytes (cells/mm ³)	16,310	8,260	8,290	5,940	4,000–11,000
Neutrophils (cells/mm ³ ;%)	11,920 (73.1%)	3,760 (45.5%)	3,460 (41.7%)	3,470 (58.4%)	2,500–7,500 (40–75%)
Lymphocytes (cells/mm ³ ;%)	1,660 (10.2%)	2,710 (32.8%)	3,440 (41.5%)	1,750 (29.5%)	1,500–3,500 (20–45%)
T CD4 cells (cells/mm ³ ;%)	–	–	1,577 (46.4%)	–	507–1,496 (31.0–56.0%)
T CD8 cells (cells/mm ³ ;%)	–	–	1,483 (43.6%)	–	303–1,008 (17.0–41.0%)
CD4/CD8	–	–	1.1	–	0.9–2.6
CD19 cells (cells/mm ³ ; %)	–	–	165 (12%)	–	140–950 (< 5%)
Eosinophils (absolute; %)	470 (2.9%)	630 (7.6%)	430 (5.2%)	260 (4.4%)	50–500 (8.0–18.0%)
IgG	601	1,084	1,107	729	600–1,500
IgG1	–	545	523	–	490–1,140
IgG2	–	316	321	–	150–640
IgG3	–	31	26	–	22–176
IgG4	–	85	82	–	–
Anti-pneumococcal antibodies: positive serotypes (µg/mL)	–	–	Positive serotypes: 6B (1.5); 9V (5.1); 14 (> 20); 18C (4.6); 19F (12.6); 23F (4.5).	Positive serotypes: 1 (1.9); 3 (3.5); 4 (4.4); 14 (9.2); 19F (5.7); 23F (1.6); 19A (2.3); 9V (3.7).	> 1.3
IgA	210	310	271	230	50–400
IgM	81	79	85	102	50–300
Complement system testing (U/mL)	–	–	139	–	72–140
C3 (mg/dL)	–	–	171	–	90–190
C4 (mg/dL)	–	–	37.8	–	10–40
IgE (kU/L)	–	–	343	–	< 100
Specific IgE–Der p (kU/L)	–	–	7.9	–	< 0.35

Table 2
Patient's cortisol and adrenocorticotrophic hormone levels over time

Parameter	2 years before admission	2 weeks after hospital discharge	4 months after hospital discharge	18 months after hospital discharge	Reference values
Cortisol (µg/dL)	< 0.02	< 0.5	0.6	13.0	6.7–22.6
Adrenocorticotrophic hormone (pg/mL)	5.5	6	26	60.0	7.2–63.3
Aldosterone (ng/dL)	6.3	–	–	11.8	< 23.1

Subsequently, during his hospital stay, the patient received methylprednisolone as an adjunct to antibiotic therapy and ultimately recovered.

Besides induction of AI, the chronic use of supraphysiologic doses of corticosteroids is associated with several local and systemic adverse effects, which constitute the Cushing's syndrome and include cataract, glaucoma, gastric ulcers, striae and skin thinning, hirsutism, acne, growth restriction, osteoporosis, weakness, fatigue, myopathy, hypertension, hyperglycemia, obesity, and immunosuppression^{2,3}. Our patient had high blood pressure, increased intraocular pressure, osteoporosis with a history of pathologic vertebral fracture, and thromboembolic episodes – all clinical manifestations commonly associated with Cushing's syndrome.

Corticosteroids have significant effects on the immune system, primarily due to their anti-inflammatory and immunosuppressive properties. They inhibit the production of pro-inflammatory substances, such as cytokines, chemokines, and prostaglandins, as well as several pathways of the innate and secondary immune responses, including the function of immune cells such as T cells and B cells, decreasing antibody production².

Nasal steroids (NS) are recommended as first-line therapy for patients with moderate-to-severe AR. The major advantage of NS administration is that high concentrations of the drug, with rapid onset of action,

can be delivered directly into the target tissues, thus avoiding or minimizing systemic effects. These drugs have a favorable efficacy and safety profile⁴. However, our patient used a fixed-dose combination product which is not appropriate as maintenance therapy for allergic rhinitis, because it contains a vasoconstrictor, antibiotic, and dexamethasone, a high-potency, long-lasting corticosteroid with high systemic bioavailability. A recent case report described a 19-year-old male patient to whom dexamethasone nasal drops were prescribed because of nasal obstruction. The patient went on to use these drops for more than 5 years, with a daily dexamethasone dose of 0.7-1.0 mg. He eventually developed Cushing's syndrome with panhypopituitarism, growth retardation, osteoporosis, and hypertension⁵.

The diagnosis of secondary immunodeficiency is classically established through the exclusion of other potential causes. In the current case, the likelihood of secondary immunodeficiency arising from nasal corticosteroid misuse is supported by the patient's clinical history, laboratory investigations, and the observed progression of the patient's condition.

Although nasal corticosteroids have been described as a cause of AI, they have not been associated with systemic immunosuppression or sepsis. To the best of our knowledge, this is the first case report of recurrent sepsis associated with nasal corticosteroids and should serve as a warning of the potential harms associated with misuse of these medications.

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No conflicts of interest declared concerning the publication of this article.

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The 2023 Latin America report of the Lancet Countdown on health and climate change

Arq Asma Alerg Imunol. 2024;8(3):274-6.
<http://dx.doi.org/10.5935/2526-5393.20240042-en>

Dear Editor,

The 2023 Latin America report of the Lancet Countdown on health and climate change: the imperative for health-centered climate-resilient development¹ has just been released and highlights very important points for achieving a healthier continent.

The renamed Lancet Countdown Latin America Regional Centre has expanded its geographic scope to include Mexico and five Central American countries (Costa Rica, El Salvador, Guatemala, Honduras and Panama) in response to the need for greater collaboration in a region with intense social disparities, including research capacity and funding.

This center is an independent multidisciplinary collaboration that monitors the relationships between health and climate change in Latin America, following the methods and 5 domains of the Lancet Countdown global report.

The 2023 Lancet Countdown Latin America report presents 34 indicators that track the relationship between health and climate change through 2022 to provide evidence for public decision-making aimed at improving the health and well-being of Latin American populations and reducing social inequalities through health-centered climate actions.

According to this report, increasing exposure to climate change will occur, including a warming trend throughout Latin America. In 2022, the population was exposed to ambient temperatures on average 0.38 °C higher than in 1986-2005, with Paraguay experiencing the largest anomaly (+1.9 °C), followed by Argentina (+1.2 °C) and Uruguay (+0.9 °C) (indicator 1.1.1).

Comparing the 1986-2005 and 2013-2022 periods, Latin American children < 1 year of age were exposed to 248% more heat wave days, while people over 65 years of age were exposed to 271% more heat wave days (indicator 1.1.2). Furthermore, the hotter weather increased moderate and high risk of heat stress during light outdoor physical activity (indicator 1.1.3), with a 140% increase in heat-related mortality between these periods (indicator 1.1.4).

Ecosystem changes have led to an increased risk of wildfires, exposing individuals to a high fire risk for longer periods (indicator 1.2.1). Moreover, the transmission potential of dengue mosquitoes increased by 54% between 1951-1960 and 2013-2022 (indicator 1.3), which is consistent with the recent outbreaks and increasing cases of dengue observed across Latin America in recent months.

This report indicates 3 key areas that the region must continue to investigate and address to achieve health-focused, climate-resilient development, which are discussed below.

Latin American countries require intersectoral public policies that simultaneously increase climate resilience, reduce social inequality, improve population health, and reduce greenhouse gas emissions.

The report's findings indicate a lack of adaptation policies in Latin America, as well as an urgent need for robust vulnerability and adaptation assessments. As of 2021, Brazil was the only country to have completed the World Health Organization's official vulnerability and adaptation statement. Similarly, efforts to develop and implement National Health Adaptation Plans are varied and limited in scope. Brazil, Chile, and Uruguay are the only Latin American countries with National Health Adaptation Plans (indicator 2.1.2).

Furthermore, municipal climate change risk assessments are very limited in the region (indicator 2.1.3). Collaboration between meteorological and health sectors is insufficient, with only Argentina, Brazil, Colombia, and Guatemala reporting some level of collaboration.

Colombia and Guatemala have reported some level of integration (indicator 2.2.1) to provide a comprehensive

response to climate-related health risks in the region. Furthermore, despite the urgent need for action, there is minimal progress in increasing urban green spaces throughout the region, with only Colombia, Nicaragua, and Venezuela showing slight improvements (indicator 2.2.2).

Compounding these challenges is the decline in funding for climate change adaptation projects in Latin America, as demonstrated by the 16% drop in resources allocated by the Green Climate Fund between 2021 and 2022.

Latin American countries must accelerate energy transition policies that prioritize health and well-being, reduces energy poverty and air pollution, and maximizes economic and health benefits.

The use of renewable energy has been growing, increasing by an average of 5.7%, although access to clean cooking fuels remains a concern: 46.3% of the rural population of Central America and 23.3% of the rural population of South America did not have access to clean fuels in 2022 (indicator 3.1.2).

Overreliance on fossil fuels, especially liquefied petroleum gas, as the main cooking fuel is worrisome: 74.6% of Latin American countries depend on liquefied petroleum gas for cooking.

Fossil fuels continue to be the dominant energy source for road transport in Latin America (96%), although biofuel use has increased in some South American countries (indicator 3.1.3). Varying trends were found in different countries regarding premature mortality attributable to fine particulate matter (PM_{2.5}) derived from fossil fuels. In Latin America, these deaths increased by 3.9% between 2005 and 2020, which corresponds to 123.5 premature deaths per million people (indicator 3.2.1). In 2020, the Latin American countries with the highest premature mortality rate attributable to PM_{2.5} were Chile, Peru, Brazil, Colombia, Mexico, and Paraguay. Of the total premature deaths attributable to PM_{2.5}, 19.1% were transportation-related, 12.3% were household-related, 11.6% were industry-related, and 11% were agriculture-related.

Greenhouse gas emission and capture, deforestation, and the expansion of agricultural land continue to be the main causes of the tree cover loss in the region, representing around 80% of the total loss (indicator 3.3).

Furthermore, the production of food of animal origin in Latin America contributes 85% of agricultural CO₂ equivalent emissions, with Argentina, Brazil, Panama, Paraguay, and Uruguay having the highest per capita emissions (indicator 3.4.1). From a health perspective, in

2020 approximately 870,000 deaths were associated with unbalanced diets, of which 155,000 (18%) were linked to high consumption of red meat, processed foods, and dairy products (indicator 3.4.2).

As this report demonstrates, air pollution, both outdoor and indoor, is a major problem across the region, with stark disparities between urban and rural areas. In 2022, Peru, Chile, Mexico, Guatemala, Colombia, El Salvador, Brazil, Uruguay, Honduras, Panama and Nicaragua were among the 100 most polluted countries in the world.

Transitioning to cleaner energy sources, phasing out fossil fuels, and promoting greater energy efficiency in the industrial and housing sectors are not only measures to mitigate climate change, but represent huge opportunities for more prosperous and healthy societies.

To pave the way for climate-resilient development, Latin American countries need to increase climate finance through permanent financial commitment and multilateral development banks.

Climate change entails significant economic costs and investment in mitigation and adaptation measures. In 2022, economic losses due to extreme climate events in Latin America were between USD 6 and 15 billion, mainly due to floods and landslides in Brazil, representing 0.28% of Latin America's gross domestic product (indicator 4.1.1). Unlike in high-income countries, most of these losses are not covered by insurance, placing a considerable financial burden on affected families and governments.

Heat-related mortality among Latin Americans over 65 years of age has reached alarming levels, with losses exceeding the equivalent average income of 451,000 people per year (indicator 4.1.2). The total potential loss of income due to heat-related reduction in work capacity represents 1.34% of regional gross domestic product, disproportionately affecting the agriculture and construction sectors (indicator 4.1.3).

The economic cost of premature mortality due to pollution was considerable, representing a significant share of the region's gross domestic product (0.61%) (indicator 4.1.4). Regional investment in clean energy increased in 2022, outpacing investment in fossil fuels. However, in 2020, all investigated countries continued to offer negative net carbon prices, with total subsidies for fossil fuels reaching USD 23 billion. Venezuela had the highest net fossil fuel subsidies relative to current health spending (123%), followed by Argentina (10.5%), Bolivia (10.3%), Ecuador (8.3%) and Chile (5.6%) (indicator 4.2.1).

Fossil fuel-based energy is now more expensive than renewable energy. The burning of fossil fuels drives climate change and damages the environment, with air pollution from fossil fuels causing 7 million premature deaths each year, in addition to a significant burden of disease.

Transitioning to healthy, emission-free energy, transitioning to healthy food systems, and accelerating adaptation efforts would be cost-effective. However, to implement mitigation and adaptation policies that also improve social well-being and prosperity, stronger and more robust financial systems are needed.

Climate finance is scarce in Latin America, largely depending on political change, which threatens an adequate response to current and future challenges. It is clear that climate progress is lagging and government engagement remains insufficient, although news coverage on health and climate change has increased, reaching its highest point in 2022, although the proportion of news articles on climate change in which health is discussed has decreased over time (indicator 5.1).

Despite the significant growth in scientific articles focused on Latin America, they still represent < 4% of the global publications on the subject (indicator 5.3). Moreover, although most Latin American countries discussed health at the 2022 UN General Debate, only a few addressed the intersection of health and climate change, indicating a lack of awareness at a government level (indicator 5.4).

The Lancet Countdown Latin America 2023 highlights cascading health impacts exacerbated by anthropogenic climate change, marked by increased exposure to heatwaves, wildfires, and vector-borne diseases. The report emphasizes 3 urgent needs:

- interdisciplinary public policies that improve climate resilience across the region;
- energy transition that focuses on co-benefits for health and well-being;
- increased climate finance through fiscal commitment and sustained engagement with multilateral development banks.

By understanding the problems, addressing the gaps, and taking the decisive and necessary measures, Latin America will be able to effectively promote a more sustainable and resilient future for its population.

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No conflicts of interest declared concerning the publication of this letter.

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The problem is bigger than we thought: summary of the 2024 report of the Lancet Countdown

Arq Asma Alerg Imunol. 2024;8(3):277-9.
<http://dx.doi.org/10.5935/2526-5393.20240043-en>

Dear Editor,

We present a summary of the recently published 2024 report of the *Lancet* Countdown on health and climate change, which is of great interest to everyone involved in the health sector. The statements are alarming, and urgent action is needed to prevent a catastrophe.

Despite the initial hope inspired by the 2015 Paris Agreement, the world is now dangerously close to surpassing the 1.5 °C multi-year mean global warming limit. In 2023, annual average surface temperatures reached a record 1.45 °C above the pre-industrial baseline, with new highs being recorded throughout 2024.

The resulting climate extremes are claiming more and more lives and are destroying livelihoods around the world. The *Lancet* Countdown: tracking progress on health and climate change was established the same year the Paris Agreement came into force in an effort to monitor the health impact and opportunities created by the global response to this historic agreement. The Countdown has brought more than 300 multidisciplinary researchers and health professionals from around the world together to take stock of the evolving relationships between health and climate change at global, regional, and national levels.

The 2024 *Lancet* Countdown report, drawing on the expertise of 122 leading researchers from United Nations agencies and academic institutions around the world, revealed the most worrying findings yet in its 8 years of monitoring.¹

The record human costs of climate change

According to this year's report, people around the world are facing record threats to their well-being, health, and survival due to rapid climate change. Of the 15 indicators that monitor the risks, exposure, and health impact of climate change, 10 reached new highs.

Three new indicators offer an increasingly comprehensive picture, measuring exposure to extreme

precipitation, desert dust, and the effect of rising nighttime temperatures on sleep loss.

Heat-related mortality among people over 65 years of age increased by a record 167% compared with the 1990s, 102 points above the 65% that would have been expected without the temperature increase (indicator 1.1.5). Heat exposure is increasingly affecting physical activity and sleep quality, which affect both physical and mental health. In 2023, heat exposure put people involved in outdoor activity at risk of heat stress (moderate or high) for a record 27.7% more hours than the average during the 1990s (indicator 1.1.2), and it also led to a record 6% more hours of sleep lost in 2023 than the 1986-2005 average (indicator 1.1.4).

People around the world are also increasingly at risk from life-threatening extreme weather events. In comparison to the 1961–1990 period, between 2014 and 2023 the number of days of extreme precipitation increased in 61% of the global land area (indicator 1.2.3), which increased the risk of flooding, the spread of infectious diseases, and water contamination. In parallel, 48% of the global land area was affected by at least 1 month of extreme drought in 2023, the second largest area affected since 1951 (indicator 1.2.2). The increase in drought events and heatwaves since the 1981-2010 period was associated moderate or severe food insecurity for 151 million more people from 124 assessed countries in 2022, the highest figure on record (indicator 1.4.2).

Warmer and drier weather conditions increasingly favor the occurrence of sand and dust storms. This climate-environmental phenomenon contributed to a 31% increase in the number of people exposed to dangerously high concentrations of particulate matter between the 2003-2007 and 2018-2022 periods (indicator 1.2.4).

Meanwhile, changing precipitation patterns and rising temperatures favor the transmission of deadly infectious diseases, such as dengue, malaria, West Nile virus and vibriosis, which put people at risk of transmission in previously unaffected areas (indicators 1.3.1-1.3.4).

Compounding these impacts, climate change is disrupting the social and economic conditions on which health and well-being depend. The average annual losses from extreme climate events increased by 23% between 2010–2014 and 2019–2023, reaching USD 227 billion – a figure that exceeds the gross domestic product of about 60% of the world's economies (indicator 4.1.1).

Although 60.5% of losses in countries with a very high human development index (HDI) were covered by insurance, in most countries with lower HDI levels the

burden of physical and economic losses were imposed on local communities due to lack of insurance (indicator 4.1.1).

Extreme weather and climate change-related health impacts are also affecting labor productivity, with heat exposure responsible for a record loss of 512 billion potential working hours in 2023, at a potential cost of USD 835 billion in lost income (indicators 1.1.3 and 4.1.3). Countries with low and medium HDI were most affected by these losses, which amounted to 7.6% and 4.4% of the gross domestic product, respectively (indicator 4.1.3). With poor communities being hit hardest, these economic impacts further reduce their ability to cope with and recover from the increasing effects of climate change, thereby amplifying global inequality.

Worryingly, the multiple hazards revealed by individual indicators are likely to have simultaneous, compounding, and cascading impacts on the complex, interconnected human systems that underpin good health, disproportionately threatening health and survival with every fraction of a degree increase in mean global temperature.

Despite years of monitoring the looming threats of climate inaction, the health risks people face have been exacerbated by years of adaptation delay, which have left people poorly protected from the growing threats of climate change. Only 61% of countries in the Alliance for Transformative Action on Climate and Health have conducted a vulnerability and adaptation assessment (indicator 2.1.1). Only 52% have National Health Adaptation Plans (indicator 2.1.2), and cities in countries with low and medium HDI are lagging behind in assessing their climate change and health risks (indicator 2.1.3).

Only 68% of countries reported high or very high implementation of legally mandated health emergency management capacities in 2023, of which only 11% were low HDI countries (indicator 2.2.5). Furthermore, only 35% of countries reported having early health warning systems for heat-related illnesses, while only 10% did so for mental and psychosocial conditions (indicator 2.2.1).

A lack of financial resources was identified as a key barrier to adaptation, with 50% of cities reporting that they do not plan to conduct climate change and health risk assessments (indicator 2.1.3).

These delays limit the ability to implement effective, evidence-based health adaptation policies. Some effective adaptation measures are underutilized, including nature-based solutions (panel 4), such as urban green spaces (indicator 2.2.3).

The lack of intersectoral collaboration, especially between meteorological and health institutions (indicator 2.2.1), further hampers adaptation efforts.

The unequal distribution of financial resources and technical capacity and the lack of universal health coverage in most countries, combined with a lack of financial support for health systems so that they can protect people from the growing climate-related health risks, leaving the most vulnerable populations even more unprotected.

The world is on track to reach 2.7 °C of warming by 2100, with 11 adaptation thresholds being increasingly close (panel 5). Sustained mitigation efforts would not only avoid the most catastrophic impacts of climate change but also prevent multiple health hazards from fossil fuel use (panel 6). The transition to clean energy sources could prevent at least 2.3 million deaths annually through reduced indoor air pollution, as well as prevent 3.3 million deaths through reduced outdoor fossil fuel-derived air pollution (indicators 3.2.1 and 3.2.2).

Mitigation efforts in the agricultural sector could save an additional EUR 11.2 million annually through healthier, plant-based diets (indicator 3.3.2) and a people-centered transformation could lead to healthier cities and lifestyles.

However, despite some progress in the renewable energy sector, many key indicators show that the world is moving farther from meeting the goals of the Paris Agreement, with many countries showing regression in the most recent data. The carbon-intense energy system has remained broadly unchanged, and energy-related emissions were set to reach an all-time high in 2023 (indicator 3.1.1), with agricultural emissions growing by 2.8% since 2016.

Health sector emissions increased by 10% between 2020 and 2021 (indicator 3.5). The delay in action shows that most countries are woefully unprepared for a healthy, net-zero greenhouse gas emissions future, with people in low- and middle-income countries most at risk (indicator 4.2.4).

Fossil fuel dependence increasingly threatens national economies, with projected losses from coal-based power of USD 164.5 billion between 2025 and 2034 (indicator 4.2.3). Meanwhile, most disadvantaged countries lag behind in clean and renewable energy and remain exposed to the ravages of energy poverty (indicators 3.1.1 and 3.1.2).

Governments and companies around the world are compounding these risks. Fueled by record profits, oil and gas giants have expanded their production plans and, as of March 2024, were on track to exceed their

1.5 °C emissions target by 189% in 2040, up 16% from the previous year (indicator 4.2.2).

Furthermore, despite soaring energy prices and continued dependence on fossil fuel, governments allocated a record USD 1.4 trillion to fossil fuel subsidies in 2022 (indicator 4.3.3), dwarfing any commitment to climate action made at the 2023 Dubai Climate Summit.

There is growing engagement among individuals, businesses, scientists, and international organizations in climate change and health (indicators 5.2, 5.3.1, 5.3.2, 5.4.2), which raises hope that a healthy and prosperous future may still be within reach. However, avoiding a catastrophic increase in mortality, disease, and destruction will require urgent, decisive, health-focused initiatives that demonstrate the potential to provide a prosperous and healthy future for all.

For more detailed information about the 2024 Lancet Countdown report, we recommend reading the full article.¹

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No conflicts of interest declared concerning the publication of this letter.

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Urticarial vasculitis: a brief essay on the importance of observation

Arq Asma Alerg Imunol. 2024;8(3):280-2.
<http://dx.doi.org/10.5935/2526-5393.20240044-en>

Dear Editor,

A patient came into my office who looked sad and tired, but also strong and determined, given that she had gotten up at dawn to travel more than 200 km from her little town, Carnaúba dos Dantas, Rio Grande do Norte, to the state capital, Natal, to find answers and a diagnosis that, until then, no one had been able to give her. “How can I help you?” I asked. She replied, “Doctor, you are my last hope! I have a serious skin problem, I have been to four doctors and none of them wanted to look at me!” That’s right, she reported that no doctor she sought out wanted to get up and have her undress so they could assess her skin lesions and perform something fundamental to our profession – a physical examination.

During the anamnesis, she reported having been diagnosed with an “allergy” approximately six months ago and that since then she had been taking high daily doses of corticosteroids and sedative antihistamines, which prevented her from continuing to work as an artisan due to intense drowsiness. During this period, she gained eight kilograms and began experiencing muscle weakness and hypertensive spikes.

During the examination, I realized that the lesions were probably compatible with a clinical picture of urticarial vasculitis (UV). I took something very simple that we can all have in the office, a glass microscope slide, and confirmed that the lesions did not disappear under pressure – a simple test for differential diagnosis between urticaria and UV.

I requested tests and a biopsy and, due to adverse effects from prolonged use, I began tapering her off corticosteroids. In a return visit, the tests showed normal levels of complement proteins (C3, C4, and C1q) and the biopsy confirmed vasculitis. Thus, I was faced with a diagnosis of normocomplementemic UV.

UV is a rare cutaneous vasculitis of small vessels characterized by recurrent episodes of papule-like lesions that tend to last for more than 24 hours and are

accompanied by residual ecchymotic postinflammatory hyperpigmentation. The histopathological pattern is that of leukocytoclastic vasculitis, consisting of fibrinoid necrosis of the dermal vessel walls and neutrophil-rich perivascular inflammatory infiltrates. Although its etio-pathogenesis remains unclear, UV is now considered to be caused by immune complexes that activate the complement cascade, leading to the exaggerated production of anaphylatoxins, which are responsible for the recruitment and activation of neutrophils. Based on serum complement levels, this condition can be categorized as normocomplementemic UV or hypocomplementemic UV (low levels of C1q and C4 and variably decreased levels of C3), the latter being associated with circulating anti-C1q autoantibodies and possible extracutaneous manifestations. Important differential diagnoses must be considered and excluded, such as bullous pemphigoid, Henoch-Schönlein purpura, lupus erythematosus tumidus, Wells syndrome, erythema multiforme, cutaneous mastocytosis, cryopyrin-associated periodic syndromes, etc.¹

Although UV is mainly idiopathic, it may be associated with medication use, malignancy, autoimmunity, or infection. In some situations it can be difficult to treat, and treatment should be guided by the severity of cutaneous and systemic involvement. Corticosteroids are effective for cutaneous symptoms in most patients with UV, but long-term administration can lead to potentially serious adverse effects. Adding immunomodulatory or immunosuppressive agents often facilitates the corticosteroid tapering process and improves therapeutic efficacy. To date, there is no consensus on the best medication, with recommendations primarily based on case reports and retrospective studies.²

In the present case, an immunosuppressant was prescribed, in addition to joint monitoring with an endocrinologist. After six months of monitoring, the patient’s symptoms were in clinical remission and she had lost weight. She no longer had hypertensive spikes and was able to return to her handicrafts, which are her family’s source of income. However, the course of UV can be long-lasting and difficult to control clinically.

What we must immediately ask is why the value of such a crucial step in our daily medical practice – the “gaze” in all its dimensions – has been lost.

Whenever I see clinical cases like this, I am reminded of Samuel Luke Fildes’ (1843-1927) *The Doctor* (1887, The Tate Britain, London), an often-cited painting in discussions of the strengths or weaknesses of the medical profession.

This iconic work portrays a doctor on a house call for the child of an impoverished worker. The child's improvised bed consists of two chairs. The house's interior is humble and befitting that of a worker. The central figure is the imposing doctor, observing his patient, while in the background the father rests his hand on the shoulder of his wife, who is in a position of supplication or prayer. Fildes' skillful use of light and perspective focuses attention on the doctor's intent gaze. Other details include a pestle, cup, and spoon, suggesting that the doctor prepared a potion or poultice to apply to the sick child. However, evidence of then-current equipment, such as a stethoscope or a thermometer, is lacking. It is likely that by this time a doctor would have been using biomedical practices, which rely on quantitative and measurable evidence rather than qualitative observation and judgment.³

The painting prompts us to reflect on the current medical practice. Indeed, its essence is "patient-centeredness," an essential characteristic of the contemporary doctor-patient relationship and an important consideration for all physicians.

Much time has passed since the artist brought this scene to life, but its strong expression of the doctor-patient relationship continues to stir up deep feelings that surround the search for a cure. Although this piece was created in a completely different medical-social context, the ideal of healing and the desire to be cured is a perennial relationship that overcomes time and external changes, which gives this work a timeless quality.

Inspired by the painting "The Doctor", writer and thinker Rubem Alves (1933-2014) wrote *O Médico*, in which he states: *"I loved this painting the first time I saw it, without understanding it. Perhaps this is the reason why, as a young man, for many years, I dreamed of being a doctor. I loved the beauty of the image of a lonely man, fighting against death. When faced with death, we are all lonely. We love the doctor not for his knowledge or his power, but for the human solidarity that is revealed in his meditative waiting. And all of his failures (for are they not all doomed to lose the final battle?) will be forgiven if, in our helplessness, we realize that he silently remains and meditates together with us"* (translated from the original Portuguese).⁴



The Doctor (1887, The Tate Britain, Londres), by Samuel Luke Fildes (1843-1927)

Doctors, who are now pressured to work exhaustively to earn a decent salary, may be forgetting the importance and beauty of the gaze that Fildes represented and the need, as Rubem Alves argues, to *remain*, in the best sense of the word, with patients in their helplessness.

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No conflicts of interest declared concerning the publication of this letter.

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Immunotherapy with fungal allergens. Can we consider it precision medicine?

Arq Asma Alerg Imunol. 2024;8(3):283-4.
<http://dx.doi.org/10.5935/2526-5393.20240045-en>

Dear Editor,

Health sciences are currently pursuing a path of precision medicine, which is characterized by individualized treatment for each patient based on genotypic, pathophysiological, and environmental characteristics. Allergen immunotherapy is one therapy type for which precision medicine is more feasible.

With the improvement of allergen extracts, we can now perform diagnosis and immunotherapy more effectively. We know that allergen immunotherapy depends on an accurate diagnosis of IgE-mediated hypersensitivity to ensure the specificity of treatment, as well as an extract that contains the exact allergens to which the patient is sensitized.

Thus, the efficacy of immunotherapy depends on the relevance of the allergen it involves. For example, what is the point of accurately diagnosing hypersensitivity to dog hair antigens and beginning immunotherapy with an extract containing precise and specific allergens if the patient is not exposed to dogs? Relevance is a fundamental factor for good immunotherapy practice.

Therefore, we ask: is recommending immunotherapy with fungal allergens precision medicine? Below we will discuss hypersensitivity, the extracts used in immunotherapy, and their relevance.

In fungal growth cultures, the type of protein expressed by the fungus is directly related to the culture medium in which it is grown and the point at which the fungus is extracted.¹ For example, *Aspergillus spp.* grown in Fava-Neto medium and extracted after 30 days of cultivation will express different proteins than those expressed by the same species grown in another culture medium and extracted after 40 days of cultivation. Since fungal allergens consist of proteins or peptides, the culture medium and the cultivation period will directly influence the type of allergens present in the extract.¹ This becomes significant when less precise extracts are used, such as extracts from a genus, e.g., *Aspergillus spp.*, rather than from isolated purified allergens. Furthermore, in addition to spores,

hyphal fragments, which secrete different proteins, can be allergenic. Therefore, if diagnosis is made using fungal extracts whose culture media or culture times differ from those used in immunotherapy, there may be a discrepancy between the diagnosed hypersensitivity and the extract used in immunotherapy.

Another problem related to fungal extracts is the endogenous concentration of proteolytic enzymes, which decreases the shelf life of the allergens. Thus, fungal extracts have a significantly shorter half-life than other extracts, such as pollen and dust mite.

Of the estimated 1-1.5 million different fungi species, only about 80,000 have been described. Of these, 112 species are considered allergen sources. Approximately 80 species of fungi have been linked to respiratory allergy. The genera *Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus* are the most prevalent hypersensitizing fungi². By 2017, an International Union of Immunological Societies subcommittee, which reports allergens to an international database, catalogued a total of 28 fungal genera as sources for 107 allergens.²

The effectiveness and efficiency of immunotherapy and allergy diagnosis depend on the standardization of fungal extracts. Standardization of fungal extracts is a limiting factor; *Alternaria alternata* is the only standardized extract available. Many studies have confirmed its efficacy and safety in allergen immunotherapy for patients with asthma or hypersensitive rhinitis. Other fungal extracts, such as *Aspergillus fumigatus*, *Cladosporium herbarum* and *Penicillium notatum*, are not supported by the same level of evidence due to poor standardization and a lack of studies.³

The European Academy of Allergology and Clinical Immunology does not recommend immunotherapy with fungal extracts for children due to a lack of evidence on its efficacy and safety.⁴ However, the American Academy of Allergy, Asthma, and Immunology suggests that immunotherapy with fungal extracts may be effective. International consensus considers immunotherapy for fungi a possibility, but only if standardized extracts are used.⁵

Fungi and their mycotoxins can stimulate the formation of immune complexes (as in cases of pneumonitis), and it cannot be ruled out that immunotherapy with fungal extracts can trigger them.⁶

Regarding relevance, the risk of prescribing an immunotherapy that does not adequately address the patient's problem is considerable. Even with an accurate diagnosis of type I hypersensitivity and standardized extract, if exposure to the fungus is irrelevant, immunotherapy

should not be indicated, given that uncertainty about which fungus the patient is exposed to can result in inaccurate and inappropriate immunotherapy with fungal extracts. Furthermore, the patient may be exposed to different fungi in external and internal environments than those with positive results in the prick test. Depending on the region, patients may be exposed to different genera and species of fungi than those used in the prick tests, leading to dissociation between hypersensitivity diagnosis and the relevance of exposure.

Immunotherapy with fungal allergens involves many significant variables related to the type of allergen expressed in the extract, which can affect both diagnosis and treatment, in addition to the relevance of the patient's actual environment exposure and, most importantly, treatment safety. We believe that there is still much imprecision when it comes to immunotherapy with fungal allergens.

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No conflicts of interest declared concerning the publication of this letter.

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