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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

The pediatrician and vaccine hesitancy

O pediatra e a hesitação vacinal

Isabella Ballalai[1]

The evolution of vaccination coverage in Brazil can be understood in three distinct historical phases, each essential for confronting vaccine hesitancy.[1] This analysis must account for the role of heuristics and cognitive biases in decision-making, mechanisms that, over the course of human evolution, have enabled rapid responses to perceived threats. In the context of vaccination, these mechanisms, mediated by emotion, can either promote adherence or amplify resistance.[2]

The historical analysis of vaccination coverage in Brazil reveals distinct patterns of public behavior toward immunization, which may be grouped into three major stages.

Phase 1 – High confidence and engagement (until the mid-1990s): Marked by a heightened perception of the risks posed by vaccine-preventable diseases and a collective memory of epidemics. Vaccination was regarded as a civic duty and an act of collective protection. Adherence was spontaneous and widespread, driven by large-scale campaigns backed by strong institutional credibility.

Phase 2 – Maintenance with signs of saturation (mid-1990s to mid-2013): The declining incidence of various diseases reduced risk perception, although vaccine coverage remained high. Motivation to vaccinate increasingly depended on active mobilization and targeted outreach to those overdue for immunization. For certain groups, vaccination ceased to be an automatic priority.

Phase 3 – Decline and the emergence of hesitancy (mid-2015 onward): Characterized by sustained reductions in coverage, driven by multiple factors including low risk perception, erosion of institutional trust, misinformation, and barriers to access. Vaccination behavior became more selective and more susceptible to the influence of inaccurate information. Thus, vaccine hesitancy cannot be attributed solely to misinformation (fake news); rather, it represents a multifaceted behavioral phenomenon.

How strong is confidence in vaccines among the Brazilian population today?

According to the Quantitative Study on Vaccine Awareness, published in June 2024, confidence in vaccines remains predominant among Brazilians, although not unanimous. In every 10 respondents, 7 (72%) report trusting vaccines, with 33% expressing strong trust. Conversely, 26% say they trust vaccines only slightly, and 8% do not trust them at all, indicating the persistence of a skeptical segment. Perceived importance elicited even stronger consensus: 90% consider vaccines important for personal, family,

1. Pediatrician, president of the Instituto Ciesa, director of the Sociedade Brasileira de Imunizações (SBIm), member of the Comitê Consultivo Brasileiro de Imunizações (DPNI- MHO), member of the Comitê Consultivo Brasileiro de Emergências em Saúde Pública (DEMSP-MHO), president of the Scientific Department of Immunizations of the Sociedade de Pediatria do Rio de Janeiro (SOPERJ).

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and community health (57% "very important," 33% "important"). Only 8% consider vaccines to be of little or no importance. The study also investigated feelings of insecurity. More than one-quarter of respondents (27%) reported having felt afraid to be vaccinated or to vaccinate a child or adolescent, an indicator that underscores the need for welcoming and empathetic communication strategies. Confidence in vaccine safety and efficacy remains high. Vaccines are considered safe by 80% – 51% "very safe" and 29% "moderately safe" – while only 19% disagree. Regarding efficacy, 86% believe that vaccines prevent disease (58% "very effective," 28% "moderately effective"). Only 11% hold a negative view, considering vaccines to be minimally or not at all effective.[3]

Taken together, these data reinforce that most of the population values vaccination as an essential public health tool. However, the persistence of doubts, fears, and resistance among a substantial segment of Brazilians highlights the ongoing challenge of strengthening confidence through clear information, facilitated access, and empathy-based communication.

Human beings are "irrational" by nature and rely heavily on affective influences when making real-time decisions. Risk perception encompasses individuals' beliefs, attitudes, judgments, and feelings regarding danger. People subjectively assess both the likelihood and severity of potential hazards in any given situation.[4]

How does an anti-vaccine physician operate? Anti-vaccine physicians typically ground their discourse in an ethics of conviction rather than an ethics of responsibility. They use their professional authority to validate distorted or unfounded claims, thereby conveying a false sense of security to patients. Their strategy often relies on sowing doubt while appearing genuinely concerned. To reinforce their message, they cite retracted or low-quality studies presented as "hidden truths" that others supposedly fear to reveal.[4,5] However, these physicians overlook fundamental principles of public health, such as precaution and solidarity, while minimizing serious diseases by claiming that "the illness is mild" or that "everyone has had it and survived." Their communication is marked by perceived empathy — they listen attentively, validate doubts, and avoid direct confrontation, leading patients to view them as humane, independent, and courageous. They also favor emotional, accessible language and rely on personal anecdotes, patient stories, and belief-based narratives. Ultimately, they elevate "individual autonomy" above collective well-being, affirming and even amplifying families' uncertainties: "You are right to question."[4]

Given this scenario, pediatricians must adopt a strategic approach with hesitant families. Rather than directly discrediting anti-vaccine rhetoric, clinicians should listen actively, demonstrate genuine empathy, and build upon this rapport to offer clear, evidence-based information in accessible language. Most importantly, they should use real stories of protection and examples of lives saved, narratives that can transform technical data into meaningful, comprehensible experiences for families.[5]

Understanding human behavior (including our own) is essential. We process risk instinctively and almost automatically, as if it were a natural reflex, responding through feelings and emotions. This reaction occurs continuously, and how we feel about a risk often outweighs our rational assessment of it. Furthermore, we always favor ease: when an immediate benefit outweighs perceived costs, we often accept risks in pursuit of comfort, practicality, and convenience.

Immediacy is another key factor, as we assign greater value to certain, immediate benefits than to distant or uncertain costs. Our past experiences also strongly shape our risk perceptions, influencing our confidence or apprehension in future situations. Finally, many of our decisions occur on "autopilot" – as creatures of habit, we often act on intuition and impulsive emotions that guide our decisions across various circumstances.[5] Therefore, communication must balance empathy with high-quality information; active listening and relational warmth are indispensable. Storytelling is one of the most powerful tools available. Sharing personal or clinical experiences offers emotive and relatable narratives that personalize medical guidance and motivate patients. Unlike scientific data, stories convey life experiences and values. They are effective because they are memorable and relatable.[6]

In summary, when faced with vaccine doubt or refusal:

– welcome the family and acknowledge their concerns;
– avoid directly attacking fake news; for those who believe such claims, their sources appear to be physicians like you;
– refrain from insisting on epidemiological data, as most people do not identify with those numbers;
– tell a story.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Hypersensitivity reactions to vaccines and immunization in patients with asthma: joint recommendations of the Brazilian Association of Allergy and Immunology and the Brazilian Immunization Society

Reações de hipersensibilidade a vacinas e imunização de pacientes com asma: recomendações conjuntas da Associação Brasileira de Alergia e Imunologia e da Sociedade Brasileira de Imunizações

Ana Karolina Barreto Berselli Marinho[1,2,3], Claudia França Cavalcante Valente[1,3,4], Ekaterini Simões Goudoris[5,6], Anete Sevciovic Grumach[6,7], Fátima Rodrigues Fernandes[1,8], Claudia Leiko Yonekura Anagusko[1,2], Clarissa Morais Busatto Gerhardt[1,2], Gisele Feitosa Zuvanov Casado[1,9], Angelica Varela Rondon[1,10], Monica Araujo Álvares Silva[1,4], Ronney Corrêa Mendes[1,11], Antonio Paulo Costa Penido[1,12], Lorena de Castro Diniz[1,13], Bianca Noleto Ayres Guimarães[1,14], Ana Paula Neves Burian[3,15], Renato de Ávila Kfouri[3,16], Mônica Levi[3,17], Fabio Chigres Kuschnir[18,19]

ABSTRACT

This article provides information and recommendations on hypersensitivity reactions to vaccines and the immunization of patients with asthma. We present an analysis of both immediate and delayed reactions, emphasizing the importance of a thorough assessment of the patient's allergy history and the use of specific diagnostic tests to identify sensitizations. We also discuss strategies such as fractionated-dose vaccination, with the goal of minimizing the risk of severe allergic reactions. Finally, we explore the safety and effectiveness of new vaccines, including those for dengue infection, COVID-19, respiratory syncytial virus, and pneumococcal diseases, in the setting of hypersensitivity reactions and immunization of patients with asthma. Ensuring safe immunization for this group of patients is essential not only for individual protection but also for public health, by preventing outbreaks of infectious diseases and increasing confidence in vaccination programs. The recommendations presented here were adapted to the Brazilian context and developed by consensus among allergy and immunology experts from the Brazilian Association of Allergy and Immunology (ASBAI) and the Brazilian Immunization Society (SBIm).

Keywords: Allergy, asthma, hypersensitivity, immunity, vaccines.

RESUMO

Este artigo oferece informações e recomendações sobre reações de hipersensibilidade a vacinas e imunização de pacientes com asma. Apresenta-se uma análise das reações de hipersensibilidade imediata e tardia às vacinas, enfatizando a importância da avaliação cuidadosa dos antecedentes alérgicos do paciente e do uso de testes diagnósticos específicos para identificar sensibilizações. Discute-se ainda a aplicação de estratégias como a vacinação em doses fracionadas, visando minimizar o risco de reações alérgicas graves. O artigo também explora a segurança e a eficácia de vacinas recentes, como as para dengue, COVID-19, vírus sincicial respiratório recombinante e doenças pneumocócicas no contexto dos pacientes alérgicos, incluindo aqueles com asma. A imunização segura desse grupo de pacientes é essencial não apenas para a proteção individual, mas também para a saúde coletiva, prevenindo surtos de doenças infecciosas e aumentando a confiança nas campanhas de vacinação. As recomendações apresentadas nesta publicação foram adaptadas ao contexto brasileiro e ajustadas por consenso entre especialistas membros da Associação Brasileira de Alergia e Imunologia (ASBAI) e da Sociedade Brasileira de Imunizações (SBIm).

Descritores: Alergia, asma, hipersensibilidade, imunidade, vacinas.

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Introduction

The establishment of national immunization programs during the 1960s transformed the reality of public health worldwide. Global immunization efforts are estimated to have saved approximately 154 million lives over the past 50 years, the majority (101 million) being children under 1 year of age.[1] This makes vaccination the main contributor to the decline in global rates of child mortality.[1]

Vaccination drastically reduces or even eliminates the risk of infection or severe manifestations of more than 20 diseases. In allergic individuals, however, immunization may require special considerations and individualized assessment, as this population may experience adverse reactions, including hypersensitivity reactions which, although rare, can be severe. This article presents recommendations for the immunization of allergic patients and proposes approaches for the investigation, prevention, and management of vaccine-related allergic reactions. It also reviews current indications for immunization in patients with asthma. The goal of this document is to provide clear and practical guidelines to ensure safe and effective immunization in this population.

Methods

The recommendations presented in this document were developed based on current, publicly available evidence and adapted to the Brazilian context. A nonsystematic literature review was conducted between June and July 2024. The MEDLINE database was searched for articles addressing different aspects of immunization in allergic patients.

Initially, we searched for studies investigating both immediate and delayed hypersensitivity reactions to vaccines, including vaccination in specific clinical settings such as asthma. Studies on new vaccines in the context of allergic patients or patients with asthma, particularly dengue, respiratory syncytial virus (RSV), COVID-19, and invasive pneumococcal disease (IPD) vaccines, were also reviewed.

The collected evidence was discussed during the 1st Immunization of Immunocompromised and Allergic Patients Forum, held on August 9, 2024, in the city of São Paulo, Brazil. Recommendations were adopted or refined by consensus among participating specialists, all members of the Scientific Department of the Brazilian Association of Allergy and Immunology (ASBAI) and/or the Brazilian Society of Immunization (SBIm).

Hypersensitivity reactions to vaccines

The global increase in the prevalence of allergic diseases[2] has also led to an increase in concerns regarding possible allergic reactions associated with vaccines and their components.

The World Allergy Organization recommends classifying immune reactions to vaccines based on the timing of symptom onset: reactions occurring within minutes to a few hours after vaccination are classified as immediate, whereas those occurring several hours or days after vaccination are classified as delayed.

This classification primarily helps distinguish between immunoglobulin (Ig) E-mediated reactions, known as type I hypersensitivity, from other types of reaction (Table 1).[3] Immediate reactions, which are typically IgE-mediated, are of particular concern because of the risk of anaphylaxis if the patient is re-exposed to the allergen.[4]

Hypersensitivity reactions to vaccines may be triggered by several components, including vaccine antigens, residual media used for organism culture, stabilizers, preservatives, or other excipients, as detailed in Table 2.

Immediate hypersensitivity reactions

Immediate allergic reactions, whether IgE-mediated or not, may involve a wide range of symptoms. The most common clinical manifestations are listed below.

– Cutaneous symptoms: flushing, pruritus, urticaria, and angioedema.

Table 1
Classification and characteristics of hypersensitivity reactions

Type of reaction	Immune response	Pathophysiology	Time to onset	Example of reaction
Type I	IgE	IgE-mediated immediate hypersensitivity	A few minutes to 6 hours	Anaphylaxis, urticaria, bronchospasm, angioedema, hypotension
Type II	IgG and complement	Antigen or hapten bound to a cell interacts with antibody, leading to cellular or tissue injury	5 to 15 days	Hemolytic anemia, thrombocytopenia, neutropenia
Type III	IgM or IgG, complement, Fc receptors	Immune complexes trigger omplement activation and/or neutrophil recruitment through interaction with IgG Fc receptors	4 to 12 hours 7 to 21 days	Arthus reaction Serum sickness, vasculitis
Type IVa	Th1 (IFN-γ, TNF-α)	Monocytic inflammation	1 to 2 days	Eczema
Type IVb	Th2 (IL-4, IL- 5)	Eosinophilic inflammation	1 to several days 2 to 6 weeks	Maculopapular exanthem DRESS or SHID
Type IVc	Cytolytic T cells (perforin, granzyme, Fas ligand)	CD4 and CD8 T-cell-mediated keratinocyte death through cytotoxicity	1 to days 4 to 28 days	Maculopapular exanthem Stevens-Johnson syndrome/toxic epidermal necrolysis
Type IVd	T cells (IL-8, CXCL-8, GM-CSF)	Neutrophilic inflammation	1 to 2 days	Acute exanthematous pustulosis

DRESS = drug reaction with eosinophilia and systemic symptoms; DIHS = drug-induced hypersensitivity syndrome.
Adapted from Demoly P et al.[5].

– Respiratory symptoms: runny nose, nasal congestion, voice changes, tightness in throat, stridor, cough, wheezing, and dyspnea.
– Cardiovascular symptoms: lightheadedness, syncope, altered mental status, palpitations, and hypotension.
– Gastrointestinal symptoms: abdominal pain, vomiting, and diarrhea.

The most severe manifestation of an immediate allergic reaction is anaphylaxis, defined as a rapidly evolving systemic allergic reaction that can be fatal.[7] Anaphylaxis to vaccines is rare, with an incidence of 0.3 to 2.9 cases per million vaccine doses.[8-11] Although anaphylaxis is a potentially life-threatening disease, in most cases it can be effectively treated with favorable outcomes and no long-term sequelae or fatalities. A review of reports submitted to the United States Vaccine Adverse Event Reporting System describes only eight deaths possibly attributable to anaphylaxis following vaccination over a 26-year period (1990 to 2016).[10]

When anaphylaxis occurs following vaccination, symptoms typically begin within 30 minutes of vaccine administration, although in rare cases they may arise only several hours later.[10] Delayed symptoms tend to be less severe and may result from the slow absorption of the allergen or exposure to another allergen after vaccination.[12] In this context, it is important to note that the occurrence of anaphylaxis or another adverse event may not have been necessarily caused by the vaccine. Many events are temporally associated or arise from unrelated underlying health conditions.

In addition, it is essential to distinguish anaphylaxis from other reactions, such as post-vaccination vasovagal events and anxiety-related symptoms.[13] Vasovagal reactions are characterized by hypotension, pallor, and fainting, in contrast to anaphylaxis, which

Table 2
Main causes of vaccine hypersensitivity

Cause of hypersensitivity	Description
Vaccine antigens	Components of organisms or toxoids present in the vaccine. Example: viral or bacterial proteins such as those in influenza vaccines or tetanus toxoid
Residual culture media	Substances used to grow organisms during vaccine production. Example: egg proteins (influenza vaccine) or yeast proteins (hepatitis B vaccine)
Stabilizers	Substances added to vaccines to maintain stability and potency. Example: gelatin
Preservatives	Compounds used to prevent contamination of vaccines. Example: thimerosal,a an ethylmercury-based preservative
Adjuvants	Substances that enhance the immune response to the vaccine. Example: aluminum salts
Antibiotics	Added in small amounts to prevent bacterial contamination during manufacturing. Example: neomycin
Latex	Material found in the rubber stoppers of some vaccine vials

[a] The use of thimerosal in vaccines has decreased substantially due to concerns about cumulative mercury exposure in children. It is now known that ethylmercury (the type present in some vaccines) is far less likely than methylmercury (an environmental contaminant) to accumulate in the body or cause harm.[6]

is commonly accompanied by flushing, pruritus, and tachycardia.[13] Post-vaccination anxiety symptoms may include vocal cord spasms, which may cause stridor and dyspnea, and panic attacks, which may cause a feeling of tightness in throat, hypertension, tachycardia, and dyspnea, among others.[14]

Individuals with egg allergy

Some vaccines are produced using embryonated eggs. In this process, the virus is inoculated into embryonated eggs, where it replicates. After replication, the virus is harvested and subsequently inactivated or attenuated for vaccine production.[15] As a result, some vaccines may contain small amounts of egg proteins, such as ovalbumin.[16] However, advances in manufacturing have significantly reduced residual protein content, making these vaccines increasingly safe for egg-allergic individuals.

The measles-mumps-rubella (MMR) and measles-mumps-rubella-varicella (MMRV) vaccines contain minimal amounts of ovalbumin.[17,18] These vaccines are considered safe for individuals with egg allergy, and there is no contraindication to their use or recommendation for prior skin testing.[17-19] Therefore, routine immunization is recommended. For patients with severe allergy and a very low threshold for reactions upon contact with egg, administration in a setting equipped to manage anaphylaxis should be considered.

The influenza vaccine, although containing traces of ovalbumin, is also safe for individuals with egg allergy.[20] A review of 28 studies involving 4,315 egg-allergic patients, of whom 656 had a history of anaphylaxis to egg, reported no severe vaccine-related reactions.[21] Therefore, influenza vaccination is recommended for egg-allergic individuals without restrictions. For patients with severe allergy and a very low threshold for reactions upon contact with egg, administration in a setting equipped to manage anaphylaxis should be considered.

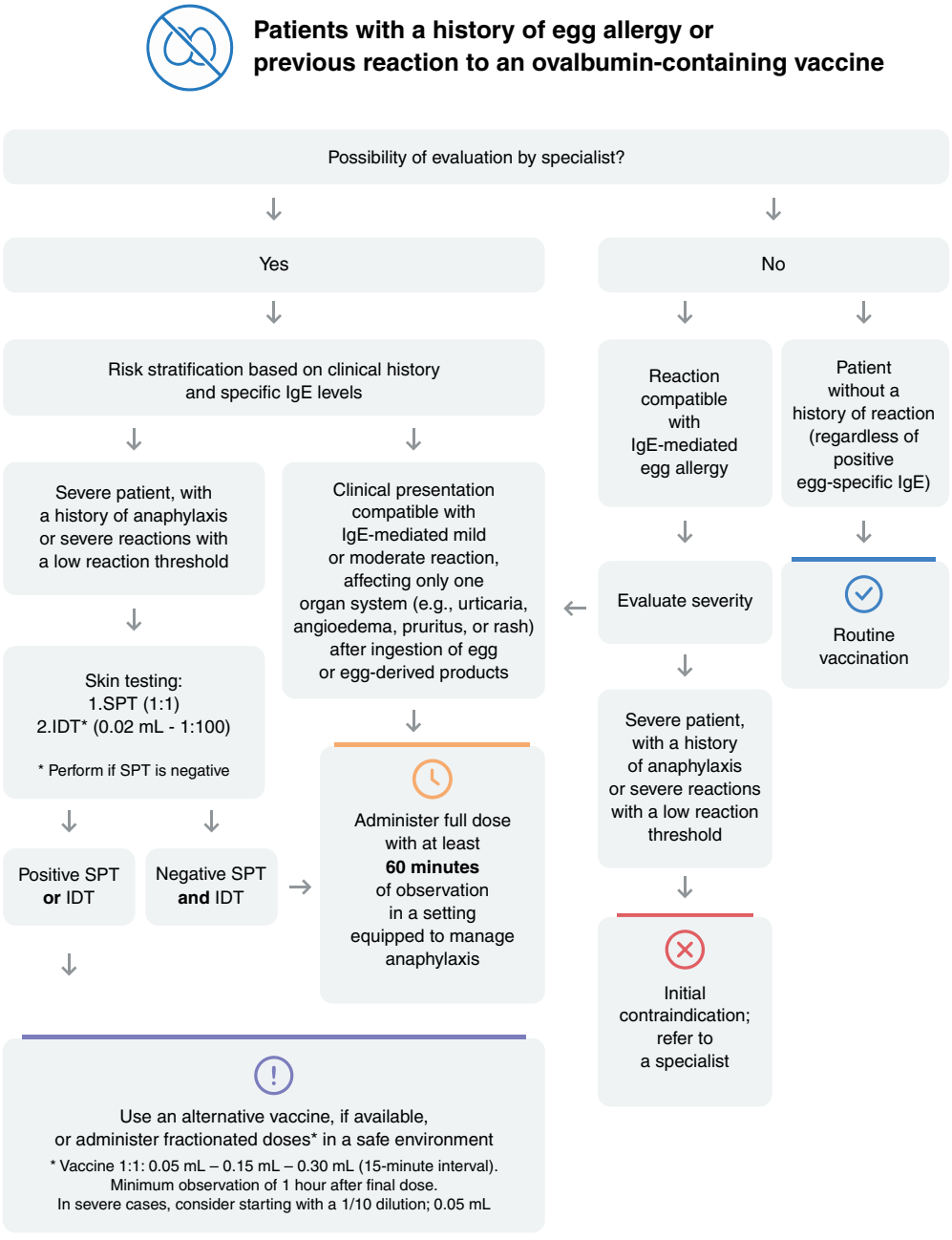
The yellow fever vaccine contains higher amounts of residual egg proteins compared to the MMR, MMRV, and influenza vaccines. While this vaccine is highly immunogenic and plays a crucial role in disease control in Brazil,[22] a structured risk stratification is required for patients with severe egg allergy to allow safe vaccination. This stratification should consider the patient's clinical history as well as specific tests, such as serum IgE to egg and its components, as shown in Figure 1. In addition, skin testing with the yellow fever vaccine (skin prick test [SPT] and intradermal testing [IDT]) may be necessary to determine the safest immunization strategy. For patients with mild to moderate allergy, vaccination in a setting equipped for anaphylaxis management is recommended. In severe cases, an SPT for immediate reactions may be helpful. If both SPT and IDT are negative, administration of the full dose in an appropriately equipped facility with 60 minutes of observation is recommended. If either test is positive, fractional dose vaccination or a desensitization protocol is recommended.[23]

Gerhardt et al.[24] evaluated yellow fever vaccination in egg-allergic patients at a quaternary-care hospital, stratifying risk based on skin testing results. Of the 43 patients evaluated, 37 had negative SPT and IDT and received the full vaccine dose without adverse reactions. Only six patients had positive IDT results and required desensitization; half of them (3/6) experienced mild hypersensitivity reactions, managed with antihistamines and/or oral corticosteroids. In another study by Cançado et al.,[25] 132 egg-allergic patients received the yellow fever vaccine without adverse events. Of these, 92 (70%) received the full dose, while 40 (30%; 17 with positive SPT and 23 with positive IDT) underwent desensitization. A separate Brazilian cohort evaluated at a reference center for special biologics[26] included 829 children with a history of egg allergy who received the yellow fever vaccine. Only 11 (1.3%) experienced immediate post-vaccination adverse events. In the same study, 25 children with a history of egg-induced anaphylaxis underwent skin testing. Fifteen had positive tests (six with positive SPT and nine with positive IDT) and underwent desensitization; only one developed urticaria. All children with negative skin tests (SPT and/or IDT) experienced no reactions following vaccination.

Individuals with cow's milk allergy

Some vaccines may contain milk-derived proteins, such as lactalbumin and casein, which are used during the manufacturing process. Among the vaccines that may include these components are the MMR vaccine produced by the Serum Institute of India, as well as the dTpa (diphtheria, tetanus, and pertussis for children under 7 years of age) and Tdap (tetanus, diphtheria, and pertussis for adolescents and adults) vaccines from specific manufacturers.

For patients with cow's milk allergy, it is recommended to use an MMR vaccine that does



Note: Consumption of egg before vaccination is not recommended, and measurement of egg-specific IgE should not be performed prior to yellow fever vaccination. If a patient has never ingested egg and an egg-specific IgE test was nonetheless obtained and yielded a positive result, the patient should preferably be referred to an allergist. This situation may lead to unnecessary delays in vaccination.

Figure 1

Algorithm for the evaluation and management of patients with a history of egg allergy or previous reaction to an ovalbumin-containing vaccine

IgE = immunoglobulin E, IDT = intradermal testing; SPT = skin prick test.

not contain milk proteins, such as the formulation produced by Fiocruz-Bio-Manguinhos. If this option is unavailable, postponing vaccination until a safe alternative becomes accessible is advisable.

dTpa and Tdap vaccines may also contain milk proteins used as a growth medium for antigen production. Although the residual quantities are very small and insufficient to trigger reactions in most patients, there have been reports of severe anaphylactic reactions in children with pronounced milk allergy, possibly due to the presence of casein derivatives.[27] For individuals with severe allergy and a very low threshold for reactions upon contact with milk, administration of these vaccines in a setting equipped to manage anaphylaxis should be considered. In all other cases, routine vaccination is recommended.

Finally, the rotavirus vaccine does not contain cow's milk protein in its formulation, and there is no scientific evidence that administration of this vaccine causes cow's milk allergy.[28] Therefore, routine rotavirus immunization is considered safe for individuals with cow's milk allergy.

Individuals with gelatin allergy

Gelatin is frequently added to vaccines as a stabilizer, particularly in live attenuated viral vaccines (depending on the manufacturer), such as MMR, varicella, and yellow fever vaccines. Studies have shown that gelatin is the main trigger of severe allergic reactions, including anaphylaxis, associated with some of these vaccines.[17,29,30]

Before administering vaccines that contain gelatin, it is essential to assess the patient's clinical history regarding previous reactions to gelatin, whether through ingestion or in response to earlier vaccinations. Patients with galactose-α-1,3-galactose (alpha-gal) allergy, a condition associated with delayed allergic reactions to red meat and related products, should also be evaluated with caution before receiving gelatin-containing vaccines.[16]

In cases where there is a history of gelatin allergy or prior reactions to gelatin-containing vaccines, the evaluation may include serum-specific IgE testing for gelatin, SPT with the undiluted vaccine, and, if the SPT is negative, IDT with the vaccine diluted 1:100.[17] If skin test results are negative, the vaccine may be administered in the usual manner as a single full dose, with the patient observed for at least 30 minutes to monitor for potential reactions.[17] If any skin test is positive, administering fractioned doses of the vaccine in a setting equipped for anaphylaxis management is recommended,[17] as shown in Figure 2. For patients with a history of severe hypersensitivity reaction after a gelatin-containing vaccine (severe anaphylaxis with respiratory failure requiring supplemental oxygen, refractoriness to bronchodilators or epinephrine, need for mechanical ventilation, or shock), administration of vaccines containing gelatin is contraindicated.

Individuals with latex allergy

Vaccines currently licensed in Brazil are supplied in vials and syringes that may contain latex. However, allergic reactions resulting from this type of exposure are extremely rare, and in most reported cases no specific investigations were conducted to determine whether latex was the actual cause of the reaction.[31]

To minimize risk in patients with latex allergy, it is recommended that vaccination be performed in a latex-free environment. In addition, for vaccines in multi-dose vials, it is recommended to administer the first dose withdrawn from the vial to latex-allergic patients. This recommendation is based on the rationale that the initial dose has a lower likelihood of contamination with latex particles.

Individuals with fungal allergy

In the manufacturing process of certain vaccines, such as hepatitis B, human papillomavirus (HPV), and some types of conjugate meningococcal vaccines (including MenB-4C and ACWY), the antigens are recombinant proteins expressed in Saccharomyces cerevisiae or other yeast species.[16] Although concerns have been raised about potential allergic reactions to these vaccines in individuals with fungal allergies, such reactions are extremely rare.

Given the rarity of yeast-associated allergic reactions, it is recommended that patients with a history of allergy to *S. cerevisiae* undergo specific skin testing. If the result is positive, supervised administration of the vaccine, preferably using fractionated doses, should be considered to minimize the risk of an adverse reaction.

Individuals with polyethylene glycol or polysorbate 80 allergy

Polyethylene glycol (PEG, or macrogol) is an ether polymer with a molecular weight ranging from 200 to

35,000 g/mol. It is used both in its pure form, such as in colonoscopy preparations and laxatives, and as an excipient in cosmetics, medications, and certain vaccines.[32] Polysorbate 80 (PS80, or Tween 80) is a nonionic surfactant whose poly(ethylene oxide) side chains share structural similarity with PEG.[32] Allergy to PEG or PS80 is considered extremely rare, although its true prevalence remains unknown.[33]

For patients with a history suggestive of PEG or PS80 allergy, a careful evaluation is recommended, including a detailed clinical history and skin testing, as outlined in Figure 3. The algorithm described in Figure 3 also applies to patients with a suspected history of allergic reaction to a vaccine, which is discussed in the section "Algorithm for the evaluation of patients with a suspected allergic reaction to a vaccine."

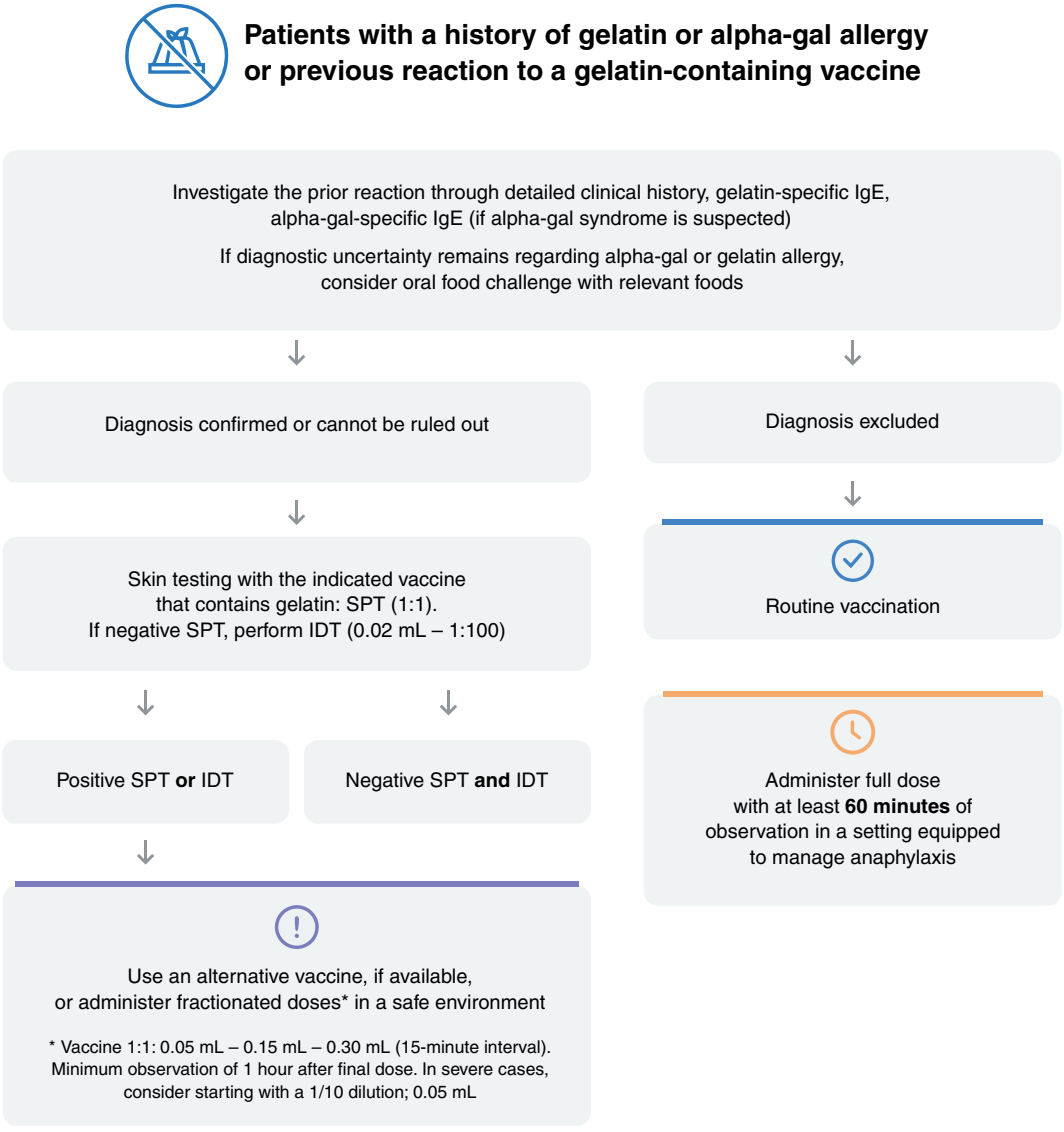


Figure 2
Algorithm for the evaluation and management of patients with a history of gelatin or alpha-gal allergy
Alpha-gal = galactose-α-1,3-galactose; IgE = immunoglobulin E, IDT = intradermal testing; SPT = skin prick test.

Summary of recommendations for the immunization of patients with a history of immediate hypersensitive reaction

Table 3 summarizes the recommendations for the immunization of patients with a history of immediate hypersensitive reaction.

Delayed hypersensitivity reactions

Local reactions, such as prolonged warmth, flushing, induration, and swelling at the injection site, are the most common delayed immunologic reactions following vaccination. These reactions may occur many hours to weeks after immunization, which can make causal assessment challenging.[34] Such local reactions generally do not progress in severity and do not contraindicate future vaccinations.[35]

In contrast, more severe reactions, such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), do contraindicate subsequent doses of the associated vaccine. However, it should be noted these reactions are extremely rare.[36-38] Erythema multiforme major is primarily associated with viral (such as herpes simplex) and bacterial infections (such as *Mycoplasma pneumoniae*) and is only rarely linked to vaccines.[39,40]

Other rare cutaneous reactions reported in association with vaccines include acute generalized exanthematous pustulosis, erythema nodosum, granuloma annulare, bullous pemphigoid, Sweet syndrome, Gianotti-Crosti syndrome, lichenoid eruptions, cutaneous lupus, lupus vulgaris, and serum sickness-like reactions.[41] In many cases, there are reports of previous active infection prior to vaccination and the onset of these conditions.[41] Most cases do not recur after booster doses of the same vaccine.[41]

Delayed hypersensitivity reactions to vaccine excipients, such as antimicrobials, preservatives, and adjuvants, have also been described and may present as generalized eruptions or as contact-type reactions at the injection site.[41] Overall, these reactions tend to be mild and locally confined. If a vaccine excipient is suspected as the cause of delayed hypersensitivity, patch testing with the intact vaccine or with the isolated excipient may be performed,[42] as described in Figure 4. There is no contraindication to subsequent doses of the same vaccine, provided that adequate clinical monitoring is ensured.

Arthus reaction

An Arthus reaction is a type III hypersensitivity reaction characterized by the deposition of antigen–antibody (IgG) immune complexes and complement in local blood vessels.[43] It tends to present with pain, edema, and induration at the injection site and, in more severe cases, may progress to local ulceration or necrosis.[43]

The Arthus reaction usually begins between 2 and 12 hours after vaccine administration and is more common in individuals who have preexisting IgG antibodies against the vaccine antigen.[44] Vaccines that have been associated with Arthus reaction include tetanus-containing vaccines, hepatitis B vaccine, rabies vaccine, and the 23-valent pneumococcal polysaccharide vaccine.[43]

Management is predominantly symptomatic and may include antihistamines, application of cold compresses to the affected area, and analgesics for pain relief. It is important to reassure patients that this is a self-limited reaction with a short course, typically resolving within about 1 week. Despite the reaction, there is no contraindication to receiving future doses of the same vaccine.

Guillain-Barré Syndrome

Neurologic complications such as Guillain-Barré syndrome (GBS) are rare adverse events associated with vaccination.[41] GBS typically presents with progressive muscle weakness beginning in the extremities and ascending toward the trunk, and may lead to respiratory failure or cranial nerve weakness.[45] Symptom onset is considered potentially related to vaccination if it occurs within 6 weeks following administration of vaccines containing tetanus toxoid, poliovirus, rabies, or influenza antigens.[41] The pathophysiology involves a delayed, immune-mediated reaction with participation of CD4+ and CD8+ T lymphocytes that exhibit cross-reactivity with components of the nervous system.[45]

Given the delayed onset of symptoms, a comprehensive understanding of GBS-related events is essential for accurate diagnosis and assessment of potential causality. Other factors, such as previous infections with *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, influenza A, *Mycoplasma pneumoniae*, or *Haemophilus influenzae*, may also trigger the syndrome.[41]

There is no contraindication to vaccinating patients with a history of GBS, provided the previous episode was not associated with the vaccine to be administered. If the patient developed GBS less than 3 months earlier, postponing vaccination is advisable.[45] If a case of GBS is suspected to have been associated with a prior vaccination, subsequent doses of the same vaccine are contraindicated.

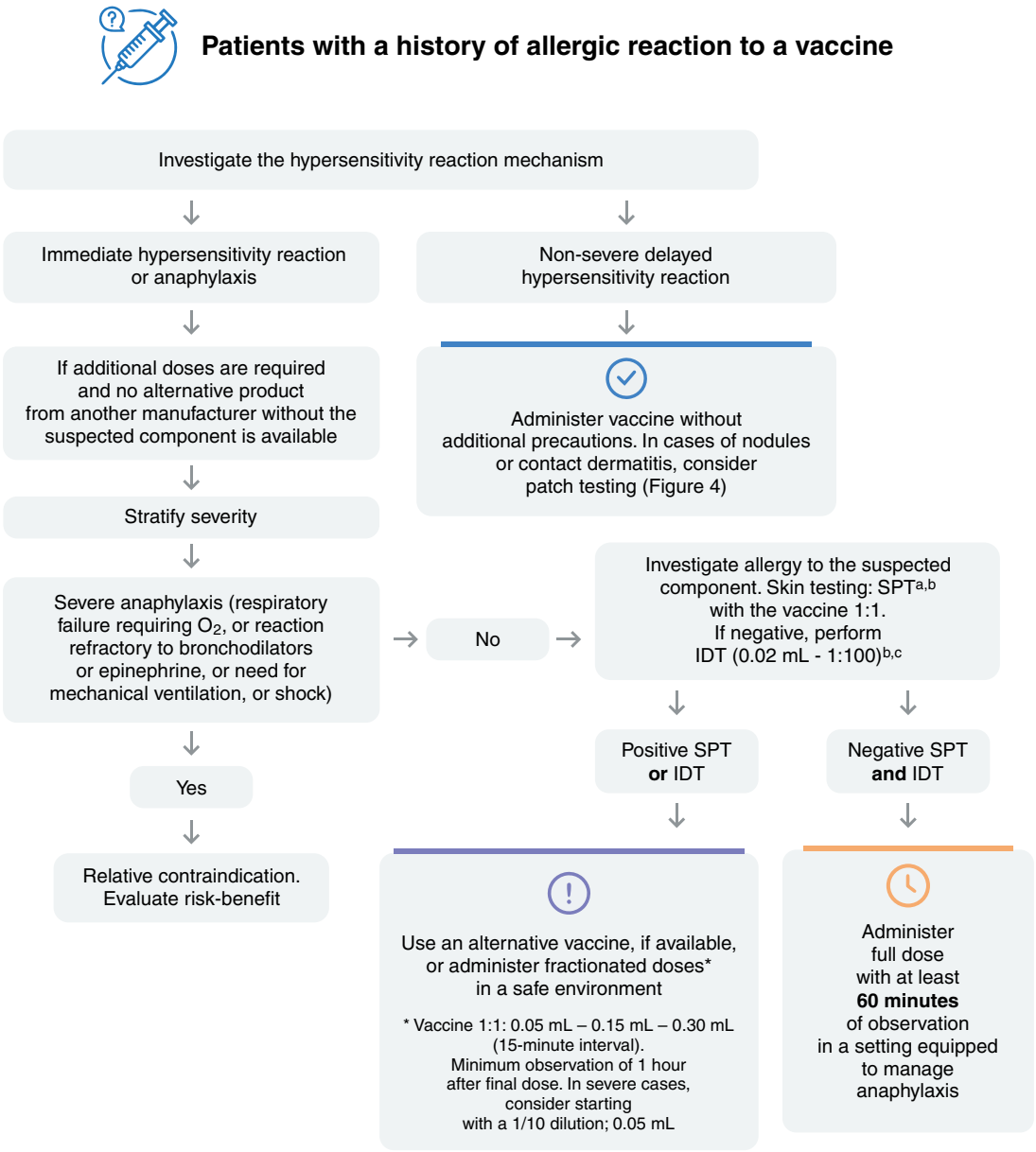


Figure 3

Algorithm for the evaluation and management of patients with a history of suspected allergic reaction to a vaccine

[a] In patients with a history of severe anaphylaxis, it is appropriate to dilute the vaccine 1:10 or even 1:100, as these concentrations are considered non-irritating.

[b] Whenever possible, perform testing with the same vaccine from the same manufacturer involved in the original reaction.

[c] Undiluted IDT is discouraged due to a high irritant rate. Whenever possible, perform testing with the same vaccine from the same manufacturer involved in the original reaction.

IDT = intradermal testing.

Table 3
Main types of allergy and recommendations for immunization in patients with a history of immediate hypersensitivity

Allergen	Vaccine	Recommendation
Egg	MMR, MMRV, and influenza	Routine vaccination. Preferably administer in a setting equipped to manage anaphylaxis, depending on medical assessment of previous reaction severity and reaction threshold
	Yellow fever	Perform risk stratification; consider skin testing and administer in a setting with anaphylaxis support if necessary (Figure 1)
Cow's milk	MMR	Do not use the formulation manufactured by the Serum Institute of India; choose an alternative without milk (eg, Fiocruz-Bio-Manguinhos).
	DTPa/Tdap	No contraindication. Individualized assessment for patients with severe cow's milk allergy and low reaction threshold; consider vaccination with at least 30 minutes of observation in a setting capable of managing anaphylaxis
Gelatin	MMR, MMRV, influenza, yellow fever, varicella, rabies	Evaluate history of gelatin allergy and perform skin testing if needed. If positive, administer fractionated doses in a setting prepared for anaphylaxis management (Figure 2)
Latex	Any vaccine in vials or syringes containing latex	Use latex-free gloves. For multidose vials, administer the first dose withdrawn from the vial to the latex-allergic patient.
Fungi *(Saccharomyces cerevisiae)*	Hepatitis B, HPV, meningococcal conjugate vaccines (MenB-4C and ACWY)	Consider skin testing; if positive, consider supervised administration with fractionated doses of the vaccine that may contain yeast
PEG and PS80	HPV DTPa/Tdap, Influenza (some formulations), hepatitis B (some formulations), COVID-19 (some formulations), RSV, pneumococcal conjugate vaccines, meningococcal conjugate vaccines	Consider skin testing with the vaccine. If positive, consider using alternative vaccines or administering fractionated doses in an anaphylaxis-prepared setting. If negative, administer the vaccine in a facility equipped to manage anaphylaxis (Figure 3)

COVID-19 = coronavirus disease 2019; DTPa = diphtheria, tetanus, and pertussis for children under 7 years of age; Fiocruz = Fundação Oswaldo Cruz; HPV = human papillomavirus; PEG = polyethylene glycol; PS80 = polysorbate 80; RSV = respiratory syncytial virus; Tdap = tetanus, diphtheria, and pertussis for adolescents and adults.

In such cases, evaluating the situation in alignment with the investigation and official response to the reported adverse event following immunization is essential.

Summary of recommendations for the immunization of patients with a history of non-immediate hypersensitive reaction

Figure 4 summarizes the recommendations for the immunization of patients with a history of non-immediate post-vaccination hypersensitivity.

Individuals with a personal or family history of atopy have no contraindications to immunization and should receive vaccines according to routine health guidelines. For those with a history of allergy to a specific vaccine component, a prior evaluation, preferably conducted by an Allergy and Immunology specialist, is recommended. In cases of local reactions such as contact dermatitis, nodules, flushing, pain, edema, or induration at the injection site, patch testing may be considered to confirm the causal agent. Testing may be performed using the intact vaccine or its individual components, alongside a negative control. These reactions generally do not contraindicate future doses of the same vaccine, and the patient may continue the immunization schedule as usual.

If a GBS episode is suspected to have been associated with a previous vaccination, subsequent

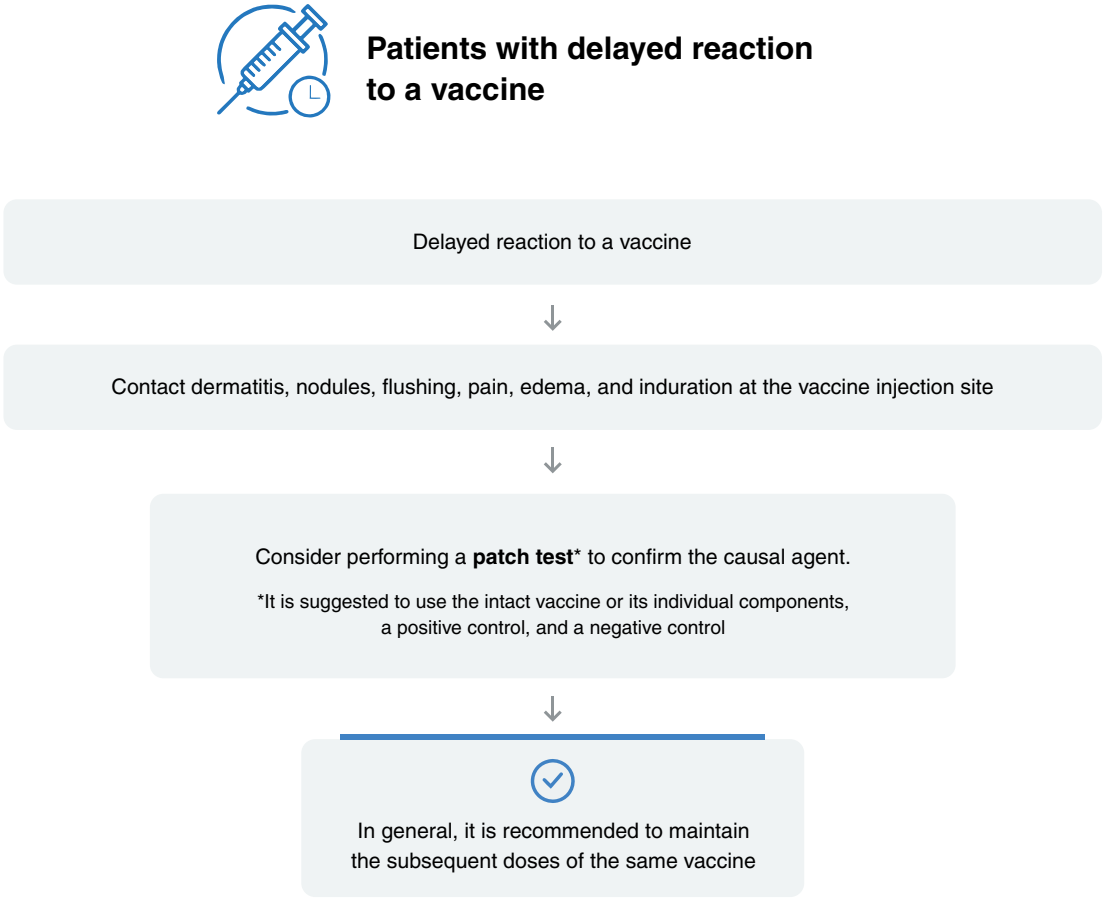


Figure 4
Algorithm for the evaluation and management of patients with a history of suspected delayed allergic reaction to a vaccine

doses of the implicated vaccine should be withheld. However, if the episode occurred more than 3 months prior and was not related to vaccination, routine immunization can be safely resumed.

Special considerations for patients with hypersensitivity reactions

Dengue vaccine (Qdenga®)

In 2023, Brazil recorded more than 1.6 million cases of dengue, with 1,179 deaths.46 By October 12, 2024 (epidemiological week 41), over 6.5 million suspected cases had been reported, with 6,613 confirmed dengue-related deaths and an additional 1,499 deaths under investigation.[46] These figures indicate a substantial worsening of the dengue epidemiological landscape in Brazil, with increases in both case numbers and mortality.

In the absence of specific treatment, dengue management relies on early identification of warning signs and severe manifestations, requiring organized healthcare systems and adequately trained personnel. Prevention efforts are challenged by the *Aedes aegypti* mosquito's resistance to insecticides.[47] Moreover, urbanization and climatic factors, such as prolonged periods of elevated temperatures, contribute to rising dengue incidence, even in areas with historically low transmission rates.[48]

Although the tetravalent dengue vaccine (CYD-TDV; Dengvaxia, Sanofi-Pasteur) is licensed in Brazil, it is recommended only for individuals with a laboratory-confirmed prior dengue infection. The approval of Qdenga® (Takeda) by Anvisa in 2022 introduced a new option for disease prevention. Qdenga® is a live-attenuated vaccine that protects against all four dengue virus serotypes: DENV-1, DENV-2, DENV-3, and DENV-4.

Considering both seronegative and seropositive individuals prior to vaccination, Qdenga® demonstrated an efficacy of approximately 61% against virologically confirmed symptomatic dengue of any severity and 84% against hospitalization up to 54 months after the second dose.[49] Throughout the vaccine's clinical development program, safety data were assessed in approximately 27,000 phase 2 and phase 3 participants from endemic and non-endemic regions.[45] An integrated safety analysis did not identify significant risks. The vaccine was well tolerated regardless of age, sex, or baseline dengue serostatus in individuals aged 4 to 60 years.[50] The most common adverse events following the first vaccine dose were injection-site pain (43% for Qdenga® vs. 26% for placebo) and headache (34% vs. 30%, respectively). Most adverse reactions at injection site were mild and resolved within 1 to 3 days.[50]

Qdenga® was incorporated into the Brazilian National Immunization Program (PNI) in December 2023, and vaccination of adolescents aged 10 to 14 years began in March 2024 across 521 municipalities selected based on epidemiological data.

Post-marketing safety data collected between March 2023 and March 2024 identified 70 hypersensitivity reactions associated with Qdenga® in Brazil, corresponding to an overall incidence of 19.15 per 100,000 administered doses.[51] Of these, 16 cases were classified as anaphylaxis, yielding an incidence of 4.38 per 100,000 doses. Most anaphylaxis cases involved cutaneous and mucosal manifestations, with a substantial proportion presenting respiratory, circulatory, or gastrointestinal involvement. No cases progressed to death.[51]

Pharmacovigilance monitoring identified 85 cases of immediate hypersensitivity reactions following Qdenga® vaccination, including 24 anaphylaxis cases (63.1 per million doses), three of which involved anaphylactic shock, among 380,358 administered doses between March 1, 2023, and March 11, 2024.[52] In 10 of these cases (41.7%), symptoms began within 15 minutes of vaccination. No deaths, sequelae, or complications related to anaphylaxis occurred. These data underscore the need for careful evaluation of allergic patients before and after vaccine administration.[8-11] It is therefore essential to assess any history of severe allergies to vaccine components or past vaccination before administering the vaccine.

Patients who, after the first dose, experienced isolated or subjective immediate symptoms, such as cough, nausea, vomiting, dizziness, or a sensation of throat tightness without objective evidence of airway compromise (e.g., edema, hoarseness, erythema, or pruritus), and who recovered quickly without medical intervention should receive the second dose and be observed for at least 30 minutes. It is also important to consider alternative diagnoses to ensure that symptoms were not attributable to other medical conditions.

For patients who developed urticaria and/or angioedema (localized or generalized) or other isolated symptoms not typical of anaphylaxis, the recommendation is also to proceed with the second

dose and monitor for at least 30 minutes for possible reactions. In addition, referral to an allergist should be considered to investigate other potential triggers of the initial reaction. For individuals who experienced urticaria or an Arthus reaction after the first dose, administration of antihistamines 30 minutes before the second dose may be considered. The duration of antihistamine use may vary depending on the severity and recurrence of allergic reactions. Importantly, the use of antihistamines before vaccination does not reduce the risk or severity of recurrent events in patients who experienced previous reactions, including anaphylaxis.

In cases of anaphylaxis involving two or more organ systems (e.g., cutaneous, respiratory, gastrointestinal, among others), patients should preferably be evaluated by an allergist. This assessment should consider the epidemiological risk and, in some cases, SPT or IDT may be required to identify the allergenic component responsible for the reaction. When administration of the second vaccine dose is considered necessary, it is recommended to follow the investigation algorithm described in Figure 3.

Finally, preparedness and response capacity are critical to minimizing risks and effectively managing any allergic reaction following dengue vaccination or other immunizations in allergic patients, whether vaccination occurs within healthcare facilities or in community settings (extramural vaccination).[53]

COVID-19 vaccine

The potential allergens contained in the COVID-19 vaccines currently available in Brazil are listed in Table 4.

Both mRNA vaccines (Comirnaty and Spikevax) share a similar structure: they contain no protein or adjuvant, only mRNA encapsulated within stabilizers inside a lipid nanoparticle coated with PEG to enhance water solubility. Although PEG was initially suspected as the primary trigger of allergic reactions to mRNA vaccines,[54] subsequent studies have indicated that the presence of PEG in the formulation does not impact the efficacy or safety of lipid nanoparticle-based COVID-19 vaccines.[55]

In addition to PEG, Moderna's mRNA-1273 vaccine (Spikevax) also contains tromethamine (trometamol), a widely used buffering agent. Some reports of anaphylaxis to injectable medications have been attributed to tromethamine.[56,57] In the second formulation of Comirnaty® (Pfizer, ready-to-use vials), tromethamine was also added. Although initial reports suggested an elevated risk of anaphylaxis with COVID-19 vaccines, more recent pharmacovigilance data indicate that the incidence of anaphylaxis with mRNA vaccines (8.96 cases per million administered doses) is comparable to rates observed with other vaccines (between 1 and 10 cases per million doses).[58,59] The incidence of anaphylactic shock was 1.46 per million doses, and fatal reactions were extremely rare, with rates of 0.04 per million doses for anaphylactic reactions and 0.02 per million doses for anaphylactic shock.[59] These findings reinforce the safety profile of these vaccines.

Some studies have described delayed local reactions following administration of mRNA COVID-19 vaccines. These reactions, characterized by erythema, induration, and tenderness at the injection site, typically occur 6 to 8 days after vaccination and may persist for up to 2 weeks.[60-63] Although uncomfortable, these reactions are not considered contraindications to subsequent doses. In most reported cases, individuals who experienced such reactions after the first dose received the second dose without recurrence or with less intense reactions.[60-63] In the phase 3 trial of Moderna's mRNA-1273 vaccine, delayed local reactions occurred in 0.8% of participants after the first dose and 0.2% after the second.[64]

For patients with a suspected history of allergic reaction to a COVID-19 vaccine, it is recommended to follow the investigation algorithm described in Figure 3.

Immunization of patients with asthma

Asthma is a chronic disease that affects approximately 300 million people worldwide.[65] In Brazil, 23.2% of the population is estimated to live with asthma,[66] which is one of the leading causes of hospitalization among children and adolescents and a common reason for emergency care visits.[67]

Vaccination against influenza

In patients with asthma, chronic airway inflammation and type II immune responses are believed to impair antiviral immunity in the respiratory tract,[68] causing greater susceptibility to severe influenza-related disease and associated bacterial infections. The mechanisms that increase susceptibility to influenza in patients with asthma include weaker innate immune responses, reduced type 1 helper T-cell activity, and

deficient interferon-α responses from plasmacytoid dendritic cells upon influenza exposure.[69] In addition, influenza infections may lead to asthma exacerbation, often requiring hospitalization.[70] During the 2009 influenza pandemic, patients with asthma were at significantly higher risk of hospitalization, with most seeking care due to exacerbation of respiratory symptoms rather than influenza infection alone.[71]

In addition to being safe, influenza vaccination is effective in individuals with asthma. A case-control study conducted in Scotland evaluated influenza vaccine effectiveness in patients with asthma during 6 seasons (from 2010/2011 to 2015/2016), using 5,910 swab samples. Vaccination was associated with a 55% reduction in laboratory-confirmed influenza infections over the 6 seasons.[72]

It is recommended that patients with asthma follow the Brazilian routine vaccination schedule, receiving annual doses of the trivalent or quadrivalent influenza vaccine starting at 6 months of age.

In 2023, a high-dose quadrivalent influenza vaccine became available in Brazil for individuals aged 60 years and older. Manufactured by Sanofi Pasteur and marketed as Efluelda®, the vaccine contains 4 times the antigen content of standard-dose quadrivalent influenza vaccines. Efluelda® demonstrated an incremental efficacy of 24.2% compared to the standard-dose vaccine. A meta-analysis evaluating data across 10 influenza seasons showed that the high-dose vaccine provides protective benefits beyond influenza prevention, including a 27% reduction in pneumonia-related hospitalizations and an 18% reduction in cardiorespiratory hospitalizations.[73-75] The vaccine is available in private vaccination clinics and offers enhanced protection for adults aged 60 years and older, whose vaccine responsiveness is lower due to immunosenescence and the frequent presence of comorbidities.

Strategies to improve adherence to influenza vaccination among patients with asthma are essential,

Table 4
Types of COVID-19 vaccines, active substances, and potential allergens

Type of vaccine	Vaccine name	Active substance	Potential allergens
mRNA vaccine encoding the SARS-CoV-2 spike glycoprotein	BNT162B2 Pfizer/BioNTech Comirnaty Herpes zoster	mRNA	PEG 2000; tromethamine and tromethamine hydrochloride (in ready-to-use vials only)
mRNA vaccine encoding the SARS-CoV-2 spike glycoprotein	mRNA-1273 Moderna Spikevax	mRNA	PEG 2000; tromethamine and tromethamine hydrochloride
Recombinant spike protein vaccine with adjuvant	NVX-CoV2373 Novavax Nuvaxovid/Covovax	Recombinant spike protein adjuvanted with Matrix-M, produced in Sf9 *Spodoptera frugiperda* insect cells	PS80

COVID-19 = coronavirus disease 2019; DTPa = diphtheria, tetanus, and pertussis for children under 7 years of age; Fiocruz = Fundação Oswaldo Cruz; HPV = human papillomavirus; PEG = polyethylene glycol; PS80 = polysorbate 80; RSV = respiratory syncytial virus; Tdap = tetanus, diphtheria, and pertussis for adolescents and adults.

as they can significantly reduce the risk of influenza-triggered exacerbations.

Vaccination against respiratory syncytial virus

RSV is the leading cause of bronchiolitis and pneumonia in children under 5 years of age.[76] Each year, RSV accounts for approximately 33 million infections, more than 3 million hospitalizations, and over 100,000 deaths among children aged 0 to 5 years worldwide, with the greatest impact occurring in economically disadvantaged regions.[76] In addition to affecting children, RSV-associated hospitalizations are also high among older adults, particularly those aged 65 years or more, and among individuals with chronic conditions,[77,78] underscoring the need to include these populations in RSV immunization strategies.

The association between severe RSV disease in infancy and the development of asthma is well established.[79,80] Although a causal link between RSV infection and asthma has not yet been proven, immunological evidence suggests skewing toward a Th2-type response, and reduction of interferon-γ antiviral immunity during RSV infection supports airway hyper-reactivity in a subset of susceptible children.[79] Bronchiolitis due to RSV has also been linked to more severe asthma, demonstrated by a 3-fold increase in asthma-related hospitalizations and medication use compared with age-matched controls without prior RSV-associated lower respiratory tract infection.[81]

In a study including approximately 25,000 adults aged 60 years or older, the adjuvanted RSV vaccine (RSVPreF3 OA, Arexvy, GlaxoSmithKline) was well tolerated and reduced the risk of RSV-associated lower respiratory tract disease by 82.6% and of RSV-associated acute respiratory infection (including mild infection) by 72%.[82] When evaluating participants with one or more chronic conditions, such as asthma, chronic lung disease, chronic heart failure, and diabetes, vaccine efficacy was even higher.[83] Among those with at least one chronic condition, the vaccine reduced the risk of RSV-associated lower respiratory tract disease by 95% and of RSV-associated acute respiratory infection by 81%.[83] In participants with two or more chronic conditions, the risk reduction for lower respiratory tract disease was 92% and for acute respiratory infection was 88%.[83] These findings indicate that the RSV vaccine may serve as an important tool for preventing severe RSV-related disease in adults aged 60 years and older with chronic health conditions, including asthma.

In Brazil, the National Health Surveillance Agency (Anvisa) recently authorized the registration of two RSV vaccines:

– Arexvy (adjuvanted), from GlaxoSmithKline, was the first RSV vaccine registered in the country (2023). Approved for use in adults aged 60 years or older, as well as adults aged 50-59 years at increased risk for RSV infection, the vaccine is administered intramuscularly as a single dose at any time of the year, regardless of viral seasonality. Current data demonstrate sustained protection across three RSV seasons (nearly 3 years).[84] Thus, booster doses are not currently recommended.
– Abrysvo, from Pfizer, was licensed by Anvisa for use in pregnant individuals between 24 and 36 weeks of gestation to protect newborns. It is administered intramuscularly as a single dose. The vaccine has demonstrated protection through two RSV seasons. It has also been authorized for administration in persons aged 60 years or older, and in adults aged 18-59 years at increased risk for RSV infection, with safety and efficacy data comparable to those of Arexvy.

The use of these vaccines in patients with asthma aged 60 years or older is recommended by both SBIm and ASBAI.

In addition to vaccines, palivizumab and nirsevimab are monoclonal antibodies indicated for the prevention of RSV infection in infants, particularly those at high risk. Palivizumab is a humanized monoclonal antibody that binds to the RSV fusion (F) protein, inhibiting viral entry into host cells.[85] Clinical studies have shown that palivizumab significantly reduces RSV-related hospitalizations in extremely premature infants (born at <28 weeks), as well as in those with bronchopulmonary dysplasia or hemodynamically significant congenital heart disease.[85,86] Prophylaxis with palivizumab requires monthly administration during the RSV season, for up to five doses.

Nirsevimab is a long-acting monoclonal antibody that also targets the RSV F protein but has an extended half-life, allowing protection with a single dose for the entire viral season.[87] Clinical trials have demonstrated that nirsevimab effectively reduces severe RSV infections and hospitalizations in healthy infants, preterm infants, and those with comorbidities.[87-89] Its efficacy was comparable to or greater than that of palivizumab, with the added benefit of a single-dose regimen.[88]

In summary, palivizumab and nirsevimab are effective for RSV prevention in infants, with nirsevimab offering the advantage of once-per-season dosing.

Vaccination against invasive pneumococcal disease

Pneumococcal disease refers to any infection caused by *Streptococcus pneumoniae* (pneumococcus),[90] which is the most common bacterial causative agent of a wide range of infections, including noninvasive (such as sinusitis, otitis media, and community-acquired pneumonia) and invasive disease, when pneumococcus enters previously sterile sites such as the bloodstream (bacteremia) or the tissues and fluids surrounding the brain and spinal cord (meningitis).[90,91] These conditions are severe, frequently require hospitalization, and may be fatal.[90]

Approximately 100 pneumococcal serotypes have been identified based on antigenic differences in their polysaccharide capsules. Polysaccharide capsules are the most important virulence factors of this bacterium and are responsible for inducing serotype-specific immunity in the host.[92] Consequently, these capsular antigens form the basis of current pneumococcal vaccine formulations used for disease prevention.

Asthma has been associated with an increased risk of pneumonia and IPD, particularly among children.[93,94] In addition, asthma may worsen pneumonia outcomes and increase mortality risk.[95] For this reason, health agencies, including the U.S. Centers for Disease Control and Prevention (CDC),[96] consider asthma an indication for pneumococcal vaccination. The GINA initiative notes that there are still limited data conclusively demonstrating pneumococcal vaccine efficacy specifically in the asthma population to recommend universal use, although it acknowledges that these patients, especially children and older adults, are at higher risk for pneumococcal infections.[65]

Pneumococcal vaccination is part of the childhood immunization schedule in about half of World Health Organization member states, including Brazil. Vaccination reduces pneumonia-related hospitalizations in children and adults and lowers the risk of invasive disease.[97,98] Two types of vaccines are available: the pneumococcal polysaccharide vaccine (PPSV) and pneumococcal conjugate vaccines (PCVs). PPSV induces serotype-specific immunity to the serotypes included in the formulation (as detailed in Figure 5), generating a short-term immune response by stimulating a subset of B cells that produce IgG2 antibodies. Conjugate vaccines, which link a polysaccharide to a carrier protein, stimulate a T-cell-dependent, serotype-specific immune response and activate memory B cells. PPSV23 has been available in Brazil since 1989, and the 7-valent PCV (PCV7) – licensed in 2000 – was the first conjugate vaccine introduced globally. It was later replaced by conjugate vaccines covering additional serotypes, and Brazil currently offers PCV10, PCV13, PCV15, and PCV20.

Routine immunization against *Streptococcus pneumoniae* is safe in patients with asthma and may help mitigate the gradual decline in lung function caused by recurrent infection-triggered exacerbations.[99] The recommended immunization schedules for the pneumococcal vaccines currently available in Brazil (PCV10, PCV13, PCV15, PCV20, and PPSV23), including guidelines for patients with asthma, are provided in Table 5. In summary, it is recommended that patients with asthma receive the PCV13, PCV15, or PCV20 vaccine. For those previously vaccinated with PCV7 or PCV10, additional protection with vaccines containing serotype 19A is important. PPSV23 is recommended from 2 years of age onward for individuals who have received PCV13 or PCV15. PPSV23 is not recommended for those vaccinated with PCV20. The number of doses will depend on the patient's age and immune status.

It is important to emphasize that serologic testing is not recommended before or after pneumococcal vaccination.

Vaccination against COVID-19

Individuals with mild to moderate asthma who contract COVID-19 are not at increased risk for severe disease.[65,100] However, those with uncontrolled asthma have a higher risk of hospitalization due to severe COVID-19 if infected.[101-103]

In Brazil, the National Immunization Program incorporated COVID-19 vaccination into the routine schedule for children from 6 months to under 5 years of age, including those with asthma. In this population, two or three doses of the most up-to-date vaccine formulation are administered, with an interval of 4 weeks between the first and second doses and 8 weeks between the second and third doses (primary immunization schedule).[104]

In 2024, booster doses were implemented for individuals aged 60 years and older and for priority groups. Patients aged 5 years or older with severe

asthma (defined as those requiring recurrent systemic corticosteroid use and/or hospitalization for asthma exacerbation in the previous year) are considered a priority group for COVID-19 vaccination and should receive annual booster doses. Immunocompromised individuals and those aged 60 years or older who meet these criteria should receive semiannual booster doses with the most up-to-date vaccine formulation available. According to Brazil's 2024 COVID-19 Vaccination Strategy, primary immunization schedules are no longer routinely recommended for individuals aged 5 years or older who are not part of priority groups. For those who have never been vaccinated, a single COVID-19 vaccine dose may be administered.[104]

Summary of recommendations for the immunization of patients with asthma

Table 6 shows the recommendations for vaccination in patients with asthma.

Algorithm for the evaluation of patients with a history of suspected allergic reaction to a vaccine

Patients with a history of hypersensitivity to vaccines should undergo evaluation whenever possible. The investigation begins with a detailed clinical history, including the clinical presentation, the extent of the reaction (local or systemic), the timing of onset and duration (immediate or delayed), and

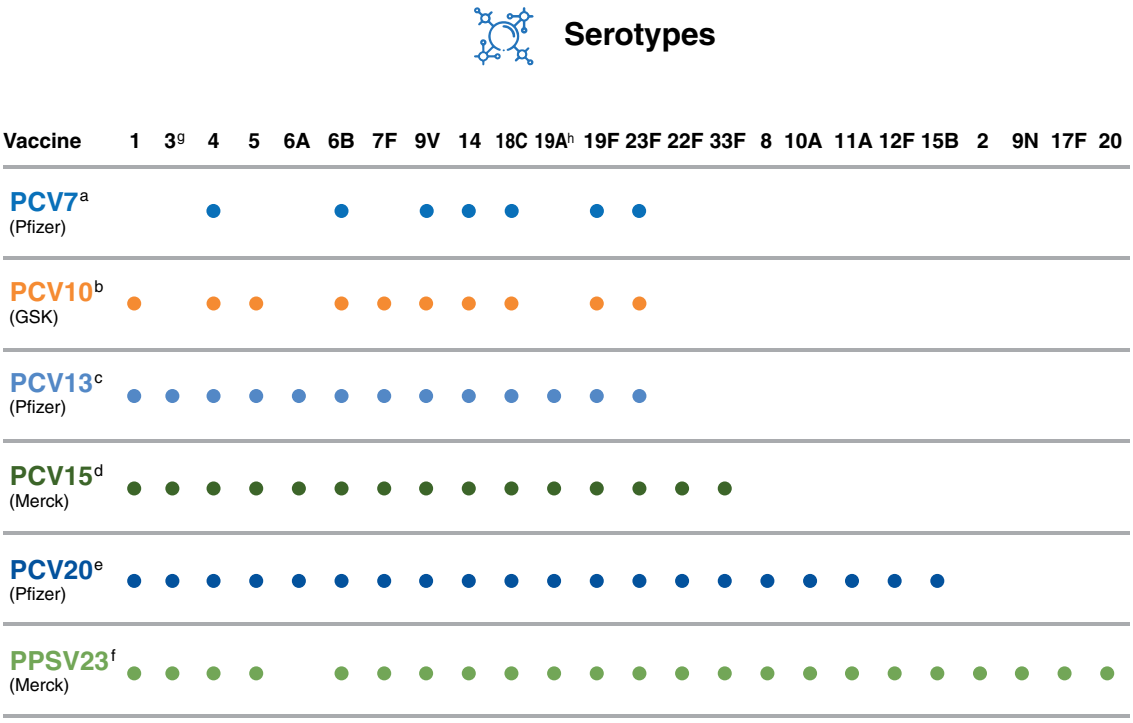


Figure 5
Pneumococcal vaccines licensed in Brazil

[a] No longer used in Brazil.
[b] Available at public primary healthcare units.
[c] Available in private clinics and at Reference Centers for Special Biologics (CRIE) for certain patient groups.
[d] Available in private clinics.
[e] Licensed for use in individuals aged ≥18 years; use in children is still under review.
[f] Licensed for use in individuals aged ≥2 years.
[g,h] Currently responsible for most cases of severe pneumococcal disease in Brazil.

Table 5
Recommended vaccination schedules for pneumococcal vaccines (PCV10, PCV13, PCV15, PCV20, and PPSV23)

Unvaccinated children up to 5 years of age

Age	Vaccine	Vaccination schedule	Notes
2-6 months	PCV10, PCV13, PCV15, or PCV20	Three doses in the first year of life, with a 2-month interval between doses, and a booster between 12 and 15 months of age	PCV10 is provided in public primary healthcare units and is part of Brazil's National Childhood Immunization Schedule
7-11 months	PCV10, PCV13, PCV15, or PCV20	Two doses in the first year of life, with a 2-month interval between doses, and a booster between 12 and 15 months of age	PCV15 and PCV20 are recommended as the preferred options when available. If not available, PCV13 should be used
12-24 months	PCV10, PCV13, PCV15, or PCV20	Two doses, 2 months apart	For children aged 2-5 years with chronic conditions that increase vulnerability to pneumococcal infections (including asthma), supplemental vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) may be necessary for those who received PCV10, PCV13, or PCV15
2-5 years	PCV10, PCV13, PCV15, or PCV20	One dose	

Children aged 6 years or older, adolescents, and adults with chronic conditions that increase the risk for IPD (including asthma) who have not yet been vaccinated

A single dose of PCV13, PCV15, or PCV20 should be administered. For those who receive PCV13 or PCV15, vaccination should be supplemented with PPSV23

Adults

- Vaccination in individuals aged between 50 and 59 years of age with PCV20, PCV15, or PCV13 is at the discretion of the clinician.
- Pneumococcal vaccines are recommended for adults of any age with chronic lung diseases, such as asthma. In these cases, a single dose of PCV20 is indicated, or a sequential schedule beginning with PCV15 or, if unavailable, PCV13, followed by one dose of PPSV23 two months later, and a second dose of PPSV23 five years after the first.

Individuals aged 60 years or older

Status	Recommendation
General	A single dose of PCV20, or a sequential schedule starting with PCV15 or, if unavailable, PCV13, followed by one dose of PPSV23 two months later, and a second PPSV23 dose five years after the first. If PCV20 is chosen, no sequential PPSV23 doses are indicated
Individuals who have already received one dose of PPSV23	Administer PCV20, PCV15, or PCV13 after a 1-year interval from the PPSV23 dose. Those who receive PCV20 do not require an additional PPSV23 dose. Those who begin a sequential schedule with PCV15 or PCV13 should receive a second PPSV23 dose 5 years after the first, maintaining an interval of 6–12 months after PCV15 or PCV13
Individuals who have received two doses of PPSV23 and no PCV	Administer one dose of PCV20 or PCV15; if unavailable, PCV13 may be used. Any of these should be given at a minimum interval of 1 year after the last PPSV23 dose
Individuals with an incomplete schedule using PCV15 or PCV13 and/or PPSV23	Immunization can be completed with a single dose of PCV20, provided that at least 2 months have passed since the last PCV15 or PCV13 dose, or 1 year since PPSV23
Individuals with a complete sequential schedule of PCV15 or PCV13 + PPSV23	A single dose of PCV20 may be recommended at clinician discretion, respecting an interval of 1 year after PPSV23 and 2 months after PCV15 or PCV13

IPD = invasive pneumococcal disease; PCV10 = 10-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

Table 5 *(continued)*
Recommended vaccination schedules for pneumococcal vaccines (PCV10, PCV13, PCV15, PCV20, and PPSV23)

Interchangeability of vaccines	
Vaccine	**Recommendation**
PCV13, PCV15, PCV20	PCV20, PCV15, and PCV13 are interchangeable, and switching between them at any point in the vaccination schedule is acceptable. Healthy children who have completed the schedule with PCV13 do not need revaccination with PCV20 or PCV15, unless they are at higher risk for IPD (including patients with asthma). In such cases, completion with PCV20 or a sequential schedule including PPSV23 is recommended
PCV10 to PCV13, PCV15, or PCV20	To ensure adequate protection against the main serotypes responsible for severe disease (19A and 3), the full age-appropriate schedule recommended for PCV13, PCV15, or PCV20 must be followed beginning at the time the first dose of the new vaccine is administered

IPD = invasive pneumococcal disease; PCV10 = 10-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

the treatment required. For etiologic assessment, it is essential to record the manufacturer and lot number of the administered vaccine and to review the package insert to identify potential allergenic components, including aluminum, formaldehyde, thimerosal, 2-phenoxyethanol, lactose, gelatin, antibiotics, latex, ovalbumin, and yeasts.

If the clinical history suggests a hypersensitivity reaction to the vaccine, diagnostic evaluation should follow the mechanism of hypersensitivity involved, according to the algorithm illustrated in Figure 3. For immediate hypersensitivity reactions or anaphylaxis, skin testing (including SPT and IDT) with the vaccine and its components should be considered. If both tests are negative, the vaccine may be administered under supervision, with observation for at least 60 minutes, in a setting equipped to treat anaphylactic reactions.

When skin tests indicate sensitization, the specialist may choose an alternative vaccine that does not contain the suspected component. If this is not possible, vaccination may be performed using fractional dosing or a desensitization protocol in a setting prepared to manage potential adverse reactions.[105,106]

Non-allergic local reactions, such as erythema, pain, and edema, as well as fever do not contraindicate subsequent vaccine doses.[12] In all cases, it is essential that immunization is not delayed, in order to prevent increased susceptibility to infectious diseases, particularly in the current context of declining vaccination coverage in Brazil.

Although severe hypersensitivity reactions to vaccines are rare, vaccination settings must be prepared to manage such events. Facilities should be adequately equipped with epinephrine, antihistamines, corticosteroids, beta-2 agonists, and oxygen supply, have trained personnel, and follow clear emergency protocols to ensure rapid and effective response in cases of anaphylaxis. Importantly, a history of hypersensitivity to one vaccine does not contraindicate all others, since reactions are caused by specific components rather than by vaccines in general. An allergist can assist in this assessment and help ensure that subsequent vaccines are administered safely.

Reporting of adverse events following immunization

Adverse events following immunization (AEFI) must be reported and investigated in accordance with the 4th

Table 6
Summary of vaccination recommendations for patients with asthma

Vaccine	Recommendation
Influenza[a]	Annual vaccination with trivalent or quadrivalent influenza vaccine starting at 6 months of age. A high-dose influenza vaccine may be used for individuals aged 60 years or older
RSV	Arexvy (adjuvanted): recommended for adults aged ≥60 years and for adults aged 50–59 years at increased risk for RSV infection. Protection demonstrated through the third RSV season. Abrysvo: licensed by Anvisa for pregnant individuals ≥24 weeks' gestation and for adults aged ≥60 years, as well as adults aged 18–59 years at increased risk for RSV infection. Protection demonstrated through the second season
Pneumococcal vaccines	PCV13, PCV15, or PCV20. PCV13 and PCV15 should be complemented with PPSV23 in individuals ≥2 years old. Follow age- and risk-appropriate schedules (Table 5)
COVID-19[b]	Primary schedule of two or three doses (depending on the manufacturer) for children aged 6 months to <5 years. For patients aged ≥5 years with severe asthma, annual booster doses are recommended.
For others vaccines	Follow the routine vaccination schedule

[a,b] Influenza and COVID-19 vaccines may be administered on the same day.
COVID-19 = coronavirus disease 2019; PCV = pneumococcal conjugate vaccine; PPSV = pneumococcal polysaccharide vaccine; RSV = respiratory syncytial virus.

edition of the Manual of Epidemiological Surveillance of Adverse Events Following Immunization.[107] Adequate and timely reporting is essential to ensuring vaccine safety, allowing rapid responses to minimize risks, and informing adjustments to vaccination strategies when necessary. Reporting may be conducted by the institution that administered the vaccine or by the attending physician.

Conclusion

Early identification of allergic reactions, combined with adequate risk stratification based on clinical history and diagnostic testing, is essential to guide vaccine selection and the safe administration of immunizations in patients with a history of hypersensitivity reactions to vaccines. In addition, strategies such as fractional dose vaccination in controlled environments are effective in reducing the risk of hypersensitivity reactions, thereby supporting safe vaccination in this population.

Adequate management of patients who experience hypersensitivity reactions requires collaboration, whenever possible, between allergy and immunology specialists and other healthcare professionals. Continuous surveillance of AEFIs, together with transparent communication with patients about risks and benefits, is fundamental to strengthening trust in vaccination. Moreover, promoting immunization among allergic patients, particularly those with asthma, protects these individuals against preventable infections, improves underlying disease control, and reduces the risk of exacerbation.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Special Article

Vaccination in patients with inborn errors of immunity or receiving immunosuppressive or biologic therapy: joint recommendations of the Brazilian Association of Allergy and Immunology and the Brazilian Immunization Society

Vacinação em pacientes com erros inatos da imunidade ou em uso de imunossupressores ou imunobiológicos: recomendações conjuntas da Associação Brasileira de Alergia e Imunologia e da Sociedade Brasileira de Imunizações

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ABSTRACT

Patients with inborn errors of immunity or receiving immunosuppressive or biologic therapy are at high risk of developing severe infections, including those preventable by vaccines. Adequate immunization is an essential strategy to mitigate this risk and must be adapted according to the underlying condition and according to the patient's degree of immunosuppression. This article reviews the available scientific evidence and best practices regarding vaccination in immunocompromised patients, providing guidance to optimize immunization in this population, with a focus on recommendations adapted to the Brazilian context. The recommendations are organized according to the types of inborn errors of immunity and the immunosuppressive or biologic therapy used. Implementing these guidelines can significantly improve the quality of care for these patients and reduce the burden of preventable infectious diseases.

Keywords: Immunosuppression, immunodeficiency, immunity, immunocompromised host, vaccination, vaccines.

RESUMO

Pacientes com erros inatos da imunidade ou em uso de imunossupressores ou imunobiológicos estão sob maior risco de infecções graves, incluindo aquelas preveníveis por vacinas. A imunização adequada é uma estratégia essencial para mitigar esse risco, e deve ser adaptada conforme a doença subjacente e o grau de imunossupressão de cada paciente. Este artigo revisa as evidências científicas disponíveis e melhores práticas relacionadas à vacinação de pacientes imunocomprometidos, oferecendo orientações para otimizar a imunização nessa população, com foco em recomendações adaptadas ao contexto brasileiro. As recomendações são organizadas com base nos tipos de erros inatos da imunidade e tratamentos imunossupressores ou imunobiológicos utilizados. A implementação dessas orientações pode melhorar significativamente a qualidade do cuidado a esses pacientes, reduzindo a carga de doenças infecciosas preveníveis.

Descritores: Imunossupressão, imunodeficiência, imunidade, imunocomprometimento, vacinação, vacinas.

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Introduction

Patients with inborn errors of immunity or receiving immunosuppressive therapy are at increased risk of infections,[1] including vaccine-preventable ones. These individuals experience both higher attack rates and an elevated likelihood of developing complications or severe forms of various diseases.[2,3]

Preventing infections through vaccination against common pathogens is an essential strategy in the management of this patient population.[4] Therefore, enhanced vaccination approaches are required, involving not only the administration of additional booster doses1 but also, in some cases, caution with certain vaccines, particularly live attenuated vaccines.[5-8]

While immunocompromised individuals require vaccine recommendations tailored to their specific conditions, vaccination coverage in this group is generally lower than in the general population.[9,10] In this context, this article reviews the available evidence and provides recommendations that may increase vaccination coverage and mitigate the risk of severe infections in patients with inborn errors of immunity or receiving immunosuppressive or biologic therapy.

Methods

The evidence and recommendations presented in this study were based on published data available to date and adapted to the Brazilian context. A non-systematic literature review was conducted between June and July 2024 using the MEDLINE database to identify articles addressing different aspects of immunization in immunocompromised patients. These aspects included the immunization of individuals with inborn errors of immunity, such as predominantly antibody deficiencies, immune dysregulation, autoinflammatory diseases, combined immunodeficiencies, and conditions associated with defects in innate immunity. In addition, the review included studies on immunization in patients receiving biologic therapy, immunosuppressants, and small molecules.

The collected evidence was discussed during the "1st Immunization Forum for Allergic and Immunocompromised Patients," held on August 9, 2024, in São Paulo, Brazil. The recommendations were agreed on by consensus among participating experts, all of whom are members of the Brazilian Association of Allergy and Immunology (ASBAI) and the Brazilian Immunization Society (SBIm).

General principles

General principle No. 1: Vaccines are based on different platforms

There are 6 major vaccine platforms (Table 1): (1) inactivated vaccines; (2) live attenuated viral or bacterial vaccines; (3) vaccines based on pathogen components (such as subunit, recombinant, polysaccharide, conjugate, or virus-like particle vaccines); (4) toxoid vaccines; (5) viral vector vaccines; and (6) nucleic acid-based vaccines (DNA or messenger RNA).

Table 1
Vaccine platform technologies

Type of vaccine	Examples
Inactivated	Hepatitis A and inactivated poliovirus vaccine
Live attenuated viruses or bacteria	BCG, measles, mumps, rubella, rotavirus, chickenpox, yellow fever, and dengue
Subunit, recombinant, virus-like particle, polysaccharide, or conjugate	*Haemophilus influenzae* type b, hepatitis B, human papillomavirus (HPV), pertussis, respiratory syncytial virus, pneumococcal conjugate and polysaccharide vaccines, meningococcal, recombinant herpes zoster, and influenza vaccines
Toxoids	Diphtheria, tetanus, and pertussis (acellular)
Viral vector	COVID-19
DNA or messenger RNA (mRNA)	COVID-19

General principle No. 2: Inactivated vaccines can be safely administered to immunocompromised individuals

Inactivated vaccines can generally be administered to immunocompromised patients when indicated, as the antigens contained in these vaccines cannot replicate and do not increase the risk of vaccine-related adverse events. However, the magnitude and duration of vaccine-induced immunity are often reduced.[11]

In complex cases, referral to a clinician with expertise in immunization and/or immunodeficiency is recommended.

General principle No. 3: Live viral or bacterial vaccines are contraindicated for most patients with severe immunosuppression

Individuals with severe immunosuppression (Table 2) or uncertain immune status should generally not receive live viral or bacterial vaccines.[12,13] In less severely immunocompromised individuals or those with specific or limited immune impairment, the benefits of routinely recommended live vaccines may outweigh the risks, as detailed in the following sections.

A patient-centered assessment should consider the degree and type of immunosuppression, as well as comorbidities and personal factors that may influence vaccine responses. Local epidemiology and risk exposure should also be considered. For example, if a patient lives in an area with a high incidence of a vaccine-preventable disease, immunization may be strongly recommended, even in the presence of some immune impairment, provided that the potential benefits justify vaccination.

General principle No. 4: Passive immunization should be used to reduce post-exposure risk

Passive immunization should be used, whenever possible, to reduce the likelihood of illness and complications from infectious diseases in immunocompromised patients with significant exposure. Examples include hyperimmune globulins for tetanus, rabies, varicella-zoster, and hepatitis B.

The following sections discuss vaccination strategies for specific groups of immunocompromised patients.

Table 2
Classification of immunosuppression in relation to vaccination decision according to CD4+ T-lymphocyte counts and age[12,13]

Degree of alteration immunological	CD4+ T-lymphocyte counts (cells/mm^3)			
	Age < 12 months	Age 1 to 5 years	Age 6 to 12 years	Age ≥ 13 years
Absent	> 1500 (> 25%)	> 1000 (> 25%)	≥ 500 (≥ 25%)	≥ 350
Moderate	740–1499 (15%–24%)	500–999 (15%–24%)	200–499 (15%–24%)	Between 200 and 350
Severe	< 750 (15%)	< 500 (15%)	< 200 (15%)	< 200

Inborn errors of immunity

Inborn errors of immunity are classified according to the immune system component that is primarily compromised. For the purposes of this document, inborn errors of immunity were organized into 5 major groups, each addressed with specific vaccination recommendations:

– Predominantly antibody deficiencies;
– Immune dysregulation disorders;
– Autoinflammatory diseases;
– Combined T- and B-cell immunodeficiencies;
– Defects in innate immunity.

Beyond their essential role in protecting against infectious diseases, vaccine responses in these patients can serve as a diagnostic tool for inborn errors of immunity. Post-vaccination antibody responses, particularly to tetanus and diphtheria toxoids, *Haemophilus influenzae* type b, and *Streptococcus pneumoniae*, are frequently used to assess immune system function.[14,15] Additionally, detection of antibodies to hepatitis A, hepatitis B, influenza virus, and isohemagglutinins may help identify immunoglobulin disorders.[15] However, it is important to emphasize that the use of vaccines for diagnostic purposes is not the primary focus of immunization in immunocompromised individuals. Accordingly, this document does not address the use of vaccines for diagnostic purposes.

Predominantly antibody deficiencies

Patients with predominantly antibody (B-cell) deficiencies exhibit increased susceptibility to bacterial infections, which typically occur in early childhood or after the third decade of life. Most infections are caused by encapsulated bacteria, such as *S. pneumoniae*, *H. influenzae* type b, and *Neisseria meningitidis*.[16] Accordingly, vaccines targeting *S. pneumoniae*, *H. influenzae* type b, and *N. meningitidis* are indicated in this group. For patients with defects of specific antibody production, vaccination remains the only means of conferring protection against seasonal influenza. Therefore, annual influenza vaccination is recommended for these individuals, even when they are receiving immunoglobulin therapy.[17-19]

Severe predominantly antibody deficiencies

Severe predominantly antibody deficiencies include common variable immunodeficiency

and agammaglobulinemia. These conditions are associated with severely impaired antibody responses, and affected individuals almost always receive immunoglobulin replacement therapy, which passively provides protective antibodies against several pathogens.[20] Inactivated influenza vaccine is an exception because (1) immunoglobulin preparations may not contain antibodies to circulating strains, and (2) the vaccine may elicit some beneficial cellular immune responses.[17,18]

Live vaccines, such as measles, mumps, and rubella (MMR) or varicella, are contraindicated in patients with severe antibody deficiencies due to the increased risk of vaccine-related disease associated with deficient antibody responses, as well as the possibility of vaccine neutralization by immunoglobulin therapy.[21] However, in scenarios of high epidemiological risk, such as measles or varicella outbreaks, these vaccines may be considered even for patients with severe antibody deficiencies, provided that cellular immunity is evaluated. If cellular responses are preserved, MMR or measles, mumps, rubella, and varicella (MMRV) vaccines may be considered. Such decisions must be individualized, taking into account immune status and the likelihood of exposure to these infections.

Other live virus vaccines, including yellow fever and dengue vaccines, are contraindicated in patients with predominantly antibody deficiencies associated with severe phenotypes.

Mild predominantly antibody deficiencies

Predominantly antibody deficiencies associated with milder phenotypes include selective IgA deficiency, specific antibody deficiency with normal immunoglobulin, and IgG subclass deficiency. Although vaccine-induced antibody responses may be reduced in these individuals, they often retain some degree of protective response and can generally be safely vaccinated with both live and inactivated vaccines, with few exceptions.

In patients with mild antibody deficiencies or other disorders, such as ataxia-telangiectasia, the response to pure polysaccharide pneumococcal vaccine is poor; however, pneumococcal conjugate vaccines are immunogenic and should be administered.[22]

Immune dysregulation disorders

Patients with adaptive immune dysregulation, such as those with familial hemophagocytic lymphohistiocytosis, autoimmune lymphoproliferative syndrome (ALPS) and its variants, frequently present hematologic complications, including cytopenias and neutropenia. Patients with Epstein-Barr virus susceptibility, inflammatory bowel disease, or endocrinopathies (such as APECED, IPEX, and their variants) may develop hypogammaglobulinemia.[23]

Although evidence is limited for many conditions within this group, vaccination in these patients must be assessed individually, taking into account the diversity and severity of clinical manifestations. In the presence of neutropenia or hypogammaglobulinemia, adherence to disease-specific immunization guidelines is essential. Inactivated and recombinant vaccines, such as those against *S. pneumoniae*, *H. influenzae* type b, *N. meningitidis*, and influenza, are generally safe and strongly recommended to prevent severe infections in patients with APECED and IPEX,[24,25] conditions that may be associated with hypogammaglobulinemia.

Regarding live attenuated vaccines, available data are insufficient for a clear recommendation. Their use should be considered on a case-by-case basis, taking into account ongoing immunosuppressive therapy and patient immune status.

Vaccination of household contacts should be encouraged, as it provides indirect protection and helps reduce exposure to infectious agents.

Autoinflammatory diseases (monogenic)

Patients with monogenic autoinflammatory diseases generally do not exhibit significant immune deficiency. However, in rare conditions, such as adenosine deaminase 2 deficiency-related myelodysplasia and sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD) syndrome, immune impairment may occur.[26,27]

Overall, there are no specific contraindications to vaccination in these patients, except when they are receiving immunosuppressive therapy. In such cases, administration of live attenuated vaccines should be carefully evaluated, and inactivated or recombinant vaccines should be preferred whenever possible.

Vaccines particularly recommended for this group include those against *S. pneumoniae*, *H. influenzae* type b, *N. meningitidis*, and influenza. Vaccination of household contacts is also strongly recommended to provide indirect protection for these patients.

Combined humoral and cellular immunodeficiencies

Patients with combined immunodeficiencies exhibit impairment of both cellular (T-cell) and humoral (B-cell) immunity.[28] Combined T- and B-cell immunodeficiencies can be grouped into two categories: complete defects and partial defects.

Combined T- and B-cell immunodeficiencies — complete defects

Combined immunodeficiencies with complete defects include severe combined immunodeficiency (SCID) and complete DiGeorge syndrome. All live attenuated vaccines (viral or bacterial) may cause severe complications in these patients; therefore, all live vaccines are contraindicated in these conditions.[29] Vaccination against *S. pneumoniae* and *H. influenzae* type b is strongly recommended for patients with complete combined immunodeficiencies, as is the indication of monoclonal antibody prophylaxis against respiratory syncytial virus.[28,29] Inactivated vaccines do not pose safety concerns; however, they are likely to be ineffective, and given their uncertain benefit, they are sometimes not administered to these patients.[29]

Combined T- and B-cell immunodeficiencies — partial defects

Partial combined immunodeficiencies include Wiskott-Aldrich syndrome, ataxia-telangiectasia, and partial DiGeorge syndrome. Live attenuated vaccines are often contraindicated in these disorders.[29] Vaccination in less severe cases (most patients) should be considered on an individual basis. Depending on the immune response, classification of immunosuppression according to age-adjusted CD4+ T-lymphocyte counts (Table 2), and the local epidemiologic risk, certain live attenuated vaccines may be considered in vaccination decision-making (Table 3).

In partial combined immunodeficiencies, inactivated vaccines may be effective in some cases and can be administered. Strongly recommended vaccines for this group include those against *H. influenzae* type b, *S. pneumoniae*, *N. meningitidis*, hepatitis A and B, DTaP or DTwP, inactivated poliovirus, influenza, HPV, recombinant herpes zoster, and COVID-19.[29]

Table 3 summarizes vaccination recommendations for patients with combined immunodeficiencies.

Defects in innate immunity

Defects in innate immunity encompass a heterogeneous group of genetic disorders that impair the ability of the immune system to respond appropriately to infection. Common conditions in this category include phagocytic disorders, complement deficiencies, toll-like receptor deficiency, and natural killer (NK) cell deficiencies.

These disorders vary widely in severity and in their impact on an individual's ability to respond appropriately to infection. Early diagnostic evaluation is essential to guide effective therapeutic interventions, which may include antimicrobial or antifungal prophylaxis and, in more severe cases, hematopoietic stem cell transplant for immune reconstitution. In general, no clinical trial has specifically evaluated vaccination practices in patients with defects in innate immunity. Therefore, recommendations are based on clinical complications observed in these populations.

Phagocytic disorders

Phagocytic disorders include congenital neutropenias, leukocyte adhesion deficiencies, and defective oxidative burst (chronic granulomatous disease and G6PD deficiency).

Neutropenia is classified as mild (absolute neutrophil count of 1000-1500/μL), moderate (500-1000/μL), and severe (< 500/μL).[30] Mild or moderate neutropenia is not associated with impaired vaccine responses or increased risk of adverse events. Unless additional relevant phenotypes or comorbidities are present, vaccination policies for these patients should not differ from those for the general population.[31]

All inactivated vaccines can be safely administered to patients with severe neutropenia. Certain specific vaccines are strongly recommended because of the elevated risk of infection in children with this condition, especially those against *S. pneumoniae* and *N. meningitidis*. Seasonal influenza and hepatitis B vaccines are also important to prevent nosocomial infections.[13,30,32,33]

Live bacterial vaccines, such as BCG, are contraindicated in severe neutropenia due to the risk of complications.[31] In many countries, however, newborns receive BCG vaccine in the first days of life, before severe neutropenia is even suspected. Although BCG-related complications are rarely reported in infants later diagnosed with severe neutropenia,

Table 3
Vaccination recommendations for patients with combined immunodeficiencies

Condition	Recommended	Benefit and efficacy unlikely Safe to administer	Consider according to cellular response	Not recommended
Combined T- and B-cell immunodeficiencies: complete defects	Palivizumab or Nirsevimab	Meningococcal conjugate Meningococcal B Hepatitis A and B DTaP or DTwP Inactivated polio Influenza HPV 23-valent pneumococcal Recombinant herpes zoster COVID-19		BCG Rotavirus Yellow fever MMR Varicella Dengue
Combined T- and B-cell immunodeficiencies: partial defects	*Haemophilus influenzae* B Pneumococcal conjugate Meningococcal conjugate Meningococcal B Hepatitis A and B DTaP or DTwP Inactivated polio Influenza HPV 23-valent pneumococcal Recombinant herpes zoster COVID-19 Palivizumab or Nirsevimab		MMR Varicella Dengue Yellow fever	BCG Rotavirus

BCG = Bacillus Calmette-Guérin (tuberculosis vaccine); DTaP = combined diphtheria, tetanus, and (acellular) pertussis vaccine; DTwP = combined diphtheria, tetanus, and (whole-cell) pertussis vaccine; HPV = human papillomavirus.

the contraindication is extrapolated from findings in patients with phagocytic cell defects, considering the limited efficacy of the vaccine.[13,30,32,33] BCG is also contraindicated in chronic granulomatous disease and in defects of the interleukin (IL)-12/interferon-gamma axis, as these conditions impair phagocyte function and significantly increase the risk of severe post-vaccination complications.

Live virus vaccines are not contraindicated in patients with severe neutropenia, but assessment of cellular and/or adaptive immunity is essential before administration. A safe practice is to formally exclude

significant cell and/or antibody immunodeficiency before administering live virus vaccines to these patients.[31]

Patients with leukocyte adhesion deficiency or cytotoxic granule defects may have impaired antiviral responses[32,34,35] and, therefore, should not receive live virus vaccines.

Complement deficiencies

Patients with complement deficiencies retain intact humoral and cellular immunity and may receive all live and inactivated vaccines. Vaccination against encapsulated organisms, such as *N. meningitidis*, *S. pneumoniae*, and *H. influenzae* type b, is especially critical, including for those with partial complement deficiencies.[33,36,37] Recommended meningococcal vaccination schedules are described below.

Meningococcal ACWY vaccine

- *Children < 1 year of age:* 2 doses at 3 and 5 months of age; booster at 12-15 months of age; booster at 5 years of age; additional boosters every 5 years.
- *Children ≥ 1 year of age, adolescents, and adults:* 2 doses 2 months apart; boosters every 5 years.

Meningococcal B vaccine

- *Children ≤ 23 months of age:* 2 doses + booster.
- *Children ≥ 24 months of age:* 2 doses.
- *Adolescents and adults:* 2 doses 1-6 months apart (depending on the vaccine used).
- *All individuals up to 50 years of age (use beyond age 50 is off-label):* a booster 1 year after the primary series and every 2-3 years thereafter.

In hereditary angioedema, a rare genetic disorder that involves the deficiency or dysfunction of C1 esterase inhibitor, a regulator of complement, fibrinolytic, coagulation, and kallikrein-kinin systems, vaccination against hepatitis A and B is also recommended for all patients.[38] For this group of patients, other vaccines should follow routine immunization schedules.

Toll-like receptor and natural killer cell deficiencies

Currently, there are no studies specifically guiding or contraindicating vaccination in patients with these deficiencies. Therefore, vaccines should follow routine immunization schedules.

Table 4 summarizes vaccination recommendations for patients with innate immune defects.

Patients who are candidates for or receiving immunosuppressive or biologic therapy

As part of the therapeutic arsenal against various immune-mediated diseases, an increasing number of individuals receive immunosuppressive agents, such as corticosteroids, 6-mercaptopurine, azathioprine, methotrexate, cyclosporine, tacrolimus, and mycophenolate mofetil. Small molecule drugs such as JAK inhibitors, as well as biologic agents including monoclonal antibodies, are also widely used in the management of immune-mediated conditions. While essential for disease control, these treatments can increase the risk of both common and opportunistic infections.[39-42] In addition, immunosuppressive drugs may negatively affect vaccine responses in certain populations.[43,44]

Non-biologic immunosuppressive agents

For patients who are candidates for or currently receiving non-biologic immunosuppressive therapy, vaccination should follow specific guidelines to ensure immunization efficacy and safety. The goal is to minimize the risk of vaccine-preventable infections while accounting for treatment-related immune impairment.

Inactivated vaccines are often safe and recommended for patients receiving immunosuppressive therapy. Ideally, they should be administered at least 2 weeks before initiating immunosuppression to allow for an adequate immune response.

When immunosuppressive therapy must be started urgently, completing the vaccination schedule beforehand may not be feasible. In such situations, inactivated vaccines may be administered during immunosuppression, provided that the first dose was given before therapy began. Studies show that, in patients receiving non-biologic immunosuppressants, the influenza vaccine remains effective, with 79% of patients achieving protective titers, compared with 98% in control groups.[45] Moreover, severe post-vaccination adverse events are not more common in patients receiving non-biologic immunosuppressive agents, supporting the safety of inactivated vaccines in this group of patients.[44] However, the optimal timing of vaccination may vary based on treatment planning. If a reduction in immunosuppressive dose is anticipated, it may be more effective to postpone

Table 4
Vaccination recommendations for patients with defects in innate immunity

Defect in innate immunity	Recommendation
Mild to moderate neutropenia	All vaccines can be safely administered
Severe neutropenia	Inactivated vaccines can be safely administered. Do not administer attenuated bacterial vaccines. Whenever possible, replace live attenuated virus vaccines with inactivated vaccines
Chronic granulomatous disease	Do not administer BCG or attenuated Salmonella typhi vaccines. All other vaccines can be safely administered
Defects of the interleukin-12/ interferon-gamma axis	Do not administer BCG or attenuated Salmonella typhi vaccines. All other vaccines can be safely administered
Leukocyte adhesion deficiency or cytotoxic granule defects	Do not administer live virus vaccines. All other vaccines can be safely administered
Complement deficiencies	Administer vaccines against encapsulated organisms for partial or complete deficiencies. In hereditary angioedema, vaccinate against hepatitis A and B. All other vaccines can be safely administered
Toll-like receptor deficiency	There are no known restrictions for vaccination; however, data on these cases are still limited
Natural killer cell deficiency	There are no known restrictions for vaccination; however, data on these cases are still limited

BCG = Bacillus Calmette-Guerin (tuberculosis vaccine).

vaccination to that period, when the immune response may be more robust.

Live attenuated vaccines, such as MMR, varicella, yellow fever, and dengue vaccines, should be used with caution. Ideally, these vaccines should be administered 4 weeks before the start of immunosuppression; if this is not possible, a minimum interval of 2 weeks may be considered, since vaccine-induced viremia typically occurs within this period. For patients already receiving immunosuppressive therapy, live attenuated vaccines are often contraindicated due to the risk of infection from the attenuated strain. In settings of high epidemiological risk, individualized risk-benefit assessment is warranted.

In planning vaccination, priority should be given to annual influenza vaccination (high-dose for adults > 60 years of age), respiratory syncytial virus vaccine, pneumococcal conjugate vaccine (PCV13, PCV15, or PCV20), followed by the 23-valent pneumococcal polysaccharide vaccine (if PCV13 or PCV15 was used), and recombinant herpes zoster vaccine for adults > 18 years of age (2 doses, 4 weeks apart). Live vaccines, such as yellow fever, MMR, and dengue vaccines (2 doses, 3 months apart), should be considered in light of the current epidemiological context. Table 5 provides minimum intervals between different vaccine administrations.

After discontinuation of immunosuppressive therapy, specific safety intervals must be observed before administering live attenuated vaccines, as described below.

– Cyclosporine: 3 months.
– Glucocorticoids > 2 mg/kg/day for > 2 weeks in children, or > 20 mg/day for > 2 weeks in adults: 1 month.
– Methotrexate > 20 mg/week or > 0.4 mg/kg/week: 4 weeks. Lower doses may not require a minimum interval.

For infants born to mothers who received immunomodulators or biologic agents during the last 2 trimesters of pregnancy, BCG vaccination should be deferred until 6-12 months after the mother's last dose, owing to potential effects on neonatal immune function. Rotavirus vaccine, however, is not contraindicated in this group. Regarding early measles vaccination (zero-dose MMR or MR) or yellow fever vaccination at 9 months of age, available evidence is insufficient to determine safety in infants born to mothers who received immunomodulators or biologic agents during the last 2 trimesters of pregnancy. Decisions should therefore be individualized, considering the infant's immune status and local epidemiological risk.

Both attenuated and inactivated vaccines can be safely administered to infants breastfed by mothers receiving immunosuppressive corticosteroid therapy with methotrexate and cyclosporine. However, caution is advised with live attenuated vaccines in infants breastfed by mothers receiving cyclophosphamide due to its greater immunosuppressive potential.[44]

Ensuring that household contacts of patients receiving immunosuppressive therapy are fully vaccinated is essential, particularly for influenza, COVID-19, varicella (for susceptible individuals), MMR, and Tdap.

Monoclonal antibodies

The use of monoclonal antibodies and the development of immunization strategies require an integrated assessment of clinical efficacy parameters and safety profiles. While monoclonal antibodies offer targeted therapeutic approaches for specific conditions, immunization remains essential for the prevention of infectious diseases. However, factors such as individual immune response, potential adverse effects, duration of protection, and associated risks should be carefully evaluated in each case (Table 6).

Monoclonal antibodies consist of an innovative class of biologic agents designed to interact specifically with precise immune targets. Some monoclonal antibodies modulate T-helper type 2 (Th2)-mediated immune responses, which play a key role in the pathophysiology of several allergic and inflammatory diseases.[46]

Th2 responses are amplified by cytokines such as IL-4, IL-5, and IL-13, which promote eosinophil activation, stimulate IgE production, and drive characteristic allergic inflammation. These medications, belonging to the IgG class, exert their therapeutic action by directly blocking these inflammatory cytokines and have demonstrated efficacy in conditions such as asthma, chronic obstructive pulmonary disease, chronic rhinosinusitis with nasal polyposis, atopic dermatitis, prurigo nodularis, eosinophilic esophagitis, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome.[46,47]

Biologic agents have become essential in managing Th2-mediated inflammatory conditions by providing targeted and effective therapeutic interventions. Examples include anti-IL-4/IL-13 therapy (dupilumab), anti-IL-5 therapy (mepolizumab), anti-IL-5 receptor-α treatment (benralizumab), and anti-IgE therapy (omalizumab). In addition to Th2-targeted monoclonal antibodies, agents that block IL-1, such as canakinumab (anti-IL-1β), have been developed for the treatment of autoinflammatory and rheumatologic diseases, whose pathophysiological process involves IL-1 overproduction.[48]

Another important example includes monoclonal antibodies targeting thymic stromal lymphopoietin (TSLP), such as tezepelumab, which acts on early inflammatory responses and is particularly effective in the treatment of severe asthma.[49] Additional biologic agents, such as infliximab and adalimumab, block tumor necrosis factor (anti-TNF) and are widely used in rheumatoid arthritis and inflammatory bowel disease.[50,51] Rituximab, which binds to CD20 on B cells, induces cell lysis through immunological mechanisms such as antibody-dependent cytotoxicity and apoptosis. This B cell depletion reduces antibody production and is effective in the treatment of autoimmune and hematological conditions, such as rheumatoid arthritis and lymphomas.

Eculizumab is a monoclonal antibody used in the treatment of autoimmune conditions and rare complement-driven diseases. It inhibits protein C5 and prevents its activation, which avoids membrane attack complex formation, thereby reducing inflammation

and tissue damage. It is indicated for conditions such as paroxysmal nocturnal hemoglobinuria, reducing premature erythrocyte destruction, and atypical hemolytic uremic syndrome, which causes renal injury and anemia due to uncontrolled activation of the complement system.[52]

Inactivated vaccines

Inactivated vaccines, including mRNA vaccines, conjugate vaccines, toxoid vaccines, and non-replicating viral vector vaccines, can be administered safely and effectively to patients receiving anti-IL-4, anti-IL-5, anti-IL-13, and anti-IgE therapies.

For other inactivated vaccines, specific safety considerations apply. Pneumococcal vaccination in patients treated with canakinumab (anti-IL-1β) has produced conflicting data regarding disease exacerbation and adverse events. One study found that patients with cryopyrin-associated periodic syndromes treated with canakinumab exhibited more frequent and more severe reactions to pneumococcal vaccines than to other inactivated vaccines.[53] In this cohort, 12 of 18 patients developed vaccine reactions (fever, swelling, erythema, pain), often within hours, lasting up to 3 weeks; most importantly, pneumococcal vaccination exacerbated disease in 2 patients. Therefore, the potential benefits of

Table 5
Minimum intervals between different vaccine administrations

Types of vaccines	Intervals	Example / Note
Inactivated and conjugate	Simultaneous or no minimum interval	Meningococcal ACWY and Influenza
Inactivated and injected attenuated	Simultaneous or no minimum interval	Hepatitis A and MMR or varicella and pneumococcus
Inactivated and oral attenuated	Simultaneous or no minimum interval	Meningococcal C and rotavirus
Between injected attenuated	They can often be administered on the same day; if not, a 30-day interval is recommended	Varicella and yellow fever
Yellow fever and MMR	Do not administer on the same day to children under 2 years of age (minimum 30-day interval)	
Qdenga® and injected attenuated	They can be administered on the same day	Qdenga® and yellow fever, both routine vaccinations at age 4 according to the Brazilian Society of Pediatrics
Pneumococcal conjugate (13v or 15v) and 23v pneumococcal	Between conjugate and 23v pneumococcal: 2 months. Between 23v pneumococcal and a pneumococcal conjugate: 12 months. Use of the 20-valent conjugate vaccine eliminates the need for the PPSV23	Always begin with a conjugate vaccine, which provides superior and longer-lasting response

MMR = measles, mumps, and rubella; PPSV23 = 23-valent pneumococcal polysaccharide vaccine.

Table 6
Vaccination guidelines for patients receiving monoclonal antibodies

Monoclonal antibody	Inactivated vaccines	Attenuated vaccines	Notes
Omalizumab	Administration at any time	It is suggested that the vaccine be administered 7 days after the first dose of the monoclonal antibody to avoid confusion between adverse events of each biologic agent	x
Dupilumab	Administration at any time	It is suggested that the vaccine be administered 7 days after the first dose of the monoclonal antibody to avoid confusion between adverse events of each biologic agent	x
Mepolizumab	Administration at any time	It is suggested that the vaccine be administered 7 days after the first dose of the monoclonal antibody to avoid confusion between adverse events of each biologic agent	x
Benralizumab	Administration at any time	It is suggested that the vaccine be administered 7 days after the first dose of the monoclonal antibody to avoid confusion between adverse events of each biologic agent	x
Tezepelumab	Administration at any time	No evidence currently supports its safety or efficacy during therapy – vaccination schedule should be completed 4 weeks prior	x
Rituximab	Ideally, complete the vaccination schedule 4 weeks prior. If not possible, postpone vaccination until the next cycle and wait 2 weeks after immunization to administer the medication	Discontinue medication for 6 months before or 4 weeks after vaccine administration	Reduced efficacy: influenza, pneumococcal, hepatitis A, and COVID-19
Anti-TNF[a]	Ideally, complete the vaccination schedule 4 weeks prior. If not possible, postpone vaccination until the next cycle and wait 2 weeks after immunization to administer the medication	Discontinue immunosuppressant for one dosing interval before vaccination and for 4 weeks after vaccine administration	Reduced efficacy: influenza (this vaccine can be administered at any time) pneumococcal, hepatitis A, and COVID-19
Canakinumab	They are safe during medication use, but there is no evidence regarding their efficacy – Complete the vaccination schedule 4 weeks prior	Discontinue immunosuppressant for one dosing interval before vaccination and for 4 weeks after vaccine administration	Caution regarding pneumococcal vaccine and exacerbation of cryopyrin-associated periodic syndrome
Eculizumab	Caution regarding exacerbation of underlying disease due to complement activation – efficacy may be impaired in meningococcal vaccines	Discontinue immunosuppressant for one dosing interval before vaccination and for 4 weeks after vaccine administration[b]	Complete the vaccination schedule 2 weeks prior – priority to meningococcal, *Haemophilus influenzae* type b, and pneumococcal vaccines

[a] Infants exposed to anti-TNF therapy in utero should receive rotavirus vaccine, while the BCG vaccine should be postponed for 6 to 12 months after the last dose of the medication during pregnancy.
[b] No data available in the literature.

immunization with the pneumococcal vaccine must be balanced against safety concerns. The study suggests that pneumococcal conjugate vaccines should be prioritized over the 23-valent polysaccharide vaccine (PPSV23).[53]

Special attention is also warranted regarding inactivated vaccine efficacy in patients receiving rituximab or anti-TNF therapies. Patients treated with anti-TNF show reduced immune responses to certain vaccines, including influenza, pneumococcal, hepatitis A, and COVID-19 vaccines.[54-56] Thus, vaccination should ideally be updated at least 4 weeks prior to initiating rituximab or anti-TNF therapy. If this is not possible, vaccination should be postponed until the next treatment cycle and the medication delayed for 2 weeks after immunization to optimize vaccine efficacy. Influenza vaccination may be administered at any time in patients receiving anti-TNF therapy due to the seasonal nature of the disease.[57]

Patients receiving eculizumab have increased susceptibility to *N. meningitidis* infection due to the drug's mechanism of action. Therefore, vaccination against *N. meningitidis*, covering serogroups A, C, W, Y, and B, is recommended at least 2 weeks before therapy initiation.[58] If treatment is initiated earlier, prophylactic antibiotics should be administered until 2 weeks after vaccination.[58] Patients aged < 18 years should also be vaccinated against *H. influenzae* type b and *S. pneumoniae* and must adhere strictly to age-appropriate national vaccination schedules. In patients treated with eculizumab, vaccination may activate complement.[58] Therefore, patients should be carefully monitored for exacerbation of underlying disease (hemolysis in paroxysmal nocturnal hemoglobinuria or thrombotic microangiopathy in atypical hemolytic uremic syndrome). Because vaccination may not confer complete protection against *N. meningitidis*, close surveillance is essential for early detection of signs of infection, with prompt treatment if necessary.[58]

Live attenuated vaccines

Live attenuated vaccines may be administered safely to patients receiving monoclonal antibodies targeting Th2 immune responses.[59] Regarding safety and efficacy, there are no contraindications for immunization in patients treated with anti-IL-4, anti-IL-5, anti-IL-13, or anti-IgE therapies.[60-64] In this group, vaccination should preferably occur 4 weeks before starting treatment. If this is not feasible, the interval between vaccination and the first antibody dose should be as long as possible (with a minimum of 7 days) to allow the identification, through temporal correlation, of whether any adverse reaction was caused by the vaccine or the monoclonal antibody, noting that monoclonal antibody-related reactions are rare but most likely occur after the first dose.

Tezepelumab targets TSLP, a cytokine central to early inflammatory signaling and both activation and amplification of multiple immune pathways. By inhibiting this inflammatory signaling from the outset, tezepelumab impacts various cells and mediators involved in the immune response. As a consequence, the immunosuppressive effect of tezepelumab may affect the immune system's ability to respond to the vaccine antigen. This early blockade hinders the assessment of the risks and benefits of administering live attenuated vaccines to patients undergoing anti-TSLP treatment, owing to limited robust and conclusive data on the safety and efficacy of immunization in this situation. Therefore, administration of live attenuated vaccines is not recommended for patients receiving tezepelumab. Vaccination should instead be completed at least 4 weeks prior to initiation of monoclonal antibody treatment to ensure that the immune system has an adequate response to the vaccination.

For patients receiving canakinumab or anti-TNF therapy, the 2022 American College of Rheumatology Guideline for Vaccinations in Patients with Rheumatic and Musculoskeletal Diseases recommends, on an individual basis, temporary interruption of immunosuppressive therapy when live attenuated vaccines are required. The medication should be discontinued for one dosing interval before vaccination and for 4 weeks after the administration of live attenuated virus vaccines.[57] We suggest extending this precaution to eculizumab, despite limited supporting evidence.

In children receiving canakinumab for autoinflammatory diseases or systemic juvenile idiopathic arthritis, discontinuation of biologic therapy may pose substantial risk of disease worsening. In such cases, a shorter period of immunosuppressant discontinuation may be considered if live attenuated vaccination is essential.[57]

Infants exposed to anti-TNF therapy in utero should receive rotavirus vaccine within the first 6 months of life.[57]

For rituximab, treatment should be discontinued for 6 months before and 4 weeks after administration of live attenuated vaccines.[57]

Regarding revaccination after completion of monoclonal antibody therapy, there is no conclusive evidence to support this practice as a standard recommendation. Decisions on the need for revaccination should be individualized, considering each patient's clinical condition and the efficacy of immune responses after treatment.

Janus kinase inhibitors

The Janus kinase (JAK) family comprises 4 tyrosine kinase proteins (JAK1, JAK2, JAK3, and TYK2) that play key roles in the immune system, particularly in adaptive immunity and hematopoiesis. These kinases participate in inflammatory signaling, leukocyte maturation, pathogen recognition, and cytokine activation.[65] JAK inhibitors are orally administered synthetic small molecules that block cytokine-mediated signaling pathways in target cells, thereby modulating inflammatory responses in several diseases.[66] Some agents, such as tofacitinib, inhibit multiple JAKs, while others, such as upadacitinib, are selective.

Currently, no evidence indicates a risk of pathogen reactivation following administration of inactivated vaccines in patients receiving JAK inhibitors.[63] Therefore, individuals in this group may follow routine age-appropriate immunization schedules according to their clinical condition. Ideally, inactivated vaccines should be administered at least 14 days before initiation of JAK inhibitor therapy, although they may be given during treatment if necessary. Simultaneous vaccination is both feasible and recommended when indicated.

Live attenuated vaccines are contraindicated during treatment with JAK inhibitors due to the risk of complications.[63] If a live vaccine is required because of lack of prior immunization or absence of immunity, it should generally be administered 14-30 days before therapy initiation or at least 3 months after treatment is discontinued.[63,67] When administration of live attenuated vaccines is unavoidable during treatment, JAK inhibitors should be discontinued for 1-2 weeks prior to vaccination and restarted 4 weeks afterward.[57] In the context of rapidly progressive underlying disease, resuming therapy after 2 weeks may be considered.

Key vaccines to consider for this group of patients are listed below.

– *Recombinant herpes zoster vaccine:* For patients ≥ 18 years of age; 2 doses 1-2 months apart. Preferably administer before initiating JAK inhibitor therapy.
– *Pneumococcal vaccines:* Administer PCV13 or PCV15, followed 2 months later by PPSV23. PCV20 may be used as a single-dose alternative. In individuals who have already received PPSV23 but not PCV13 or PCV15, PCV13 or PCV15 should be administered after a 12-month interval, followed by a second PPSV23 dose 5 years later if indicated. Studies show that pneumococcal vaccine responses vary depending on the JAK inhibitor used. Patients receiving upadacitinib and baricitinib show satisfactory immune responses to both PCV13 and PPSV23,[68,69] whereas those receiving tofacitinib exhibit inadequate responses to PPSV23, even after a 2-week drug discontinuation. However, responses to conjugate vaccine PCV13 remain satisfactory.[70]
– *Influenza vaccine:* Recommended annually for individuals ≥ 6 months of age (high-dose formulations for adults aged > 60 years). A second dose of trivalent or quadrivalent vaccine may be considered beginning 3 months after the annual dose.
– *HPV vaccine:* Some JAK inhibitors have been associated with increased cancer risk.[71] Therefore, adolescents and immunocompromised adults aged < 45 years should receive the 3-dose HPV vaccine series. The 9-valent HPV vaccine (HPV9) is preferred due to its broader coverage, and revaccination should be considered in individuals previously immunized with HPV2 or HPV4.
– *COVID-19 vaccine:* A 3-dose primary series of monovalent vaccine is recommended, with 4 weeks between doses 1 and 2 and 8 weeks between doses 2 and 3 (primary schedule for immunocompromised patients). Adolescents and adults who have completed the primary series should receive mRNA booster doses every 6 months.
– *Hepatitis B vaccine:* Patients receiving JAK inhibitors require particular attention to hepatitis B immunization due to both potential hepatotoxicity of these medications and the increased risk of severe complications from hepatitis B during treatment. Ideally, the full 3-dose series should be completed before JAK inhibitor therapy is initiated.[72] If this is not possible, hepatitis B screening is essential, especially to identify active infection. Active hepatitis B constitutes a contraindication to JAK inhibitor therapy given the risk of hepatic deterioration and complications.

To ensure patient safety, household contacts of individuals receiving JAK inhibitors should be fully vaccinated according to their age-specific schedules.

Considerations on the use of BCG and herpes zoster vaccines in immunocompromised individuals

BCG vaccine

The BCG vaccine is used to prevent severe forms of tuberculosis, such as tuberculous meningitis and miliary tuberculosis. However, because it contains live attenuated *Mycobacterium bovis*, its administration in patients with inborn errors of immunity or other immunosuppressive conditions requires caution. Contraindications include primary or acquired immunodeficiencies, malignancies, prolonged use of high-dose systemic corticosteroids (for ≥ 2 weeks), newborns whose mothers received immunomodulators or biologic agents during the last 2 trimesters of pregnancy, and pregnancy.[73] In immunocompromised individuals, BCG may trigger serious adverse reactions, ranging from local manifestations to potentially fatal disseminated infections.[74]

Recent studies reinforce the need for a cautious approach to BCG vaccination in immunocompromised patients. In a systematic review, Fekrvand et al. identified 46 different inborn errors of immunity associated with adverse events following BCG vaccination, with SCID being the most common and carrying the highest mortality.[75] A Brazilian retrospective study reported complications in up to 65% of patients with SCID who were vaccinated with BCG before diagnosis, with high associated mortality.[76]

Patients with chronic granulomatous disease and Mendelian susceptibility to mycobacterial disease (MSMD) also face elevated risk of local and disseminated complications following BCG. In a retrospective study of 134 Chinese children with disseminated reactions to BCG, 48.6% were subsequently diagnosed with chronic granulomatous disease, 26.1% with MSMD, and 16% with SCID.[77] In Recife, state of Pernambuco, Brazil, a study of 53 patients with adverse reactions to BCG found that 16.8% had underlying inborn errors of immunity. While most cases (90%) involved locoregional reactions, all cases of disseminated reactions occurred in children later diagnosed with an inborn error of immunity, including 4 with chronic granulomatous disease, 3 with MSMD, and 2 with SCID.[78]

In patients with suspected inborn errors of immunity, it is currently recommended to delay BCG vaccination until specific diagnostic testing can confirm or exclude the disorder. Depending on age and resource availability, appropriate tests may include complete blood count, immunoglobulin measurement, lymphocyte immunophenotyping, TREC/KREC assay (if not performed during newborn screening), and dihydrorhodamine (DHR) assay.[75] Regional axillary lymphadenopathy should be regarded as a warning sign for inborn errors of immunity, as should any family history of adverse BCG reactions.[14]

For patients diagnosed with SCID who received BCG at birth, antimicrobial prophylaxis, such as isoniazid, may be used until hematopoietic stem cell transplant is possible. A triple-drug regimen (rifampicin, isoniazid, and ethambutol) may also be used, although toxicity is a potential concern.[76] In cases of disseminated BCG infection, the European Society for Immunodeficiencies recommends a therapeutic regimen with multiple antituberculosis drugs (rifampicin, ethambutol, isoniazid, and clarithromycin) until complete resolution of the infection. Thereafter, two antimycobacterial agents should be maintained until complete immune reconstitution after stem cell transplant. When toxicity occurs, agents such as levofloxacin are indicated.[79]

Recombinant herpes zoster vaccine

Immunocompromised individuals are at substantially increased risk of developing herpes zoster and its severe complications compared with immunocompetent adults of the same age group.[80-82] The recombinant herpes zoster vaccine is an inactivated, protein-based vaccine that uses the recombinant glycoprotein E antigen rather than a live virus. For this reason, it is considered safe for immunosuppressed populations.

In adults ≥ 50 years of age, pivotal trials demonstrated > 90% efficacy in preventing acute herpes zoster episodes.83 Among immunocompromised patients, reported efficacy includes 68.2% in hematopoietic stem cell transplant recipients[84] and 87.2% in patients with hematologic malignancies.[85]

The recombinant herpes zoster vaccine is recommended beginning at age 18 for immunocompromised individuals, administered as

2 doses spaced 2 months apart. When possible, the vaccine should be administered before starting immunosuppressive therapy, with a minimum interval of 1 month before immunosuppression. If this is not feasible, vaccination should occur at the most favorable clinical moment, ideally when the most intense phase of immunosuppression has subsided.

For individuals with prior herpes zoster infection, vaccination should be delayed for 6 months.

Herpes zoster vaccination recommendations for immunocompromised patients are provided in Table 7.

Summary of recommendations

Tables 8 and 9 outline the main vaccination recommendations for immunocompromised patients. Table 9 focuses on guidance regarding inactivated vaccines, which are often safe for this group of patients. Table 8 addresses live attenuated vaccines,

Table 7
Herpes zoster vaccination recommendations for immunocompromised patients

Clinical condition	Recommendation
Patients with severely compromised cellular immunity, untreated active tuberculosis, and pregnant women	Vaccination not recommended
Mild immunosuppression (patients receiving low doses of methotrexate, anti-TNF, systemic corticosteroids, or HIV+ patients with immune reconstitution [CD4 ≥ 200 cells/mm^3])	Vaccination may be considered
Bone marrow transplant	Administer the vaccine 6 to 12 months after transplant, preferably 2 months before discontinuing antiviral medication
Solid organ transplant	Vaccinate before transplant; if not possible, wait 6 to 12 months after the procedure, using low-dose immunosuppressants
Patients with cancer	Vaccinate before chemotherapy, radiation therapy, or immunosuppression, or after the most intense phase of immunosuppression has subsided
Immunosuppressive therapy	Non-biologic agents: administer at least 2 weeks before initiating treatment. They can be administered during immunosuppression, provided that the first dose was given before initiating treatment. Monoclonal antibodies: can be safely administered during treatment. JAK inhibitors: administer preferably before initiating treatment
Autoimmune diseases	Vaccinate before initiating aggressive immunosuppression, whenever possible

TNF = tumor necrosis factor; JAK = Janus kinase.

emphasizing contraindications and the specific situations in which they may be administered under strict monitoring, such as with yellow fever and varicella vaccines.

Conclusion

Immunization of immunocompromised patients requires a careful and structured approach to ensure adequate protection against infections. A key initial step is for health care professionals to assume responsibility for assessing and maintaining the vaccination status of both patients and their close contacts, since protecting the immediate household may be essential to preventing infections in this population.

A detailed understanding of the patient's medical history, including underlying immunosuppressive conditions and current treatments, is crucial to guide vaccine selection according to specific indications and contraindications. Immunocompromised patients should be referred to Referral Centers for Special Biologic Agents (CRIE), within the Brazilian Unified Health System (SUS), or to private immunization

Table 8
Summary of recommendations on the use of live attenuated vaccines in immunocompromised patients

Vaccine	Recommendation
BCG [a]	Contraindicated in patients with severe immunosuppression, such as those with combined immunodeficiencies, phagocytic disorders, or receiving immunosuppressive therapy
Measles-mumps-rubella	Generally contraindicated. It may be considered in patients with mild immunosuppression, depending on the patient's cellular response. Assess the epidemiological and immunological risk individually. Allowed in household contacts
Rotavirus	Contraindicated in patients with severe immunodeficiency or receiving immunosuppressive therapy. Allowed in household contacts
Yellow fever	Contraindicated in patients with severe immunosuppression. It may be considered in settings of high epidemiological risk, after careful assessment of the patient's immune status. Allowed in household contacts
Varicella	Contraindicated in patients with severe immunodeficiency and household contacts. It may be administered with caution in cases of mild immunosuppression after assessment of the patient's immune status.
Rabies	It should be administered even to individuals with inborn errors of immunity in situations of exposure to risk. The only exception is in cases of severe combined T- and B-cell immunodeficiencies
Dengue	Recommended with caution in endemic areas. It should be administered before initiating immunosuppression. Contraindicated in patients with severe immunosuppression. Assess the risk-benefit ratio in each case

[a] The BCG vaccine should be postponed in children undergoing newborn screening for immunodeficiency at birth. If the newborn screening results are normal, the child should be vaccinated as soon as possible.

Table 9
Summary of recommendations on the use of inactivated vaccines in immunocompromised patients

Vaccine	Recommendation
Influenza	Recommended annually for all immunocompromised patients. The vaccine is safe, but the immune response may be reduced
IPV	Recommended for immunocompromised patients, it is a safe alternative to OPV. Vaccination should occur before initiating immunosuppression, whenever possible
Pneumococcal	Highly recommended. It should be administered to all immunocompromised patients. Administer pneumococcal conjugate vaccine (PCV13/PCV15) followed by the polysaccharide vaccine (PPSV23) after 2 months, with a booster PPSV23 dose after 5 years, or the 20-valent vaccine (PCV20) alone. Vaccination should occur before initiating immunosuppression, whenever possible
Meningococcal (ACWY and B)	Recommended for most immunocompromised patients. Vaccination should be considered a priority in patients with immunodeficiencies that increase the risk of meningococcal infections, such as complement deficiencies, combined immunodeficiencies, chronic granulomatous disease, and severe neutropenia. Vaccination should occur before initiating immunosuppression, whenever possible
Haemophilus influenzae type b	Recommended for all immunocompromised patients. Vaccination should occur before initiating immunosuppression, whenever possible
Hepatitis B	Recommended. Immunocompromised patients usually receive a double dose and may require additional or booster doses. Vaccination should occur before initiating immunosuppression, whenever possible
Herpes zoster	Recommended for immunocompromised individuals aged 18 years and older. Administer 2 doses with a 2-month interval. Prioritize before initiating immunosuppression
HPV	Recommended for immunocompromised individuals using the 3-dose series
COVID-19	Highly recommended. Administer the 3-dose primary series and booster doses every 6 months. The vaccination schedule can be accelerated in immunocompromised individuals, and a 1-month interval between doses 1 and 2 can be considered. It can be administered during immunosuppression, but vaccination should be prioritized before initiating treatment, if possible
Respiratory syncytial virus	Recommended for patients at increased risk for RSV disease from 18 years of age (Abrysvo: 18 to 59 years and Arexvy: 50 to 59 years) and all adults aged 60 years and older

Note: Palivizumab or nirsevimab monoclonal antibodies should be used in immunocompromised children under 24 months of age.

units, accompanied by a report from their immunology specialist.

Optimizing the timing of vaccination is also important. In general, live attenuated vaccines should ideally be administered 4 weeks before the initiation of immunosuppression, whereas inactivated vaccines should be administered at least 2 weeks prior.

Finally, it is essential that health care professionals identify and overcome barriers that may hinder vaccine uptake. This includes addressing patients' concerns and hesitancy regarding vaccines, as well as eliminating health system obstacles that may limit access to immunization.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Advances in the treatment of bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation: a scoping review

Avanços no tratamento da Síndrome da Bronquiolite Obliterante pós-transplante de células-tronco hematopoiéticas - uma revisão de escopo

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ABSTRACT

Hematopoietic Stem Cell Transplantation (HSCT) is the treatment of choice for a variety of neoplastic and non-neoplastic diseases in children. However, respiratory complications in the post-transplant period are common and result in increased morbidity and mortality rates. Graft-versus-Host Disease (GVHD) is among the major complications in the late phase, with bronchiolitis obliterans syndrome (BOS) being the most frequent clinical syndrome. It is characterized by an obstructive pattern and progressive nature, caused by the obliteration of the small airway. This is a challenging condition as there is no specific treatment with proven efficacy, coupled with a scarcity of data in the pediatric population. The aim of this article is to review studies highlighting the effectiveness of existing treatments for this condition, across different modalities ranging from conventional therapies to the most recent approaches, aiming to inform attending physicians involved in the care of this patient group. Precise and effective management of BOS is crucial to halt the impairment of pulmonary function in the medium and long term, promoting increased survival for patients post-HSCT.

Keywords: Bronchiolitis obliterans, transplantation, treatment, pulmonary complications.

RESUMO

O Transplante de Células-Tronco Hematopoiéticas (TCTH) é o tratamento de escolha para uma variedade de doenças neoplásicas e não neoplásicas em crianças. No entanto, complicações respiratórias no pós-transplante são comuns e resultam em aumento dos índices de morbidade e mortalidade. A Doença Enxerto Contra Hospedeiro (DECH) está entre as principais complicações na fase tardia, sendo a síndrome da bronquiolite obliterante (BOS), a síndrome clínica mais frequente. Caracteriza-se pelo padrão obstrutivo e de caráter progressivo, ocasionado pela obliteração da pequena via aérea. É uma condição desafiadora, uma vez que não existe tratamento específico com eficácia comprovada, além da escassez de dados na população pediátrica. O objetivo deste artigo é revisar estudos que apontam a efetividade dos tratamentos existentes para esta condição, nas diferentes modalidades, desde as terapias convencionais até as abordagens mais atuais, buscando informar os médicos assistentes envolvidos no atendimento deste grupo de pacientes. O manejo preciso e eficaz da BOS é fundamental para interromper o comprometimento da função pulmonar em médio e longo prazo, favorecendo uma maior sobrevida para os pacientes no pós-TCTH.

Descritores: Bronquiolite obliterante, transplante, tratamento, complicações pulmonares.

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Introduction

Hematopoietic stem cell transplantation (HSCT) represents a potentially curative treatment option for several diseases, including hematological malignancies, inborn errors of immunity, and non-neoplastic conditions. Among the possible complications of HSCT, pulmonary graft-versus-host disease (GVHD) can contribute significantly to post-transplant morbidity and mortality.[1,2]

Pulmonary complications affect 25–50% of HSCT recipients, presenting either as acute manifestations, defined as those occurring within the first 120 days after the procedure, or in subacute/chronic form, with onset approximately 6 months after transplantation. Acute complications are associated with a high mortality rate, with viral and fungal infections, as well as non-infectious complications such as pulmonary edema, diffuse alveolar hemorrhage, and idiopathic pneumonia syndrome, being most common. Subacute/chronic complications have a more insidious course and include pulmonary chronic GVHD, a term which covers two distinct syndromes: bronchiolitis obliterans syndrome (BOS), characterized by an obstructive pattern on pulmonary function tests, and cryptogenic organizing pneumonia (COP), characterized by a restrictive pattern.[1]

BOS is the pulmonary manifestation of GVHD and is characterized by airway obstruction secondary to a fibroproliferative inflammatory process. Collagen deposition occurs in the subepithelial layer, causing partial or complete fibrosis and lymphocyte infiltration associated with hyperplasia or squamous metaplasia of the epithelium, leading to obliteration of the small airways.[3]

The underlying pathophysiological process is complex and multifactorial. Damage to the host bronchiolar epithelium occurs through both immune and non-immune mechanisms. Macrophages and neutrophils play an important role, resulting in the release of inflammatory, chemotactic, and profibrotic mediators. Studies that examined the bronchoalveolar lavage fluid of patients with BOS found increased neutrophils, interleukin (IL)-8, IL-1ra, transforming growth factor beta (TGF-β), monocyte chemotactic protein-1 (MCP-1), and tumor necrosis factor alpha (TNF-α).[4]

The disease is usually asymptomatic, developing insidiously within the first two years after HSCT. Diagnostic suspicion is raised by a progressive decline in lung function in the absence of other etiologies.[5] The recommended criteria are those of the 2014 National Institutes of Health (NIH) Consensus modifications: FEV_1 < 75% or below the fifth percentile of predicted or a ≥ 10% decrease in FEV_1 the last 2 years; FEV_1/FVC ratio < 0.70 or below the fifth percentile of predicted; evidence of air trapping on CT scan with bronchi al thickening or bronchiectasis or due to an increase in residual volume > 120% of predicted in pulmonary function tests; and absence of respiratory tract infection. Nevertheless, biopsy with histopathological analysis remains the gold standard for diagnostic confirmation.[6]

Despite the modifications, the aforementioned criteria may fail to identify early declines in lung function, given their use of an absolute cutoff point for FEV_1. Therefore, the NIH recommends that pulmonary function tests be performed every 3 months for the first 2 years after HSCT, especially in high-risk patients, such as those with extrapulmonary GVHD.[7,8]

Risk factors related to the development of BOS include decreased serum IgG levels, a history of acute GVHD, advanced recipient or donor age, a lower pre-transplant FEV_1/FVC ratio, viral respiratory infections in the first 100 days post-HSCT, conditioning with busulfan or high-intensity conditioning, female-donor-to-male-recipient gender discordance, and a previous episode of interstitial pneumonitis.[1] A pre-transplant history of lung disease and cytomegalovirus (CMV) seropositivity are also associated with an increased risk of BOS.[9]

This is a particularly challenging condition, since no combination of therapeutic agents studied has been completely effective to date; furthermore, many patients may remain asymptomatic for long periods even when evidence of moderate to severe obstruction is already present on pulmonary function tests. BOS is associated with significant impairment of quality of life and increased mortality after HSCT.[1,6,10]

Objectives and methods

To address our main research question (the approach to treatment of BOS after HSCT in adults and children), we chose to conduct a scoping review, seeking to synthesize relevant studies on the subject through a broad literature search of electronic databases, using the keywords bronchiolitis obliterans, transplantation, treatment, and pulmonary complications. The review followed the steps described in the Joanna Briggs Institute method.[11]

Table 1 provides a detailed description of this review (guiding questions, objectives, inclusion and exclusion criteria, source of evidence, characteristics, and instrument used to extract results), ensuring greater rigor and transparency.[11]

Figure 1 shows a flow diagram of article selection, including the final number of records selected for review.

Results

First-line therapies

Corticosteroids

Based on the theory that immune dysregulation might be implicated in GVHD and possibly in BOS as well, immunosuppression with systemic corticosteroids is a common approach to management of such cases. Prolonged therapy with high-dose corticosteroids is the most traditional and widely described approach for treatment of GVHD and some acute post-transplant complications, such as idiopathic pneumonia syndrome and diffuse alveolar hemorrhage; in BOS, however, it has limited impact and is associated with adverse effects.[12]

A study conducted by Ratjen et al. (2005) sought to evaluate the effectiveness of corticosteroids, in the form of methylprednisolone pulse therapy, in children undergoing HSCT who developed BOS as a complication. The sample included a total of 9 patients. The protocol consisted of a 3-day course of methylprednisolone at a dosage of 10 mg/kg/day. This treatment regimen was flexible insofar as it could be repeated monthly, if symptoms persisted, for up to 6 cycles. All patients also received inhaled budesonide for the duration of pulse steroid therapy.[13]

The investigators found a significant increase in oxygen saturation in the patients, with normalization

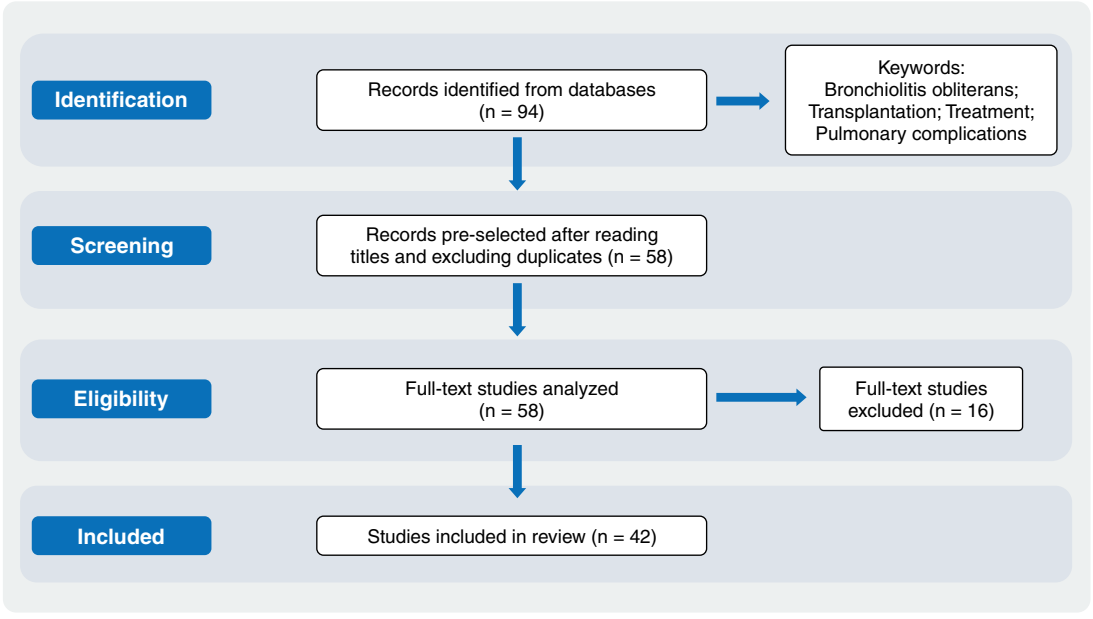

Figure 1
Selection of studies included in the review

Table 1
Detailed description of scoping review

Title of scoping review: Therapeutic approaches to post-transplant bronchiolitis obliterans syndrome (BOS)
Objectives of the review: – to review pharmacological and non-pharmacological treatments for post-transplant bronchiolitis obliterans syndrome (BOS); – to review treatments considered as first-line and second-line therapies; – to review details of the use of these treatments in adults and children, data providing confirmatory evidence of efficacy, and the main adverse events reported; and – to research innovations in the treatment of BOS.
Review questions: – what are the most commonly described current treatments for BOS? – which treatments have shown the greatest efficacy in controlling the disease in adults and children? – which treatments have the fewest adverse events?
Inclusion/Exclusion criteria ***Population:*** adults and children with a diagnosis of post-HSCT BOS. ***Inclusion:*** original articles reporting on treatments for post-HSCT BOS in adults and children (controlled trials, case reports, case-control studies), systematic reviews and meta-analyses with appropriate methodologies, and review articles supported by reference scientific societies. ***Exclusion:*** studies with unclear methodology, studies based on unscientific opinions, and studies with conflicts of interest with the pharmaceutical industry.
Concept: treatments for BOS which demonstrate effectiveness in disease control (improving patients' symptoms and preventing loss of pulmonary function) in adults and children.
Context: studies that address treatments for BOS in children and adults and that have been published in reputable journals.
Types of sources of evidence ***For review articles:*** methodology previously described for meta-analyses and systematic reviews (PROSPERO, PICO, PRISMA, SPIDER registry) and quality assessment of included studies (STROBE, GRADE, CONSORT, Newcastle–Ottawa, etc.). ***For non-systematic reviews:*** only those supported by leading scientific societies, such as the U.S. National Institutes of Health (NIH) or European Society for Blood and Marrow Transplantation, are accepted. ***Case reports or case-control studies:*** those presenting clear data and documenting the diagnostic workup.
Details and characteristics of the source of evidence ***Citation details (e.g., author(s), date, title, journal, volume, number, pages):*** throughout the text and tables. ***Country:*** all countries. ***Context:*** as described above. ***Participants (details, e.g., age/sex and number):*** all ages (children and adults), all sexes, no restriction on number of participants.
Details/results extracted from the source of evidence (regarding the concept of the scoping review) – Treatments for post-HSCT BOS most cited in the literature in recent decades; – Those considered first-line treatments and evidence of their efficacy; – Those considered second-line treatments and evidence of their efficacy; – Treatments under investigation.

of this parameter at the end of therapy. Notably, seven of the nine patients remained clinically stable throughout the follow-up period, with no further deterioration in pulmonary function.[13] These positive findings notwithstanding, this study lacked a control group, a key methodological limitation which precludes any more assertive conclusions regarding the effectiveness of the treatment regimen. Therefore, despite providing valuable insights, the Ratjen study must be interpreted with caution.

Prolonged treatment with high doses of prednisone is associated with several complications and a high risk of morbidity. Patients may experience weight gain, hypertension, infections, osteoporosis, glucose intolerance and, in children, impaired growth. Given this, much research has focused on the possibility of corticosteroid-sparing regimens, which combine other medications aiming for better efficacy and reduced toxicity from chronic corticosteroid use.[14]

Current recommendations on post-HSCT BOS from the two largest relevant international scientific societies, the 2020 European Society for Blood and Marrow Transplantation consensus[15] and the 2021 National Institutes of Health Workshop,[6] do not impose choices on clinicians. Both comment on low-dose systemic corticosteroid therapy in combination with other drugs—fluticasone, azithromycin, and montelukast (FAM), etanercept, among others—and express concern about the need for therapies that can effectively slow or halt the development of functional impairment in post-HSCT BOS.[6,15]

Azithromycin

Azithromycin is frequently used in the treatment of BOS due to its prophylactic and immunomodulatory effect, and may halt or reverse the decline in pulmonary function in some patients.[16]

In 2011, Lam et al. compared patients who received azithromycin versus a placebo group for 12 weeks, analyzing a symptom questionnaire and spirometry before treatment and at 1, 2, 3, and 4 months (with the last assessment performed 1 month after the end of treatment). Ten patients received azithromycin, and 12 patients were in the control group. The study found no significant changes in respiratory symptom scores or FEV_1 measurements between groups.[17] However, a 2005 study by Khalid et al. evaluated 8 patients with post-HSCT BOS who received azithromycin every other day for 12 weeks, comparing pre- and post-treatment pulmonary function tests as well as a respiratory symptom questionnaire. All patients tolerated the treatment well; 7 showed significant improvement in FVC and FEV_1 after treatment, for a response rate of 87%. The mean increase in parameters was 21.57% in FVC ($p < 0.052$) and 20.58% in FEV_1 ($p < 0.067$).[18]

Since 2017, long-term azithromycin therapy has been a matter of debate, even though most studies reported promising findings. In the ALLOZITHRO trial, which was terminated early in 2017, Bergeron et al. found an increased rate of hematological relapse and lower survival in the azithromycin group.[19] In response to this study, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issued warnings, as did the Brazilian Health Regulatory Agency (Anvisa), which also recommended against long-term off-label use of azithromycin for BOS prophylaxis in patients who have undergone HSCT.

Another study conducted by Cheng et al. in 2020 investigated the use of azithromycin in 227 patients with BOS and its relationship with cancer risk (recurrence of the same cancer or another neoplasm), regardless of the time elapsed since HSCT.[20] The study found that exposure to azithromycin after a diagnosis of BOS was associated with an increased incidence of subsequent neoplasms, but not of relapse of the original malignancy.[20] The study also showed that patients who used azithromycin had a lower risk of death free of neoplasm (i.e., from non-cancer causes). These adverse effects of azithromycin are potentially related to its inhibitory effect on various cell types, altering inflammatory pathways and modulating the immune system.[20]

Further reinforcing the latest studies, the 2020 European Society for Blood and Marrow Transplantation consensus stressed that prolonged use of azithromycin in patients with BOS is not recommended due to the risk of hematological relapse.[15]

These findings highlight the importance of a careful assessment of the benefits and risks of this medication in the setting of post-HSCT BOS, a process which should include evaluation of the BOS phenotype, in order to assess its potential effectiveness.

FAM therapy

The combination of fluticasone, azithromycin, and montelukast is known as FAM therapy. To this day, it is still used in many centers that treat patients with

post-HSCT BOS. In 2011, Norman et al., seeking to assess the effectiveness of alternatives to systemic immunosuppressant therapy, tested the FAM regimen in light of its anti-inflammatory and/or antifibrotic properties.[21] A group of 8 patients was followed for 6 months, receiving FAM therapy alone or in combination with systemic corticosteroids, compared to 14 controls who received corticosteroids alone. Both groups had their corticosteroid doses reduced according to the institution's tapering protocol. In most patients, pulmonary function remained stable throughout this period, with no between-group difference. A rapid reduction in prednisone doses was achieved in the group treated with FAM therapy, as well as a lower mean cumulative corticosteroid dose.[21] Despite these positive results, the study had limitations, mainly due to its small number of patients, its retrospective and uncontrolled design, and the fact that some patients in the FAM group (3 cases) did not receive corticosteroids at all, which may have introduced confounding in data analysis.

In 2016, Williams et al. assessed 36 adult patients in the first 6 months after diagnosis of BOS who had received prednisone 1 mg/kg/day for 2 weeks in combination with FAM therapy.[22] The FAM regimen consisted of inhaled fluticasone (220 to 440 µg twice daily), montelukast (5 to 10 mg daily), and azithromycin (5 mg/kg up to a maximum of 250 mg every other day). After 15 days, systemic corticosteroid therapy was tapered by 0.25 mg/kg/day per week. Of the 36 patients, 6 (17%) had no response and 23 (63%) achieved some response (3 with > 10% improvement in FEV_1 from baseline, 7 with > 5% improvement in FEV_1 from baseline, 5 with stable FEV_1, and 8 with a 1–10% decline in FEV_1). Regarding corticosteroid withdrawal, 48% of patients achieved a 50% reduction in corticosteroids within 3 months, and 71% achieved a 50% reduction within 6 months. These findings suggest that FAM therapy was well tolerated, corticosteroid-sparing, and associated with a reduced decline in pulmonary function.[22]

The two studies described above demonstrated good tolerability of this therapeutic regimen and its importance in reducing chronic corticosteroid exposure. However, for optimal results and to inform recommendations for clinical use in the management of these patients, ideally each medication should be studied independently, in separate clinical trials; studies with a larger number of participants are also necessary.

Inhaled budesonide/formoterol

A study conducted by Bergeron et al. in 2015 evaluated the efficacy and tolerability of the fixed-dose combination of inhaled budesonide and formoterol as an alternative treatment for post-HSCT BOS. The study was double-blind, randomized, and placebo-controlled, and included 32 patients allocated into two groups (one received budesonide/formoterol and the other placebo, for 6 months).[23] The primary outcome was change in FEV_1 from baseline after one month of treatment. Patients who received budesonide/formoterol experienced an increase in FEV_1 of 260 mL on average, versus a 5-mL increase in the placebo group ($p = 0.012$).[23] Furthermore, the change in FEV_1 from baseline was greater in the treatment group, with a median difference of 1240 mL after 1 month of treatment ($p = 0.0001$), with the effect maintained in all 13 patients who completed 6 months of treatment. The administered dosage was 800 µg budesonide and 24 µg formoterol twice daily for 1 month, followed by a maintenance dose of 400 µg budesonide and 12 µg formoterol twice daily for 6 months.[23] This double-blind, randomized, placebo-controlled study showed promising results, with a significant improvement in FEV_1 in the group receiving the budesonide/formoterol combination. Considering the effectiveness, safety, and wide availability of this medication at an affordable cost, it is a promising option and, above all, a truly systemic corticosteroid-sparing treatment, which should be considered in the management of patients with BOS.

Budesonide/formoterol, montelukast, and N-acetylcysteine

Additional drug combinations have been studied with the primary goal of reducing the role of systemic corticosteroids in the treatment of BOS. In 2016, Kim et al. assessed a combination of budesonide/formoterol, montelukast, and N-acetylcysteine.[24] In this study, 61 patients diagnosed with BOS received this drug combination and were reassessed after 3 months. Pulmonary function tests and respiratory symptom scores were administered at baseline and after therapy. The results showed a response rate of 82%, an average increase in FEV_1 of 220 mL ($p < 0.001$), and a decrease in residual volume of 200 mL ($p = 0.005$).[24] The authors concluded that combination therapy with budesonide/formoterol, montelukast, and N-acetylcysteine improved pulmonary function and respiratory symptoms, with no significant adverse effects.[24]

Budesonide/formoterol and tiotropium

One treatment option being studied is the use of inhaled tiotropium bromide. Tiotropium is a long-acting anticholinergic administered via a proprietary device that produces a fine mist, causing bronchodilation. In a study published in 2023, Lim Ju et al. evaluated whether the addition of inhaled tiotropium bromide to the budesonide/formoterol regimen would improve pulmonary function in patients with post-HSCT BOS.[25] The study included 86 patients diagnosed with post-BMT BOS according to the modified NIH criteria (2014), who were already on budesonide/formoterol, subsequently had tiotropium added to their regimen and used it for at least 2 months. Pulmonary function tests were compared before and after addition of tiotropium. FEV_1 increased significantly: from 1.47 to 1.53 in absolute values ($p = 0.023$) and from 45% to 46.8% of predicted ($p = 0.031$). Furthermore, 41.7% of patients experienced an increase in $FEV_1 > 100$ mL and improvement in diffusion capacity of the lungs for carbon monoxide.[25] A score for assessment of respiratory symptoms was administered; however, no significant difference was found. The study concluded that adding tiotropium to the budesonide/formoterol combination significantly improved pulmonary function, but not respiratory symptoms, in post-HSCT BOS.[25]

Given that bronchiolitis obliterans is a disease characterized by irreversible airway obstruction, the effect of bronchodilators is expected to be less effective than in other airway diseases in which reversibility is somewhat preserved. However, the study above provides an important reflection on the effect of bronchodilators in BOS, since the addition of tiotropium improved lung function in patients who were already on a bronchodilator-containing regimen. Perhaps this effect can be explained by the findings of studies conducted in patients with chronic obstructive pulmonary disease (COPD), in which the combination of a long-acting beta-agonist and a long-acting antimuscarinic resulted in a more pronounced improvement in bronchodilation than either drug alone.[25,26]

Despite its limitations, such as its retrospective design, lack of a control group, and short-term follow-up, this study is notable for the positive effect observed with addition of a long-acting antimuscarinic; considering the safety of tiotropium and experience with its use in other diseases, it can be considered as a treatment option for these patients.

Second-line and alternative therapies

Extracorporeal photopheresis

Extracorporeal photopheresis (ECP) has demonstrated effectiveness in the treatment of GVHD in clinical trials. However, its utility in the setting of BOS remains uncertain. In 2011, Lucid et al. conducted a prospective study investigating the use of ECP in 9 patients with symptomatic BOS refractory to conventional treatment (azithromycin, inhaled corticosteroids, and montelukast).[27] Adding ECP to the patients' current treatment regimen resulted in faster improvement of BOS symptoms and pulmonary function tests, with 67% of patients responding to treatment and 2 of the 3 patients who did not qualify as responders still showing improvement in symptoms and stable or declining FEV_1. These findings suggest that ECP can be an effective alternative for patients with BOS refractory to conventional treatment.[27]

Although ECP has demonstrated efficacy and safety in autoimmune diseases, including GVHD, few centers are able to perform this procedure. Specific equipment is required for extracorporeal cell apheresis and UV exposure, as well as a specialized, specifically trained team, and the procedure is extremely costly.[28]

Cytokine modulators (TNF-α inhibitors and rituximab)

TNF-α inhibitors (etanercept and infliximab)

Insight into the role of proinflammatory cytokines in the pathogenesis of BOS led to the investigation of TNF-α inhibitors as potential treatment alternatives. In 2012, Yanik et al. conducted a study in 34 patients (aged 8 to 65 years) with chronic pulmonary GVHD; 25 had an obstructive pattern and 9 had a restrictive pattern. All received etanercept (a dimeric fusion protein which binds TNF-α) at a dose of 0.4 mg/kg subcutaneously, twice weekly, for 4 to 12 weeks. Of the 34 participants, 33 were already on corticosteroids, which were continued throughout. The overall response rate was 32%; 5-year survival was 61% for all patients and 90% for those who responded to therapy. Etanercept was well tolerated, with no treatment-emergent infectious complications. Despite some limitations, such as the lack of a control group for comparison, the toxicity profile of etanercept supports the conduct of larger, randomized trials to further investigate its role in the treatment of patients with pulmonary GVHD.[29]

Infliximab, a monoclonal antibody against TNF-α, has also been studied as a treatment option for BOS, considering the key role of TNF-α in inflammation. In 2005, Fullmer et al. reported the case of an 8-year-old child with BOS, diagnosed 5 months after HSCT, who received infliximab after failure of corticosteroid therapy. Infliximab was administered at 10 mg/kg twice a week for 4 doses, then weekly for a further 4 doses, then once every 2 weeks for 2 months. One month after the end of treatment, there was a response to therapy, with cessation of cough, resolution of obstructive pulmonary disease as measured by spirometry, and improvement in chest CT findings. The use of infliximab and other immunosuppressive therapies aims to reduce progression of inflammation and improve pulmonary function, but further research is still needed to confirm its effectiveness in the specific setting of post-transplant BOS.[30]

Rituximab

Although GVHD has traditionally been considered a process driven by donor-derived alloreactive T cells, there is growing evidence implicating B cells in the pathogenesis of chronic GVHD. Rituximab, an anti-CD20 monoclonal antibody, is used to suppress B-cell function and has been studied in the treatment of post-HSCT BOS.[31]

In 2017, Brownback et al. evaluated pulmonary function tests in patients with steroid-refractory post-HSCT BOS, seeking to determine the effect of rituximab on corticosteroid dosage in these patients and whether combining rituximab with other treatment modalities could improve clinical response. Thirteen patients, aged 19 to 65 years, were evaluated for 12 months after rituximab therapy. The rate of decline in pulmonary function was seen to improve, from -5.12 mL/month before rituximab infusion to -0.31 mL/month after 3 months and -2.27 mL/month 12 months later. Seven of the 13 patients experienced increases in FEV_1 after rituximab treatment. Furthermore, the average daily dose of prednisone decreased from 27 mg before treatment with rituximab to 11 mg 12 months after treatment. There were no complications associated with rituximab infusions. Five of the 13 patients died: 4 from complications of GVHD and 1 due to disease recurrence.[31] All patients were on inhaled corticosteroids, azithromycin, and montelukast. The patients who showed improvement in FEV_1 were receiving concomitant ECP, and most were also being treated with ruxolitinib. This may represent a synergistic effect of combination therapies leading to improvement of pulmonary function in patients with post-HSCT BOS. The role of rituximab in immunosuppression and modulation of GVHD makes it an interesting option for the management of post-HSCT pulmonary complications, as a safe therapy which can be used to supplement current BOS treatment regimens.[31]

Mesenchymal stem cells

Given the complexity of managing BOS, studies have been conducted seeking effective and safe alternative treatment approaches. One of these studies, conducted by Chen et al. in 2019, assessed the efficacy of mesenchymal stem cells (MSCs).[29] In this prospective, multicenter cohort study, 81 patients with BOS received MSC infusions in combination with prednisone and azithromycin or in isolation. Significant improvements in FEV_1 and reductions in corticosteroid doses were achieved. Furthermore, MSC therapy proved to be more effective than treatment with steroids and azithromycin alone, with a response rate of 71% in the group that received cell therapy compared to 44% in the group that did not receive it.[32]

MSCs have an immunomodulatory effect on both adaptive and innate immunity, and may be a promising avenue for treatment in the context of BOS.[32] This study reported interesting results, but it has limitations. The study design did not include blinding, randomization or a placebo group, and results were assessed at only 3 months of therapy; the duration of response after this period was not considered. Consequently, these findings should be interpreted with caution, and the effects of MSCs require more in-depth evaluation in larger, randomized studies with long-term outcome assessment.

Inhaled ciclosporin

A phase 2 trial evaluated inhaled ciclosporin in 20 patients diagnosed with BOS, aged 14 to 71 years. Response was evaluated by pulmonary function tests after 18 weeks of ciclosporin therapy. Cytology and inflammatory mediators in bronchoalveolar lavage fluid were evaluated at baseline and after 18 weeks. The study was completed with only 11 patients, as nine discontinued treatment due to side effects (cough and bronchospasm), worsening FEV_1, or recurrence of primary disease. Among those who completed the

trial, 4 showed improvement in FEV_1 (10% increase from baseline), 5 achieved disease stabilization (smaller increase in FEV_1 or decline in FEV_1 <10% from baseline), and 2 did not respond to therapy. Bronchoalveolar lavage showed a predominance of neutrophils at baseline and at the end of treatment, with an increase in matrix metalloproteinase-9 and a reduction in PD-L1 protein at 18 weeks.[33]

Inhaled ciclosporin led to improvement or stabilization of pulmonary function tests and/or a decrease in systemic immunosuppression in 9 of the 11 patients who completed the trial. However, the small sample size, absence of a control group, and significant number of treatment-related adverse effects must be noted.[33]

Imatinib and belimumab

Imatinib

Imatinib mesylate, an antineoplastic tyrosine kinase inhibitor, has recently been studied in GVHD. In 2020, Faraci et al. evaluated 26 cases of bronchiolitis obliterans in a series of 293 children who had undergone bone-marrow transplantation. This retrospective observational study compared patients who received imatinib and those who did not (n=13 in each group). Imatinib was given at doses of 100 to 300 mg/day (mean, 100 mg). It was well tolerated, with no adverse effects. In addition to imatinib, patients were on a range of other medications, including azithromycin, montelukast, methylprednisolone (50% of patients), ciclosporin (53.8%), tacrolimus (15.4%), and ciclosporin plus methylprednisolone (15.4%).[34]

The estimated 1-year survival rate was 71.9% (95% CI, 47.6±86.49) in the group that did not receive imatinib versus 83.3% (95% CI, 27.3±97.5) in the imatinib-treated group. At 4 years, overall survival had decreased in the non-imatinib group (42.6%) but remained stable in the imatinib group (83.3%). Mortality was also significantly lower in the group that received imatinib (7.7% vs. 84.6%; $p < 0.001$). Pulmonary function was also monitored. Improvement in FEV_1 over time was observed in the imatinib group, whereas this parameter worsened in the non-imatinib group.[34]

Despite the positive survival difference among patients who received imatinib, this was a retrospective, observational study of a very small group of patients, and further prospective studies are needed to confirm these findings.

Belimumab

B-cell activating factor (BAFF), a member of the tumor necrosis factor family, has been extensively studied since its discovery in 1999, particularly in the field of autoimmunity, where it plays a crucial role. Patients with chronic GVHD have been found to have increased serum levels of BAFF, strongly suggesting a role for B cells in the pathogenesis of GVHD. The combination of high serum BAFF levels and CD19+ CD21lo cell counts has been used successfully to assess the risk of BOS in HSCT recipients.[35,36]

Belimumab is a fully human recombinant IgG1-λ monoclonal antibody that inhibits the binding of BAFF to its receptors on B cells, thereby reducing the survival of autoreactive B cells. While its efficacy is well established in autoimmune diseases, such as systemic lupus erythematosus and active lupus nephritis, ongoing studies are currently evaluating its potential use in other conditions associated with B-cell dysregulation, including post-HSCT BOS.[35,36]

A single-center, phase 1 study conducted by Pusic et al. in 2021 evaluated whether targeting BAFF early after allogeneic HSCT would have a favorable effect on the incidence or severity of chronic GVHD. The included patients were all adults in complete remission who tested negative for minimal residual disease 30 days after transplantation. Patients received belimumab at a dose of 10 mg/kg every 2 weeks for 3 doses, followed by 4 more doses at monthly intervals. Treatment began 50 to 80 days after transplant. Patients who received at least 1 dose were evaluated for safety, and those who received at least 2 doses were evaluated for efficacy. Eight of the 9 patients successfully received all 7 planned doses of belimumab. After more than 20 months of follow-up, 5 were alive with no evidence of chronic GVHD. Two patients developed moderate to severe GVHD of the skin, eyes, mouth, and liver, and 2 patients experienced disease recurrence, but both had high-risk malignancies. No adverse events of grade 3 or higher were reported. There were also no significant infections or myelosuppression.[37] This was the first trial to describe the use of belimumab for prophylaxis of chronic GVHD. Results were encouraging, as it was well tolerated and there was no increased rate of serious infections. Nevertheless, further studies with larger sample sizes are needed for a more in-depth assessment of the impact of belimumab on the incidence of GVHD.[37]

Antifibrotic therapies (nintedanib and pirfenidone)

In 2020, Tang et al. reported the case of an 18-year-old patient who began experiencing cough and dyspnea approximately 1 year after HSCT. The CT scan showed bronchiectasis, thickening of septa, and interstitial involvement. Pulmonary function tests showed an FVC of 36.9%, an FEV_1 of 38.7%, and a residual volume of 125% of predicted. The patient had received montelukast, azithromycin, and inhaled budesonide/formoterol, as well as methylprednisolone, with no improvement. The authors suggested a trial of nintedanib, an intracellular tyrosine kinase inhibitor which affects vascular endothelial growth factor and fibroblasts and has been approved for the treatment of idiopathic pulmonary fibrosis, hypothesizing that it might thus be useful in post-HSCT BOS as well. Cough and dyspnea improved after 2 weeks of treatment. After 1 month of therapy, improvements in pulmonary function tests and CT scan findings were also observed.[38]

Following the same rationale, pirfenidone, a compound with anti-inflammatory and antifibrotic properties, acts by downregulating collagen synthesis stimulated by TGF-β, thus reducing fibroblast proliferation. In a 2022 non-randomized phase 1 trial, Matthaiou et al. evaluated the tolerability of pirfenidone and its impact on pulmonary function tests over 1 year of follow-up in patients diagnosed with post-HSCT BOS. Twenty-two patients were evaluated, of whom 13 (59%) tolerated therapy. There was a 7% mean annual increase in FEV_1, as well as patient-reported improvements in physical capacity and dyspnea.[39]

In this phase 1 trial, treatment with pirfenidone was safe. Stabilization of pulmonary function tests and improvements in patient-reported outcomes suggest pirfenidone has potential for the management of post-HSCT BOS and supports the conduct of a randomized controlled trial to evaluate its efficacy in this setting.[39]

Lung transplantation

In cases of severe lung disease with high morbidity and mortality and poor response to therapy, lung transplantation can be a viable treatment option. In 2005, Sano et al. reported the case of a 29-year-old woman who developed post-HSCT BOS refractory to all attempted treatment options (ciclosporin, prednisone, methotrexate, tacrolimus, and home oxygen therapy).[40] Given her clinical deterioration, with spontaneous pneumothorax and progression to frank respiratory failure, the decision was made to pursue living-donor lung transplantation. Thirty-eight months after the transplant, at the time of writing the case report, the patient was in good health, with no evidence of acute rejection, infection, or BOS.[40]

In 2001, Rabitsch et al. documented the case of a 37-year-old patient who developed BOS refractory to corticosteroids, extracorporeal phototherapy, and ciclosporin.[41] One year after HSCT, she underwent lung transplantation. Twenty-three months after the transplant, when the report was written, there was no evidence of rejection and pulmonary function tests were within normal range.[41]

Isolated case reports with satisfactory results, demonstrating improvements in quality of life and survival for patients with advanced post-HSCT BOS, suggest this treatment modality can be an option for severely ill patients. However, further studies are needed to assess the effectiveness of this procedure more comprehensively, considering that lung transplant is a complex, high-risk intervention with very specific indications, requiring careful patient selection.

Investigational therapies

An ongoing phase 1b/2 trial is evaluating alvelestat (MPH966), an oral neutrophil elastase inhibitor, for the treatment of patients with GVHD and post-HSCT BOS.[42]

In addition to drugs specifically targeting BOS, proper management of comorbidities and exacerbation triggers, control and treatment of infections, proper management of post-transplant immunosuppression, and pulmonary rehabilitation are all essential.[9]

Individualized nutritional monitoring, ensuring adequate intake of macro and micronutrients, is also essential in slowing the progression of pulmonary disease, especially in patients with weight loss.[5]

The results of the key studies covered in this review are shown in Table 2.

Conclusion

Pulmonary complications, such as BOS, are common after HSCT and represent an important cause of morbidity and mortality in adults and children alike. Early detection and appropriate treatment are key prognostic factors for these patients.

Individually varied responses are expected. The relentless search for drugs, alone or in combination, that can spare these patients prolonged use of high-dose systemic corticosteroids remains a noble goal, particularly for the pediatric population.

The treatment of post-HSCT BOS continues to pose a challenge for specialists worldwide. Studies that thoroughly elucidate bronchiolar inflammation and other factors involved in post-HSCT BOS are needed to achieve a better understanding of the pathophysiology of this condition and serve as a starting point for the development of effective, precise treatments.

Table 2
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
			First-line therapies		
High-dose corticosteroid therapy	High-dose corticosteroid therapy for bronchiolitis obliterans after bone marrow transplantation in children	Ratjen et al. (2005)	Retrospective pediatric study. Case series of methylprednisolone pulse therapy	9 patients aged 1 to 17 years with a diagnosis of post-HCST BOS	Increased oxygen saturation and normalization of pulmonary function at the end of treatment; absence of functional deterioration in children with BOS (improvement of FEV_1 after 2 months of therapy)
Azithromycin	Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study	Khalid et al. (2005)	Observational study investigating the potential effect of azithromycin on pulmonary function tests in patients with post-HSCT BOS	8 out of 153 patients with post-HSCT BOS, aged 18 to 63 years	Significant improvement in FVC and FEV_1 after treatment; response rate 87%. The mean increase in parameters was 21.57% in FVC ($p < 0.052$) and 20.58% in FEV_1 ($p < 0.067$)
	Effects of azithromycin in bronchiolitis obliterans syndrome after HCT—a randomized double-blinded placebo-controlled study	Lam et al. (2011)	Randomized, double-blind, placebo-controlled clinical trial of azithromycin therapy	Patients aged > 18 years with post-HSCT BOS (age range, 24-57 years)	No significant changes in respiratory symptom scores or in FEV_1 measurements between groups

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

Table 2 *(continued)*
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
			First-line therapies		
	Effect of Azithromycin on Airflow Decline–Free Survival After Allogeneic Hematopoietic Stem Cell Transplant: The ALLOZITHRO Randomized Clinical Trial	Bergeron et al. (2017)	Randomized, multicenter, double-blind, placebo-controlled clinical trial assessing whether early administration of azithromycin can improve airflow decline-free survival after allogeneic HSCT	Patients aged > 16 years with post-HSCT BOS. Assessment of pulmonary function, disease-free survival, and post-BMT BOS for a period of 2 years of disease recurrence.	There was no difference in FEV_1 or other pulmonary function tests or post-BMT BOS throughout the study period between groups. The authors conclude it is unlikely that azithromycin may reduce the risk of post-BMT BOS. Study interrupted due to increased disease recurrence. FDA, EMA, and ANVISA issued warnings recommending against off-label prescribing of azithromycin
	Azithromycin use and increased cancer risk among patients with bronchiolitis obliterans after hematopoietic cell transplantation	Cheng et al. (2020)	Retrospective study. Assess the impact of azithromycin exposure on the occurrence of recurrent or subsequent (new) neoplasm in patients with post-HSCT BOS treated with azithromycin alone or in combination with other agents	Patients with post-HSCT BOS, aged > 18 years, with at least 6 months elapsed since HSCT. 316 patients with BOS included, 277 on azithromycin	In the azithromycin group, there was an increased incidence of subsequent neoplasms, but not recurrence of the original malignancy; however, there was a reduction in mortality from other non-cancer causes
FAM therapy	Fluticasone, Azithromycin, and Montelukast (FAM) Therapy in reducing corticosteroid exposure in BOS after allogeneic HSCT. A case series of 8 patients	Norman et al. (2011)	Retrospective case series. Assess whether corticosteroid exposure can be reduced in post-HSCT BOS patients who received FAM therapy	Adult patients, aged > 20 years, with post-HSCT BOS	Rapid reduction in prednisone doses in patients treated with FAM therapy who were on corticosteroids. Stable pulmonary function throughout study period, with no between-group difference

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

Table 2 *(continued)*
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
			First-line therapies		
	FAM treatment for new onset bronchiolitis obliterans syndrome after hematopoietic cell transplantation	Williams et al. (2016)	Open-label, single-arm, multicenter study. Assess the effectiveness of FAM, combination therapy to treat BOS of recent onset in post-HSCT patients	Adult patients aged 23 to 72 years with recent-onset post-HSCT BOS (up to 6 months since diagnosis)	FAM therapy was well tolerated. Less decline in lung function; allowed for a reduction in systemic corticosteroid therapy
Budesonide/ formoterol	Budesonide/ formoterol for bronchiolitis obliterans after hematopoietic stem cell transplantation	Bergeron et al. (2015)	Randomized, double-blind, placebo-controlled, multicenter trial. Assess efficacy and tolerability of budesonide/ formoterol as an alternative treatment for post-HSCT BOS	Patients aged ≥ 16 years with post-HSCT BOS	Significant increase in average FEV_1 in the group that received budesonide/formoterol and increase in FEV_1 from baseline
Budesonide/ formoterol + montelukast + N-acetylcysteine	Therapeutic effect of budesonide/formoterol, montelukast and N-acetylcysteine for bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation	Kim et al. (2016)	Retrospective study. Assess therapeutic effect of budesonide/ formoterol, montelukast, and N-acetylcysteine as a treatment option for post-HSCT BOS	61 patients with post-HSCT BOS (mean age 46.5 years)	Response rate 82%. Improvement in FEV_1 and respiratory symptoms
Budesonide/ formoterol + tiotropium	Efficacy of inhaled tiotropium add-on to budesonide/formoterol in patients with bronchiolitis obliterans developing after hematopoietic stem cell transplantation	Lim JU et al. (2023)	Retrospective cohort study. Patients with post-HSCT BOS who were already on budesonide/ formoterol and had tiotropium added to their regimen	86 patients with post-HSCT BOS, mean age 45.9 years	Increased FEV_1. Improvement in carbon monoxide diffusion capacity and pulmonary function, but no improvement in respiratory symptom scores

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

Table 2 *(continued)*
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
Second-line and alternative therapies					
Extracorporeal photopheresis	Extracorporeal photopheresis in patients with refractory bronchiolitis obliterans developing after allo-SCT	Lucid et al. (2011)	Prospective study. Determine the clinical efficacy of extracorporeal photopheresis in the treatment of BOS through assessment of clinical improvement and pulmonary function tests	Patients with post-BMT BOS aged 21 to 54 years (mean of 38 years), with failure of conventional therapies	The addition of extracorporeal phototherapy resulted in faster improvement of symptoms and pulmonary function tests. Response rate 67%
Etanercept	Soluble Tumor Necrosis Factor Receptor: Enbrel (Etanercept) for Subacute Pulmonary Dysfunction Following Allogeneic Stem Cell Transplantation	Yanik et al. (2012)	Open-label, prospective study. Assess the response rate to etanercept added to prednisone in patients with pulmonary GVHD	34 patients aged 8 to 65 years with pulmonary GVHD, 25 of whom had an obstructive pattern and 9 had a restrictive pattern	Response rate 32%; 5-year survival: 61% overall and 90% for those who responded to therapy. No treatment-emergent infectious complications
Infliximab	Successful Treatment of Bronchiolitis Obliterans in a Bone Marrow Transplant Patient with Tumor Necrosis Factor - Blockade	Fullmer et al. (2005)	Case report. Report the case of a pediatric patient with post-HSCT BOS who received infliximab after failure of corticosteroid therapy	8-year-old patient with post-HSCT BOS, confirmed by biopsy 5 months after transplantation	Response to therapy with resolution of respiratory symptoms, improved spirometry, and CT changes
Rituximab	Effect of Rituximab on Pulmonary Function in Bronchiolitis Obliterans Syndrome due to Graft-Versus-Host Disease	Brownback et al. (2017)	Prospective, non-randomized study. Determine the effects of treatment with rituximab on pulmonary function in patients with post-HSCT BOS	13 patients, aged 19 to 65, evaluated over 12 months of treatment with rituximab	Improvement in the rate of decline in pulmonary function. Increased FEV_1 in 7 of 13 patients
Mesenchymal stem cells	The efficacy of mesenchymal stem cells in bronchiolitis obliterans syndrome after allogeneic HSCT: A multicenter prospective cohort study	Chen et al. (2019)	Multicenter, prospective cohort study. Assess the efficacy and safety of mesenchymal stem cells in patients with post-BMT BOS	81 patients with post-BMT BOS, aged 18 to 59 years, received infusions of mesenchymal stem cells alone or in combination with prednisone and azithromycin	Significant improvements in FEV_1 and dose reduction of corticosteroids; furthermore, mesenchymal stem cell therapy proved more effective than treatment with steroids and azithromycin alone

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

Table 2 *(continued)*
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
			Second-line and alternative therapies		
Inhaled ciclosporin	Effect of cyclosporine inhalation solution (CIS) on lung function and inflammatory biomarkers in patients with hematopoietic stem cell transplant (HSCT) associated bronchiolitis obliterans syndrome (BOS)	Athale et al. (2019)	Phase 2 trial. Assess response to treatment with inhaled ciclosporin in patients with post-HSCT BOS through pulmonary function tests at 18 weeks of therapy. Cytology and proinflammatory mediators in bronchoalveolar lavage fluid assessed at baseline and after 18 weeks	20 patients with post-HSCT BOS, aged 14 to 71 years	Improvement or stabilization of pulmonary function tests. Among those who completed the trial, 4 exhibited improvements in FEV_1, 5 achieved stable disease, and 2 did not respond. New-onset cough and bronchospasm in 9 patients
Imatinib mesylate	Imatinib mesylate as second-line treatment of bronchiolitis obliterans after allogenic hematopoietic stem cell transplantation in children	Faraci et al. (2020)	Observational and retrospective pediatric study. Assess overall survival in children with post-HSCT BOS treated with imatinib mesylate	26 cases of BOS in a series of 293 children who underwent BMT mean age 8.3 years (3.5–12.5 years)	Lower mortality rate and higher survival rate in the imatinib group
Belimumab	Use of belimumab for prophylaxis of chronic graft-versus-host disease	Pusic et al. (2021)	Single-center phase 1 trial. Assess the use of belimumab after allogeneic HSCT and its effect on the incidence or severity of chronic GVHD	9 adult patients who received belimumab 50–80 days after transplantation	No ≥ Grade 3 adverse events reported. No significant infections or myelosuppression; 5 patients alive and without chronic GVHD after 20 months of follow-up
Nintedanib	Nintedanib in Bronchiolitis Obliterans Syndrome After Allogeneic Hematopoietic Stem Cell Transplantation	Tang et al. (2020)	Case report. Describe the case of a patient with post-HSCT BOS who was treated with nintedanib, a drug approved for idiopathic pulmonary fibrosis	18-year-old patient with post-HSCT BOS who received nintedanib	Improvement in respiratory symptoms, pulmonary function tests, and chest CT scan findings

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

Table 2 *(continued)*
Summaries of the results of key publications on the management of post-HSCT BOS

Drug	Article	Authors/year	Objectives/methods	Study population	Results/ comments
Second-line and alternative therapies					
Pirfenidone	The Safety and Tolerability of Pirfenidone for Bronchiolitis Obliterans Syndrome after Hematopoietic Cell Transplant (STOP-BOS) trial	Matthaiou et al. (2022)	Phase 1, non-randomized, single-center trial. Assess the tolerability of pirfenidone and pulmonary function tests over 1 year in patients diagnosed with post-HSCT BOS	22 patients diagnosed with post-HSCT BOS, mean age 53.8 years	Drug was well tolerated. Stabilization of pulmonary function tests. Improvement in patient-reported outcomes (physical capacity and dyspnea)
Lung transplantation	Living-donor lobar lung transplantation for bronchiolitis obliterans after bone marrow transplantation	Sano et al. (2005)	Case report of a patient with post-HSCT BOS who underwent lung transplantation	29-year-old woman with BOS refractory to treatment with ciclosporin, prednisone, methotrexate, and tacrolimus	Patient doing well 38 months after transplant
	Successful lung transplantation for bronchiolitis obliterans after allogeneic marrow transplantation	Rabitsch et al. (2001)	Case report of a patient with post-HSCT BOS who underwent lung transplantation	37-year-old woman underwent lung transplantation 1 year after BMT due to BOS refractory to corticosteroids and extracorporeal photopheresis	Patient doing well 23 months after transplant

BOS = bronchiolitis obliterans syndrome, HSCT = hematopoietic stem cell transplant, FEV_1 = forced expiratory volume in the first second, GVHD = graft-versus-host disease, BMT = bone-marrow transplant; FAM = fluticasone, azithromycin, and montelukast.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Chronic cough and cough hypersensitivity syndrome

Tosse crônica e síndrome de hipersensibilidade à tosse

Rosana Câmara Agondi[1]

ABSTRACT

Chronic cough is a prevalent condition worldwide, affecting individuals across all age groups. It is a complex and difficult-to-treat disorder, as multiple pulmonary and extrapulmonary conditions can present with chronic cough, which in turn may occur without an identifiable cause or be resistant to therapies targeting the various associated conditions. Most patients with chronic cough exhibit cough reflex hypersensitivity – that is, they cough in response to relatively innocuous stimuli –, causing significant impairment in quality of life and psychological burden. In recent years, there has been a paradigm shift in the diagnosis of refractory chronic cough, recognizing it as a distinct condition resulting from cough reflex hypersensitivity rather than merely a symptom of underlying conditions. In this review, we provide an update on chronic cough, highlighting cough reflex hypersensitivity.

Keywords: Chronic cough, hypersensitivity, neurotransmitter receptors, reflex.

RESUMO

A tosse crônica é uma condição prevalente no mundo, em todas as faixas etárias. Trata-se de um distúrbio complexo e de difícil tratamento, pois diversas condições pulmonares e extrapulmonares podem se manifestar com tosse crônica, que, por sua vez, pode ocorrer sem uma causa identificável ou ser resistente a terapias destinadas a tratar as diversas condições associadas à tosse crônica. A maioria dos pacientes com tosse crônica apresenta hipersensibilidade ao reflexo da tosse, ou seja, apresenta tosse em resposta a estímulos relativamente inócuos, o que causa considerável comprometimento de qualidade de vida e impacto psicológico. Nos últimos anos, houve uma mudança de paradigma no diagnóstico de tosse crônica refratária, reconhecendo-a como uma condição distinta, resultado da hipersensibilidade ao reflexo da tosse ao invés de ser apenas um sintoma decorrente de condições subjacentes. Nesta revisão, temos uma atualização sobre tosse crônica, realçando a hipersensibilidade ao reflexo à tosse.

Descritores: Tosse crônica, hipersensibilidade, receptores de neurotransmissores, reflexo.

Introduction

The cough reflex is a vital physiological mechanism for protecting the airways from chemical and mechanical irritants and preventing aspiration. Coughing preserves gas exchange function in the lungs by helping eliminate aspirated particulate matter and irritants that are inhaled or formed at mucosal inflammation sites.[1,2] The cough reflex is regulated by coordinated interaction between peripheral sensory nerves, which are distributed throughout the respiratory tract, and the cough center, which is located in the nucleus of the solitary tract in the brainstem.[1]

Coughing can also be a warning sign of pathological conditions, such as vomiting, rib fractures, urinary incontinence, syncope, muscle pain, fatigue, and depression. Quality of life is significantly impaired in patients with refractory or unexplained chronic cough,

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including negative effects to physical and psychological health. Recent studies have focused on discovering the mechanisms that regulate the peripheral and central processes involved in the cough reflex.[3-5]

This reflex mechanism is divided into 3 phases: (1) an inspiratory phase; (2) forced expiratory effort against a closed glottis; (3) and opening the glottis with rapid expiration, which generates a characteristic cough sound.[3]

The cough reflex involves afferent vagal nerve pathways, which are abundant throughout the upper and lower respiratory tract, including the larynx, trachea, carina, intrapulmonary bronchi, and lung parenchyma.[6] Afferent branches of the vagus nerve are also present in the esophagus, tympanic membrane, diaphragm, and pericardium.[7,8]

Inflammatory, mechanical, or chemical stimuli activate peripheral receptors in the sensory nerves of the airways: Aδ fibers (mechanoreceptors) and C fibers (chemoreceptors), which originate from the jugular or nodular ganglia. These stimuli are then transmitted through the vagus nerve to the paratrigeminal nucleus and the nucleus of the solitary tract in the medulla oblongata.[9] Central cough receptors send signals via efferent pathways in the vagus, phrenic, and spinal motor nerves to activate the diaphragm and expiratory muscles involved in coughing.[8]

Epidemiology and classification of cough

Coughing is one of the most common symptoms in individuals who seek medical attention. Coughs are classified according to duration. *Acute cough* persists < 3 weeks, *subacute cough* persists 3-8 weeks, and *chronic cough* persists > 8 weeks.[10]

Although acute cough is usually the result of a viral infection of the upper respiratory tract, it can also have other etiologies, such as pneumonia or foreign body aspiration. Symptomatic upper respiratory tract infection occurs 2 to 5 times a year in adults and 7 to 10 times a year in school-aged children. However, only 40% to 50% of patients present with a cough. In the absence of an underlying comorbidity, acute cough is usually benign and self-limiting. Acute cough can also manifest exacerbation of a chronic disease, such as asthma or chronic obstructive pulmonary disease.[10]

Cough lasting between 3 and 8 weeks is called subacute cough. The most likely diagnoses are post-infectious cough or an exacerbation of asthma or chronic obstructive pulmonary disease. For subacute cough induced by viral infection, the proposed mechanism includes increased cough reflex sensitivity due to the infection.[11]

Chronic cough, defined as lasting > 8 weeks in adults, has a global prevalence of 4% to 10% and is frequently associated with pain, dizziness, urinary incontinence, and even loss of consciousness. As a result, chronic cough is associated with considerable psychological stress, social stigma, lower quality of life, and impaired activities of daily living and work productivity. Furthermore, due in part to the inefficacy of current antitussive treatment, people with coughs frequently undergo repeated medical consultations, involving expensive and extensive diagnostic tests, as well as unsuccessful therapeutic trials.[12,13]

Chronic cough

Chronic cough affects approximately 40% of the world's population at some point in their lives.[14] At the end of the 20th century, an "anatomical diagnostic protocol" was proposed for investigating isolated persistent cough in the absence of an identified underlying pathology. Chronic cough has been considered merely a symptom of an underlying condition, such as asthma, gastroesophageal reflux disease (GERD), or rhinosinusitis, and treatment could be used empirically even without typical features of these diseases.[15]

Main causes of chronic cough are[16]:

- Upper airway cough syndrome
- GERD
- Medications: ACE inhibitors
- Asthma
- Cough variant asthma
- Non-asthmatic eosinophilic bronchitis
- Chronic bronchitis
- Bronchiectasis
- Tuberculosis
- Occupational exposure
- Interstitial lung diseases
- Bronchoaspiration/foreign body
- Smoking
- Cardiac causes
- Tumors
- Psychogenic disorders

Upper airway cough syndrome[17]

Chronic rhinitis or rhinosinusitis has been shown to be an independent risk factor for chronic cough. However, the exact mechanisms of chronic cough in patients with rhinosinusitis are not fully understood. Initially, the pathogenesis of upper airway cough syndrome (UACS) was considered a consequence of post-nasal drip. However, studies have shown that only a small proportion of patients with post-nasal drip complained of chronic cough, and conversely, some patients with UACS did not present with post-nasal drip. Chronic cough related to UACS includes allergic rhinitis, non-allergic rhinitis, and chronic rhinosinusitis.[18]

In the general population, UACS is reported as the cause of chronic cough in 9% to 82% of cases. This wide variation is mainly due to the slow adaptation of the term to clinical practice and the difference in treatment patterns between different countries. There is relative agreement that, in non-smokers, UACS is considered the first or second most common cause of chronic cough worldwide. UACS is also frequently associated with other conditions that can cause chronic cough.[17]

It is postulated that the pathogenesis of UACS is secondary to factors such as post-nasal drip, chronic upper airway inflammation, and sensory nerve hypersensitivity. Upper airway secretions would signal a chemical, thermal, or mechanical response that could provoke the cough observed in UACS. Nerve signaling is predominantly mediated by unmyelinated C fibers. These C fibers are sensitive to a large number of chemical and inhaled mediators, including capsaicin. Capsaicin receptors are found in transient receptor potential vanilloid 1 (TRPV1), which are highly expressed in sensory afferent nerve fibers in the airways.[17]

Gastroesophageal reflux disease[19,20]

GERD is a clinical condition caused by the chronic retrograde reflux of acidic stomach contents into the esophagus, resulting in uncomfortable symptoms, complications, or both. GERD is diagnosed based on clinical symptoms (heartburn, regurgitation, and non-cardiac chest pain) and empirical response to proton pump inhibitors.

Because studies have shown the limitations of non-objective diagnosis, diagnostic evaluation, such as upper gastrointestinal endoscopy, is recommended based on the clinical scenario, especially in patients with warning signs such as dysphagia.[21]

Chronic cough can be an extraesophageal manifestation of GERD.[19] The pathophysiology of GERD is multifactorial, and proposed mechanisms include hypotonia of the lower esophageal sphincter, hiatal hernia, and elevated intra-abdominal pressure. Three possible pathophysiological mechanisms contribute to the development of GERD-related chronic cough. The first is called "reflux theory," which includes acid reflux, microaspiration, and bronchial reflux. The second mechanism, "reflex theory," includes the esophagogastroduodenoscopy reflex, which is associated with increased sensitivity to the cough reflex and the development of neurogenic inflammation. The third proposed mechanism is esophageal dysmotility. The "reflex theory" proposes that stimulation of subesophageal mucosal receptors by reflux substances activates the cough center through the esophagus and causes the cough reflex.[22]

Medications: angiotensin-converting enzyme inhibitors

Common side effects of ACE inhibitors include dry cough, hypotension, hyperkalemia, headache, dizziness, and renal failure. Their mechanism of action is based on the ACE blockade, which is responsible for converting angiotensin-I to angiotensin-II, as well as for the degradation of several hemodynamically active peptides, including bradykinin. Persistent dry cough is the most common adverse effect of ACE inhibitors, an effect probably related to increased bradykinin production. The prevalence of dry cough in patients using ACE inhibitors ranges from 10% to 35%. It can develop in the first week, the first month, or after several years after beginning the medication; it is dose-independent and is more frequent in women.[23-25]

Cough variant asthma and non-asthmatic eosinophilic bronchitis

Both are considered bronchial inflammatory conditions that frequently manifest as chronic cough, with different diagnostic criteria and different responses to asthma therapy commonly used for diagnosis.[26]

Cough variant asthma

Sometimes coughing can be the only symptom of asthma. Transient ischemic attack refers to asthma when coughing is the only or the predominant

symptom, without complaints such as wheezing or chest tightness. This diagnosis was first described in the late 1970s, when patients with bronchial hyperresponsiveness to methacholine experienced cough improvement after treatment with a short-acting β2-agonist, which was associated with 12% reversibility, indicating a direct relationship between airway caliber and cough. However, these criteria may no longer be valid, given that a study found that up to one-third of patients with cough variant asthma (CVA) have normal spirometry and no bronchodilator response. In such situations, the diagnosis can be established by demonstrating bronchial hyperresponsiveness to methacholine or mannitol.[26]

Non-asthmatic eosinophilic bronchitis

First described in 1989, non-asthmatic eosinophilic bronchitis is characterized by chronic cough and airway eosinophilia without objective evidence of asthma, i.e., without reversibility and/or bronchial hyperresponsiveness. Bronchial eosinophilia should be investigated through induced sputum collection, bronchoalveolar lavage, and/or bronchial biopsy. The eosinophil count in patients with non-asthmatic eosinophilic bronchitis is > 2.5%. Another non-invasive test that could be performed would be the measurement of the fraction of exhaled nitric oxide (FeNO), but they are not routinely recommended. Non-asthmatic eosinophilic bronchitis does not respond to bronchodilators, and symptoms are typically responsive to inhaled corticosteroids.[26]

In most immunocompetent, non-smoking adults with normal chest X-ray results who do not have tuberculosis and are not using ACE inhibitors, the underlying cause of chronic cough is due to one or more of the following: (1) lower airway cough syndrome (asthma, cough-variant asthma, or non-asthmatic eosinophilic bronchitis); (2) upper airway cough syndrome; or (3) GERD.[27]

Although chronic cough can affect up to 10% of the general population, approximately 5% of these patients present with unexplained or refractory chronic cough despite extensive investigation and treatment of a diagnosed underlying disease.[28]

Individuals with chronic cough often report a persistent urge to cough and increased sensitivity to stimuli, such as ambient temperature changes and exposure to aerosols and perfumes. In some situations, the simple act of talking or singing can trigger coughing fits.[13]

Chronic cough is now considered indicative of nervous system dysregulation. Both central and peripheral nerve pathways regulate coughing and, although the mechanisms that drive the development of cough hypersensitivity are not fully understood, sensitization of these nerve pathways contributes to cough reflex hypersensitivity.[12,13]

Transient receptor potential and purinergic receptors

The cough reflex can be triggered by various inflammatory or mechanical changes in the airways or other locations, such as the lower third of the esophagus. The sensory nerve receptors that respond to these stimuli are defined by their conductive properties (rapidly adapting receptors, slowly adapting receptors, or C-fiber receptors). Rapidly adapting receptors are stimulated by cigarette smoke, acidic and alkaline solutions, hypotonic and hypertonic saline solutions, mechanical stimulation, pulmonary congestion, atelectasis, bronchoconstriction, and reduced pulmonary compliance — all of which can cause coughing. C-fiber receptors, a type of nociceptor, are highly sensitive to chemicals such as bradykinin, capsaicin (a vanilloid extract from peppers), and hydrogen ions (acidic pH).[29]

Chemoreceptor neurons (or nociceptors) send signals from the periphery, through afferent fibers, to the cough center in the central nervous system, mediating transmission between the central and peripheral nervous systems. These neurons express a wide variety of receptors and ion channels that are distributed along the peripheral fibers. The most important family of ion channels that detects and transmits noxious stimuli is the transient receptor potential (TRP) family. This family consists of proteins that are conserved, non-selective, and permeable calcium channels. In general, TRP channels act as molecular sensors of multiple stimuli, ranging from changes in pH, chemical agents, temperature, and osmolarity.[30]

The TRP superfamily consists of 28 members, which are subdivided into 6 subfamilies according to their sequence homology: TRPC (canonical, 7 members), TRPV (vanilloid, 6 members), TRPM (melastatin, 8 members), TRPA (ankyrin, 1 member), TRPP (polycystin, 3 members), and TRPML (mucolipin, 3 members). TRP proteins share a common structure consisting of 6 transmembrane domains. TRP channels consist of 4 pore-forming

TRP protein subunits that can assemble as homo- or heterotetramers. TRP channels modulate cellular function by opening voltage-gated ion channels, which leads to intracellular events such as neuronal depolarization and smooth muscle contraction.[29]

TRPV1, the transient receptor pontential vanilloid 1, is present throughout the respiratory tract, from the nose to the bronchi and vascular wall. TRPV1 is activated by exogenous chemical irritants (e.g., ethanol), elevated temperatures (> 43 °C), low extracellular pH, and some endogenous mediators. The main exogenous ligand is capsaicin, the active ingredient in chili peppers. Pro-inflammatory agents or physical stimuli can reduce the activation threshold for TRPV1 agonists. Under normal conditions, only temperatures > 43 °C activate TRPV1, but this threshold can decrease to 35–37 °C after acidification of the medium. This phenomenon is very important in inflammation because it drastically reduces the pH (to 6.4) and rapidly activates TRPV1. TRPV1 sensitization facilitates channel activation by low-intensity stimuli, and the process occurs after inflammation or tissue damage, which is triggered by various pro-inflammatory substances such as substance P, bradykinin, and prostaglandins. TRPV1 mediates signaling initiated by GPCR receptors, including bradykinin and prostaglandin E2.[29,30]

TRP subfamily ankyrin member 1 (TRPA1), an ion channel that functions as a sensor of cold temperatures, can be activated by temperatures below 17 °C. Isothiocyanates, components found in natural products such as wasabi, mustard, and horseradish, can also activate TRPA1 channels.[30]

TRP subfamily melastatin member 8 (TRPM8) is expressed throughout lung tissue and bronchial epithelial cells in humans. TRPM8, primarily recognized as a thermoregulator, is activated by low temperatures (between 15 and 28 °C), but it can also be activated by exogenous chemicals that produce a cooling sensation, such as menthol and eucalyptol.[29] Table 1 provides a summary of the main TRPs.

Purinergic receptors are another family of receptors involved in various cellular activities, such as coughing. They are activated by purine nucleotides, such as adenosine 5'-triphosphate (ATP) and adenosine (or adenine), as molecules that signal cellular stimulation. One such receptor is P2, a subtype of purine receptor. It includes ligand-gated ion channels, known as P2X, and G protein-coupled receptors, known as P2Y.[31,32]

P2X receptors are homotrimers or heterotrimers, and their activation induces the influx of extracellular cationic ions, such as sodium and calcium, into the cell, thereby depolarizing the cell membrane. P2X receptors are expressed throughout the body and are associated with a variety of physiological and pathological processes.[31]

There are 7 types of P2X receptor (P2X1-7), and the expression of P2X3 receptors in afferent neurons of the vagus nerve has become extremely important for understanding the mechanisms involved in chronic cough. Aberrant activation of these receptors leads to hypersensitivity of these nerve endings, which is one of the characteristics of "cough hypersensitivity syndrome" (which will be described below).[31]

ATP is the primary ligand of the P2X3 receptor. ATP, which is released from cells in response to damage by exogenous and endogenous factors, subsequently participates in airway extracellular fluid, acting as an alarmin, i.e., producing further inflammation. The underlying cause of ATP release is still a matter of debate; it is likely due to inflammatory stimuli, air pollution, tobacco smoke, or gastroesophageal reflux.[32]

Cough hypersensitivity syndrome

At the end of the 20th century, an "anatomical diagnostic protocol" was proposed to investigate the causes of isolated persistent cough in the absence of an easily identifiable pulmonary pathology, in which symptoms were categorized to guide diagnostic investigation and direct targeted therapy. The etiology of chronic cough has changed significantly in recent years; previously it was considered merely a symptom of underlying conditions such as asthma, gastroesophageal reflux, or rhinosinusitis, often treated empirically in the absence of typical characteristics of these diseases. Currently, refractory chronic cough (persistent cough despite optimal treatment of conditions associated with chronic cough) or cough with an unidentified underlying cause is considered a unique entity and is essentially a disease in itself (Figure 1).[9,15,33]

Refractory chronic cough could be the diagnosis in about 40% of patients with chronic cough who are referred to specialists. Diseases previously supposed to be the main causes of chronic cough, such as asthma, are now considered treatable factors, so their causative contribution is overestimated in many patients.[15]

Table 1
Key transient receptor potentials TRPs involved in chronic cough

Receptor		Subfamily	Temperature activation	Stimuli
Transient potential receptor (TRP) family	TRPV1	Vanilloid	> 43 °C	Capsaicin and pH reduction
	TRPV4	Vanilloid	> 25 °C	Pro-inflammatory substances such as PGE2, histamine, and serotonin
	TRPM8	Melastatin	< 25 °C	Menthol, eucalyptol, and cold temperature
	TRPA1	Ankyrin	< 17 °C	Garlic, menthol, acrolein, isothiocyanates (mustard, wasabi, and horseradish)

The 2021 European Respiratory Society guidelines on chronic cough adopted a different paradigm. Most patients with chronic cough present with cough reflex hypersensitivity, which is characterized by laryngeal paresthesia and an increased response to tussigenic stimuli or innocuous stimuli that would not trigger a cough in a healthy individual. Hence, chronic cough was considered "the disease." This hypothesis arose from the observation that most patients reported cough triggered by low levels of thermal, chemical, or mechanical exposure, including cold air, perfumes, odors, and aerosols. These external stimuli suggest hypersensitivity to other innocuous stimuli. Cough reflex hypersensitivity was considered the underlying pathophysiological mechanism of chronic cough, which has been called cough hypersensitivity syndrome.[33]

The proposed mechanisms for cough reflex hypersensitivity include airway hyperinnervation, increased central cough activation, and reduced central cough suppression. Investigations into cough reflex hypersensitivity should exclude treatable traits, i.e., secondary factors that worsen chronic cough. If possible, a cough provocation test should be performed, for example, with capsaicin or ATP. Non-pharmacological interventions for cough reflex hypersensitivity include avoiding triggers and managing treatable factors. Speech therapy and physical therapy have also proven effective. Drug treatment targets abnormal pathways of the cough reflex, both peripheral and central. The neuromodulators amitriptyline, gabapentin, and pregabalin have been tested with moderate success, although side effects are common.[15]

New antitussives that target peripheral receptors, such as P2X3, effectively reduce cough frequency and appear to be safe. Gefapixant was the first P2X3 receptor antagonist to successfully complete phase 3 trials and, in late 2023, was approved for use in the European Union, Switzerland, and Japan. Drug efficacy is consistent across all ages, sexes, and cough frequency and severity. Although antagonism of heterotrimeric P2X2/3 receptors also results in dysgeusia, the side effects of gefapixant are mostly mild, reversible upon discontinuation, and generally tolerable, resulting in 22.1% treatment discontinuation vs 5.7% with placebo at 52 weeks in clinical trials. Other antagonists, currently in phase 3 trials, are more selective for the P2X3 receptor and are associated with less dysgeusia.[15] Eliapixant, filapixant, and camlipixant are currently being tested as more selective P2X3 receptor antagonists.[28]

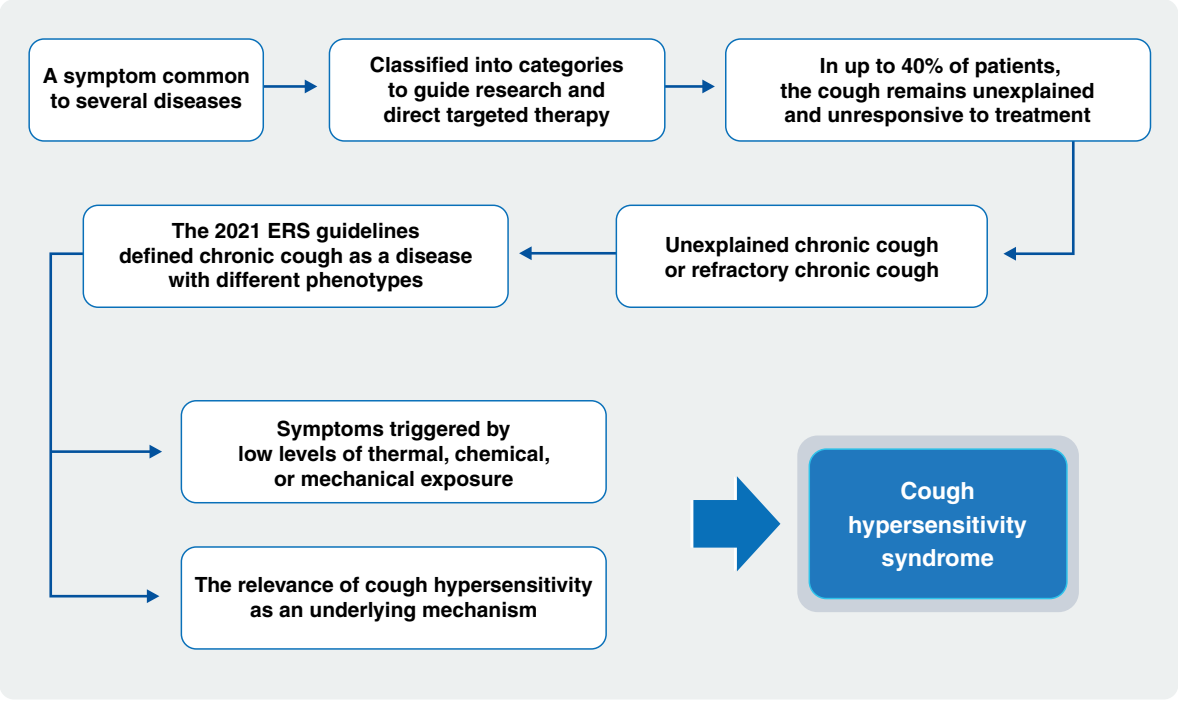

Figure 1
Paradigm shift in chronic cough[9,33]
ERS: European Respiratory Society.

Neuromodulators

Although most patients with refractory chronic cough benefit from neuromodulators, tachyphylaxis and dependence can occur, and patients should be monitored for these complications.[34]

Low-dose morphine sulfate

Studies using 5 mg and 10 mg of slow-release morphine sulfate have found that approximately 60% of patients with refractory chronic cough achieved good clinical response. However, side effects were frequent, with 40% experiencing constipation. Morphine is primarily an opioid receptor agonist and acts on central inhibitory cough pathways. The main concern regarding the use of low-dose morphine has been the potential for dependence and abuse. Some countries do not recommend it for chronic cough.[34]

Amitriptyline

Amitriptyline is a tricyclic antidepressant and serotonin reuptake inhibitor that can be an effective and well-tolerated as short- and long-term treatment for refractory chronic cough in adults. Amitriptyline reduces the frequency and severity of cough and improves quality of life in patients with refractory chronic cough. Dose reduction and restarting are often necessary. Larger studies and randomized clinical trials are needed to better understand the outcomes of amitriptyline for idiopathic cough.[35,36]

Gabapentin

A lipophilic structural analog of the neurotransmitter gamma-aminobutyric acid, gabapentin is a calcium channel modulator that acts on both central and peripheral cough reflex nerve pathways. It can also

modulate TRP channels, NMDA receptors, protein kinase C, and inflammatory cytokines, in addition to reducing TNF-α and IL-6 levels in the spinal cord of rats. It also has a dose-dependent effect. Gabapentin can reduce the peripheral sensitivity of the cough reflex by modulating peripheral TRP channels and inflammatory factors at cough-related sites.[28,37]

Gabapentin efficacy for refractory chronic cough has been investigated in randomized controlled trials. Quality of life improved in patients who received gabapentin, although its action on central receptors is associated with side effects, including sedation and unsteadiness. Serious adverse events described in the literature include rhabdomyolysis and acute renal failure in patients with diabetes. It also presents the potential for dependence.[28,35]

Pregabalin

Pregabalin and gabapentin have similar structures. Pregabalin acts on calcium channels in the central nervous system, reducing the release of neurotransmitters such as glutamate, norepinephrine, and substance P. Although studies have found improved laryngeal hypersensitivity scores, the side effects are frequent and include blurred vision, cognitive changes, dizziness, and weight gain.[28,35]

Baclofen

A gamma-aminobutyric acid receptor agonist, baclofen inhibits the release of substance P and interacts with serotonin, dopamine, and other neurotransmitters. Baclofen inhibits capsaicin-induced cough, and research suggests it is quite beneficial for refractory GERD and GERD-associated chronic cough. The vasovagal reflex relaxes the lower esophageal sphincter and predisposes individuals to acid reflux. In some clinical trials, baclofen had a significant effect on transient lower esophageal sphincter relaxation. Central nervous system side effects can include dizziness, drowsiness, asthenia, and nausea. These effects are dose-dependent and are related to its binding to presynaptic gamma-aminobutyric acid receptors in the brainstem and other parts of the central nervous system while simultaneously reducing the release of excitatory neurotransmitters.[38,39]

Conclusions

Chronic cough is rapidly becoming recognized as a unique entity that may or may not be associated with other comorbidities such as asthma, rhinosinusitis, and/or GERD. Greater understanding of cough receptors and the cough reflex has led to a new paradigm for the diagnosis, investigation, and treatment of chronic cough. Safe and effective therapies are being developed, primarily targeting peripheral cough receptors, where hypersensitivity to the cough reflex likely originates.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Biologics in allergic diseases – challenges and new directions

Imunobiológicos em doenças alérgicas – desafios e novos rumos

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ABSTRACT

The introduction of the first monoclonal antibody for asthma treatment two decades ago marked the beginning of a new era in the management of allergic diseases. Since then, new therapies using monoclonal antibodies targeting cytokines involved in type II hypersensitivity reactions or their receptors have been successfully developed, allowing control of several immunoallergic disorders, including asthma, atopic dermatitis, eosinophilic esophagitis, eosinophilic granulomatosis with polyangiitis, chronic rhinosinusitis with nasal polyps, hypereosinophilic syndrome, and chronic spontaneous urticaria. While scientific advances provide important answers, they also raise new questions. The objective of this article was to discuss and explore these issues, including the combined use of biologics, the concept of clinical remission, their potential influence on the atopic march, and the therapeutic possibilities emerging from clinical trials of new biologics for immunoallergic diseases.

Keywords: Monoclonal antibodies, immunotherapy, sublingual immunotherapy, remission induction, spontaneous remission

RESUMO

O desenvolvimento e a disponibilização do primeiro anticorpo monoclonal para o tratamento da asma, ocorrido há duas décadas, deu início a uma nova era no tratamento das doenças alérgicas. Desde então, novas terapias foram experimentadas com sucesso utilizando-se anticorpos monoclonais direcionados contra as principais citocinas envolvidas nas reações alérgicas tipo 2 ou os seus receptores, possibilitando o controle de diversas desordens imunoalérgicas como asma, dermatite atópica, esofagite eosinofílica, granulomatose eosinofílica com poliangeíte, rinossinusite crônica com pólipos nasais, síndromes hipereosinofílicas e urticária crônica espontânea. Os avanços científicos, ao mesmo tempo que trazem respostas, levantam novas questões. O presente artigo procura discutir e aprofundar estas questões como, por exemplo, o uso combinado de imunobiológicos, o conceito de remissão clínica, a potencial influência sobre a marcha atópica e as possibilidades terapêuticas que se descortinam com os ensaios clínicos de novos biológicos para as doenças imunoalérgicas.

Descritores: Anticorpos monoclonais, imunoterapia, imunoterapia sublingual, indução de remissão, remissão espontânea.

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Introduction

Two decades ago, the development and introduction of omalizumab, the first anti-IgE monoclonal antibody approved for asthma treatment, marked the beginning of a new era in the management of allergic diseases.[1] The first clinical trials of omalizumab, which targets the Fc fragment of immunoglobulin E (anti-IgE), demonstrated remarkable efficacy in controlling asthma and allergic rhinitis, especially in patients with severe asthma receiving high-dose inhaled corticosteroids, in combination with a second or third controller, or even in oral corticosteroid-dependent patients.[2]

The enthusiasm surrounding this novel therapeutic approach was initially so great that many authors speculated that the challenges of managing asthma and other IgE-mediated conditions had come to an end. However, it later became evident that anti-IgE therapy represented only the beginning of a new era: the era of precision medicine in allergic diseases.[3,4]

Since then, new therapies have been successfully developed using monoclonal antibodies targeting key cytokines involved in type 2 allergic reactions or their receptors. These advances have improved the management of several immunoallergic disorders, such as asthma, atopic dermatitis (AD), eosinophilic esophagitis (EoE), eosinophilic granulomatosis with polyangiitis (EGPA), chronic rhinosinusitis with nasal polyps (CRSwNP), hypereosinophilic syndromes (HES), and chronic spontaneous urticaria (CSU).[3,4]

Recently, the Brazilian Association of Allergy and Immunology (ASBAI) published a Practical Guide on the use of biologics, covering their mechanisms of action, indications, and contraindications for the medications currently approved for allergic diseases in Brazil: omalizumab, mepolizumab, benralizumab, dupilumab, and tezepelumab.[4] However, in clinical practice, scientific progress both resolves long-standing questions and raises new ones.

The objective of this study was to discuss and explore emerging issues in the use of biologics for immunoallergic diseases, including the potential for combination therapy, the concept of clinical remission, the possible influence of biologics on the atopic march, and the therapeutic possibilities arising from clinical trials of novel agents.

Biologics in combination with immunotherapy

Allergen immunotherapy (AIT) is a treatment for allergic diseases aimed at inducing immune tolerance. Despite its proven efficacy, AIT is associated with potential risks of adverse events, particularly anaphylaxis.

The combination of AIT and biologics is considered a promising approach to enhance treatment safety. Emerging evidence also suggests that this combination may improve the efficacy of AIT in the treatment of allergic rhinitis, asthma, and insect venom hypersensitivity.[5]

Rationale for the use of biologics as adjuvants in AIT

The use of biologics is based on their ability to immunomodulate the type 2 inflammatory response, thereby reducing this response and allowing patients to tolerate higher allergen doses with greater safety during the desensitization process.[5]

Anti-IgE

Omalizumab, an anti-IgE monoclonal antibody, prevents free IgE from binding to FcεRI receptors in mast cells and basophils, reducing the activation of these cells and the subsequent release of inflammatory mediators such as histamine and leukotrienes, responsible for immediate allergic reactions such as anaphylaxis. In addition, by lowering circulating

IgE levels, omalizumab decreases FcεRI receptor expression, thereby reducing cellular activation upon allergen exposure.[6] Omalizumab has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe asthma, CSU, CRSwNP, and food allergy to multiple allergens.[7] In Brazil, it is approved for all of these indications except food allergy.[4]

Anti-IL-4/IL-13 receptor

Dupilumab is a monoclonal antibody that binds to the alpha chain of the interleukin (IL)-4 receptor, also present in the IL-13 receptor, thereby blocking both receptors related to the production of key cytokines in the type 2 inflammatory pathway. Thus, dupilumab clinically reduces type 2 inflammation and can lessen the severity of allergic reactions.[8] In addition, it may positively influence immune modulation in the long-term, promoting greater allergen tolerance without requiring frequent maintenance doses.[9,10] The FDA has approved dupilumab for AD, severe asthma, CRSwNP, EoE, prurigo nodularis, and eosinophilic chronic obstructive pulmonary disease.[11] In Brazil, it is approved for all of these indications as well.[4]

Anti-IL5 / Anti-IL-5R

Mepolizumab is a humanized monoclonal IgG1/k antibody that binds human IL-5 with high affinity, inhibiting this cytokine from interacting with the alpha subunit of the IL-5 receptor (IL-5R).[6]

Benralizumab is a humanized, afucosylated, monoclonal IgG1/k antibody that binds to the IL-5R alpha subunit, preventing receptor conformation and IL-5 binding. In addition to blocking IL-5 from binding with the receptor, benralizumab interacts with natural killer (NK) cell receptors via its Fc portion, inducing apoptosis of resident and circulating eosinophils through antibody-dependent cellular cytotoxicity (ADCC).[6]

IL-5 is a key cytokine in the type 2 immune response, essential for eosinophil maturation in the bone marrow and their release into the bloodstream, thus playing a central role in eosinophilic inflammation. It may also modulate basophil and mast cell development and function, enhancing mediator release via IL-5R binding. Consequently, by inhibiting IL-5, one can minimize reactions triggered, in particular, by the degranulation of eosinophils, basophils, and mast cells.[6]

Anti-TSLP

Tezepelumab is a human monoclonal antibody (IgG2λ) that specifically binds to thymic stromal lymphopoietin (TSLP), thus inhibiting its interaction with the TSLP receptor complex on various target cells. TSLP is an innate immunity cytokine belonging to the alarmin group, acting as an activator of cellular and molecular pathways that drive airway inflammation. It interferes with the function of several immunoinflammatory and structural cells that coexpress the TSLP receptor. Together with other alarmins, such as IL-25 and IL-33, TSLP promotes the survival of type 2 innate lymphoid cells (ILC2s) and stimulates them to produce large amounts of IL-5, IL-9, and IL-13 (Figure 1).[6]

Combination of aeroallergen immunotherapy and biologics

AIT with aeroallergens provides a disease-modifying approach for allergic disorders such as allergic rhinitis and asthma. Unlike traditional medications, which offer temporary symptomatic relief, AIT aims to alter the immune system's response to allergens through the gradual administration of increasing doses of diluted allergen extracts over a recommended period of 3 to 5 years.

The procedure may be administered either subcutaneously (SCIT) or sublingually (SLIT) and can be divided into two phases: an induction phase, involving gradually increasing standardized doses of specific allergens, and a maintenance phase, using fixed doses of aeroallergens. International guidelines recommend that AIT be maintained for at least 3 years to ensure sustained long-term benefits.[12]

The combination of AIT and biologics targeting the T2 response may enhance the short-term efficacy and safety of immunotherapy. Increasingly robust evidence supports the effectiveness of this approach, particularly for omalizumab.[13]

Although the approach seems promising, the indication remains under investigation, with ongoing studies aimed at assessing its long-term benefits, such as its potential to induce durable clinical and immunologic tolerance.

Omalizumab

The use of omalizumab as an adjuvant to aeroallergen AIT seems to be particularly beneficial in reducing systemic adverse reactions during the SCIT induction phase. However, it may also enhance

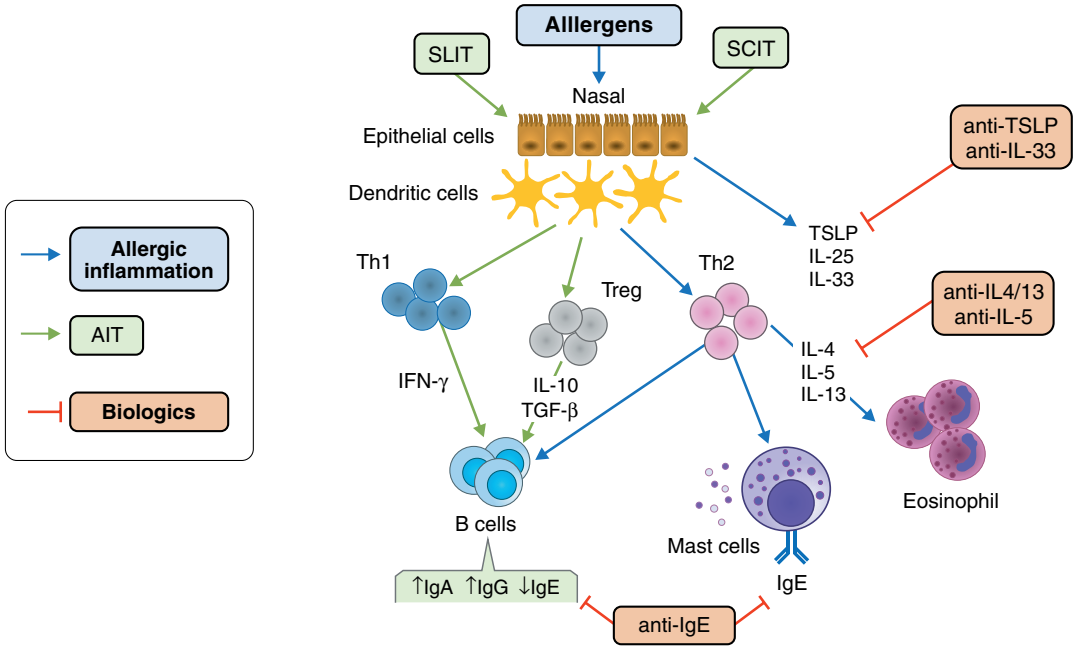

Figure 1
Interplay between AIT and biologics in modulating allergic inflammation. SLIT and SCIT shift allergic inflammation from a Th2 to a Th1 profile. Biologics target TSLP, IL-33, and IL-4/IL-13 axis, affecting epithelial alarmins and Th2 cytokines, and anti-IgE biologics prevent IgE-mediated mast cell degranulation[5]

AIT: allergen immunotherapy, IG: immunoglobulin, IL: interleukin, SCIT: subcutaneous immunotherapy, SLIT: sublingual immunotherapy, TSLP: thymic stromal lymphopoietin.

the overall efficacy of immunotherapy. Double-blind, placebo-controlled trials suggest that combining aeroallergen SCIT with omalizumab decreases the need for rescue medication, alleviates rhinitis and asthma symptoms, and improves quality of life compared with placebo.[14-18]

In accelerated schemes, such as rush and cluster regimens, there is evidence that omalizumab improves safety, significantly reducing the rate of systemic adverse reactions.[17-19]

Table 1 summarizes the main available clinical evidence on the use of omalizumab in combination with aeroallergen AIT.[14-19]

Dupilumab

In recent years, the role of dupilumab in combination with aeroallergen AIT has been the object of research. In a double-blind, placebo-controlled trial involving patients with allergic rhinitis receiving SCIT with grass pollen in combination with dupilumab, significant improvement was observed in the nasal allergen challenge test and in total nasal symptom scores after 16 weeks of therapy, compared with patients receiving SCIT alone. The combination significantly enhanced the response to the allergen, reduced adverse events, and increased treatment tolerance, with less need for epinephrine to treat adverse reactions and a higher rate of patients achieving the maintenance dose.

Table 1
Summary of evidence on omalizumab use as adjuvant in aeroallergen immunotherapy

Study	Patients	Study design	Results
RDBPCT (Casale et al., 2006)	N = 159 Age: 18 to 50 years. Seasonal allergic rhinitis with sensitization to ragweed pollen	OMZ or placebo – 9 weeks pre-SCIT Rush SCIT + OMZ or rush SCIT + placebo – 12 weeks	OMZ group x placebo: ↓ rhinitis symptom severity score (p = 0.04) ↓ risk of anaphylaxis (p = 0.02)
RDBPCT (Kamin et al., 2010)	N = 221 Age: 6 to 16 years. Seasonal allergic rhinitis with sensitization to pollen (grass and birch)	SCIT – 12 weeks. Randomization to placebo or OMZ for 24 weeks	OMZ group x placebo: ↓ adverse reactions during SCIT (p < 0.05)
RDBPCT (Kopp et al., 2009; Kopp et al., 2013)	N = 140 Age: 11 to 46 years. Asthma and allergic rhinitis with sensitization to grass pollen	Stage 1 OMZ or placebo – 2 weeks pre-SCIT SCIT + OMZ or SCIT + placebo – 18 weeks Stage 2 SCIT maintenance after discontinuation of OMZ – 2 following years	Stage 1 OMZ group x placebo: ↓ rhinitis symptoms (p < 0.04) ↓ severity of symptoms (p = 0.004) Improved asthma control (p = 0.02) Improved QoL in asthma (p = 0.02) Improved QoL in rhinitis (p = 0.05) Stage 2 No significant difference between the two groups
RDBPCT (Massanari et al., 2016)	N = 248 Age: 18 to 55 years. Persistent asthma with sensitization to cat, dog, and house dust mite	SCIT regimen: Cluster SCIT – 4 weeks Maintenance SCIT – 7 weeks Groups: OMZ + SCIT OMZ + placebo	OMZ group x placebo: ↓ systemic adverse reactions (p = 0.01) > percentage of patients to achieve target maintenance dose (p = 0.004)
Retrospective real-world study (Valdesoiro-Navarrete et al., 2022)	N = 29 Age: 4 to 16 years. Severe asthma with sensitization to house mites, *Alternaria spp.* or pollen, after asthma control with OMZ	After OMZ for one year and controlled asthma, OMZ maintained and cluster SCIT initiated, followed by maintenance regimen (2 years)	OMZ x OMZ + SCIT: – Improvement in symptom control (p < 0.001) – Improvement in FEV_1 (p < 0.001) – Systemic adverse reactions (n): cluster SCIT – 3/64 applications maintenance SCIT – absence of reactions

FEV_1: forced expiratory volume in 1 second; OMZ: omalizumab; RDBPC: randomized, double-blind, placebo-controlled trial; SCIT: subcutaneous immunotherapy; QoL: quality of life.

Furthermore, the use of dupilumab as an adjuvant to SCIT significantly decreased serum levels of grass pollen-specific IgE (sIgE) while increasing serum levels of allergen-specific immunoglobulin G and immunoglobulin G4 (sIgG4). Thus, the sIgG4/sIgE ratio increased compared with SCIT alone, which may explain the improved tolerability during SCIT up-dosing.[20]

An observational study assessing the use of SLIT in combination with dupilumab also reported benefits from this association. Hoshino et al. assessed 47 patients with allergic rhinitis and asthma sensitized to house dust mites over a 48-week period receiving SLIT with dust mite extracts in combination with dupilumab, and found an improvement in asthma control, better quality of life for both asthma and rhinitis, an increase in forced expiratory volume in 1 second (FEV_1), and a decrease in fractional exhaled nitric oxide (FeNO).[8]

Tezepelumab

The use of tezepelumab in combination with AIT is currently under investigation, and preliminary results seem promising.

A recent clinical trial assessed the combination of SCIT with cat dander extract and intravenous tezepelumab in patients with allergic rhinitis. When comparing patients receiving SCIT alone with those receiving the combination of SCIT and tezepelumab, the results showed that combination therapy was more effective at reducing total nasal symptom scores during the nasal allergen challenge test with cat dander, with effects sustained after one year of treatment.[21]

Thus, combining tezepelumab with conventional SCIT may potentially yield greater efficacy than SCIT alone and result in greater long-term tolerance.

Combination of venom immunotherapy (VIT) and biologics

Allergic reactions to *Hymenoptera* venom can range from localized manifestations to severe systemic responses such as anaphylaxis. It is estimated that between 0.3% and 7.5% of adults may experience a systemic reaction following insect stings.[22]

Desensitization through VIT can achieve success rates of up to 96%, depending on the insect species (bees, wasps, or ants) and the venom used.[23]

Biologics have been explored as an adjuvant option in VIT, especially in patients with severe allergies and recurrent anaphylactic reactions, for whom conventional treatment may be associated with a higher risk of severe adverse events. This combination has allowed patients to achieve and maintain VIT doses that would otherwise be intolerable.[24] However, the current evidence consists mostly of case reports and retrospective studies.

The use of omalizumab as an adjuvant to VIT has been documented in patients who experience severe anaphylactic reactions during VIT, especially among individuals with a history of multiple systemic reactions.[23]

A comparative series of 10 cases showed that combining omalizumab with a high maintenance venom dose (200-300 µg) resulted in durable tolerance to VIT in patients who had previously experienced severe adverse reactions. All 10 patients in the omalizumab group successfully tolerated the induction phase to completion, whereas in the control group (5 patients), VIT had to be permanently discontinued due to repeated systemic reactions.[25]

Recently, the American College of Allergy, Asthma & Immunology (ACAAI) published guidelines recommending the use of omalizumab to reduce the risk of anaphylaxis during VIT in select cases, particularly in patients with mastocytosis.[26]

Combination of oral immunotherapy (OIT) for food allergies and biologics

Food allergies affect approximately 4% to 8% of children and 3% to 4% of adults and may manifest with severe allergic reactions, such as anaphylaxis. Although spontaneous tolerance can occur in up to 80% of cases, some patients develop persistent and severe conditions.[27]

OIT has recently been incorporated into clinical practice as a treatment capable of inducing tolerance in persistent food allergy cases, including those with anaphylactic reactions, offering a potentially safer alternative to strict exclusion diets. However, a systematic review and meta-analysis concluded that, while OIT is effective and generally safe, it considerably increases the risk of anaphylactic reactions.[28] Therefore, safer approaches, such as the use of biologics as adjuvants, have been investigated.

A pilot study investigated the benefits of combining omalizumab with OIT in 13 patients with IgE-mediated peanut allergy at high risk for anaphylactic reactions.

The results showed the benefits of combining omalizumab with OIT, particularly regarding the likelihood of achieving the maintenance dose in a higher percentage of patients.[29]

Wood et al. conducted the first double-blind, randomized, placebo-controlled trial to assess the combination of omalizumab and OIT for cow's milk. After 32 months, sustained tolerance to the allergen was observed in 48% of patients in the OIT + omalizumab group vs. 35% in the OIT-alone group, with no statistically significant difference between the two groups (p = 0.42). However, there was a significant difference in the rate of adverse events requiring treatment, with 2.1% in the OIT + omalizumab group compared with 16.1% in the OIT-alone group (p = 0.0005).[30] These data support the role of omalizumab in improving the safety of OIT.

A phase 2 trial assessed the benefits of omalizumab combined with OIT in patients with multifood allergies. The primary endpoint was the proportion of participants who successfully completed double-blind, placebo-controlled food challenges to at least 2 of the offending foods used in OIT. A higher proportion of patients in the OIT + omalizumab group (83%) achieved the primary endpoint compared with the OIT + placebo group (33%) (p = 0.004). No serious adverse events were reported, and no statistically significant differences were observed in the overall adverse event rate between the two arms of the study. The authors concluded that in patients with multifood allergies, omalizumab was able to enhance the efficacy of multifood OIT, allowing for faster and safer desensitization.[31]

In February 2024, the FDA approved omalizumab for the treatment of food allergy, based on data from the phase 3 clinical trial "Omalizumab as Monotherapy and as Adjunct Therapy to Multiallergen OIT in Children and Adults with Food Allergy (OUtMATCH)", which assessed the efficacy of this biologic in patients allergic to peanuts associated with at least 2 other food allergens.[7,32] The study was divided into 3 stages, but only the results from Stage 1 (omalizumab vs. placebo) have been published to date. At this stage of the study, 177 patients aged 1 to 17 years were enrolled, 118 in the omalizumab group and 59 in the placebo group. The primary endpoint was defined as the ability to ingest at least 600 mg of peanut protein without dose-limiting symptoms. The study found that 67% of patients in the omalizumab group achieved the primary endpoint, compared with only 4% in the placebo group.[33]

Additional clinical trials are ongoing and are expected to provide a higher level of evidence regarding the efficacy and safety benefits of omalizumab as an adjuvant to OIT. Table 2 summarizes the main studies investigating the adjunctive role of omalizumab in OIT.[29-33]

Combined use of biologics

Combined use of biologics in allergic diseases

Indications for biologic therapy in allergic diseases are expanding. As it develops, patients may benefit from different biologic products for the same condition, such as severe asthma, or for distinct conditions, such as CSU concomitant with AD, EoE, or nonallergic asthma.

Despite several isolated case reports, case series investigating this approach are limited. Only one recent clinical trial has investigated the treatment of asthma with the combined use of dupilumab (anti-IL-4R) and itepekimab (anti-IL-33), and it did not find an increased risk of adverse events or any additional efficacy.[34-38]

A case series described 25 patients treated with a variety of combinations of biologics, 15 of which used combinations of biologics approved for asthma (anti-IL-5 + anti-IgE, anti-IgE + anti-IL-4/IL-13, and anti-IL-5 + anti–IL-4/IL-13). The duration of combination therapy in that study ranged from 3 to 49 months, and there were no reports of adverse events that limited treatment.[39]

Recently, Pitlick and Pongdee, in a case series, described 25 patients using combinations of biologics that included: omalizumab + mepolizumab, omalizumab + dupilumab, omalizumab + benralizumab, mepolizumab + dupilumab, and omalizumab + mepolizumab + dupilumab. The mean duration of treatment with a combination of biologics was 17.5 months (range, 1 to 60 months). No patient experienced anaphylaxis or other allergic reactions at any time during the use of multiple biologics. There were no reports of malignancies, renal or hepatic failure, pneumonia, or immune dysfunction after combination therapy, and no patient became pregnant during treatment.[40]

Other studies have described patients with severe asthma or allergic bronchopulmonary aspergillosis (ABPA) treated with omalizumab in combination with mepolizumab, benralizumab, or dupilumab. Four patients were identified as receiving combined anti-IgE and anti-IL-5 therapies after failure with single-agent

Table 2
Summary of evidence on omalizumab use as adjuvant in oral immunotherapy for food allergy

Study	Patients	Study design	Outcomes / Results
Pilot study (Schneider et al., 2013)	N = 13 Age: 8 to 16 years. High risk for peanut-induced anaphylaxis. Mean peanut-specific IgE = 229 kU/L; mean total serum IgE = 621 kU/L	OMZ before (12 weeks) and during OIT (8 weeks)	Primary: Maintenance dose – 4 g Results: – 92% of patients tolerated maintenance dose within 8 weeks. – Patients (n) with reactions to OIT during induction: Absent reaction – 3 Grade 1 – 9 Grade 2 – 2 Grade 3 – 0
		After week 21, discontinuation of OMZ and maintenance of OIT (maintenance)	– Patients with no reaction to OFC in week 32 – 85% – Patients (n) with reactions to OIT during maintenance: Absent reaction – 6 Grade 1 – 5 Grade 2 – 4 Grade 3 – 2
RDBPCT (Wood et al. 2016)	N = 48 Cow's milk	OIT+ OMZ OIT+ placebo 32 months	Primary Tolerance maintained: OIT + OMZ – 48% OIT + placebo – 35% (p = 0.42; NS) Rate of adverse events requiring treatment: OIT + OMZ – 2.1% OIT + placebo – 16.1% (p = 0.0005)
RDBPCT (Andorf, 2018)	N = 48 Age: 4 to 15 years. 2 to 5 food allergies	OIT + OMZ (N = 36) 12 weeks. OIT + placebo (N = 12) 36-week study	Primary: 2 g maintenance dose for each of 2 foods used in OIT. Results: OIT + OMZ: 83% OIT + placebo: 33% (p=0.004) No statistically significant differences compared to overall adverse event rate
Phase 3 clinical trial OUtMATCH (Wood et al., 2022) (Wood et al., 2024)	N = 177 Age: 1 to 55 years. Allergy to peanuts and at least 2 other foods (milk, egg, wheat, cashew nut, hazelnut, and nut)	Stage 1: OMZ vs. placebo. Stage 2: OMZ monotherapy vs. multiallergen OIT + OMZ. Stage 3: long-term results (12 to 36 months) including introduction of foods to induce or maintain desensitization	Primary: Ingestion > 600 mg of peanuts without limiting symptoms Secondary: – Ingestion of > 1000 mg of other food allergen without limiting symptoms. – Assessment of adverse events. Results: Stage 1: OMZ group – 67% Placebo group – 4% (p < 0.001)

OIT: oral immunotherapy; NS: not significant; OFC: oral food challenge; OMZ: omalizumab; OUtMATCH: Omalizumab as Monotherapy and as Adjunct Therapy to Multiallergen OIT in Children and Adults with Food Allergy; RDBPC: randomized, double-blind, placebo-controlled trial.

monoclonal therapy. Three met the diagnostic criteria for ABPA. The authors concluded that combined anti-IgE and anti-IL-5 therapy should be considered in patients with severe asthma or ABPA who continue to require systemic corticosteroids or have frequent exacerbations despite single biologic therapy.[41]

Yang et al. conducted a study of patients with AD, in which those with refractory disease or insufficient response to dupilumab were divided into groups to receive combined treatment with JAK inhibitors (JAKi) or immunosuppressants. The authors concluded that the dupilumab + JAKi combination was significantly effective, without the occurrence of significant adverse events.[42]

Despite the small number of publications on the topic, the existing data provide preliminary evidence on safety for physicians treating patients with severe allergic diseases to consider the combined use of biologics and small molecules. However, prospective longitudinal studies are needed to determine efficacy and define the ideal patient population that may benefit from such combination therapy.

Combined use of biologics in allergic and inflammatory/autoimmune diseases

The combined use of medications in the treatment of allergic, inflammatory, and autoimmune diseases has proven to be an effective and promising approach in clinical practice, given that these conditions often share underlying pathogenic mechanisms, such as hypersensitivity mechanisms and inflammatory pathways.

The combined management of allergic diseases and inflammatory/autoimmune disorders requires a collaborative approach involving multiple medical specialties. The integration of traditional therapies with therapeutic innovations, such as biologic agents, has significantly improved outcomes for many patients with different immune-mediated diseases.

Due to the potential increased risk of infections and other adverse events, developing a personalized treatment plan involving a multidisciplinary team (allergist/immunologist, dermatologist, rheumatologist, gastroenterologist, etc.), as well as ensuring close monitoring throughout treatment, is essential. Assessing the sustained efficacy of concomitant therapies, given the high costs associated with biologic treatments, is equally important.

The association of type 2 inflammatory diseases with conditions such as psoriasis, psoriatic arthritis, rheumatoid arthritis, lupus, and inflammatory bowel disease may present a therapeutic challenge. Although rare, some patients present with 2 of these systemic inflammatory diseases simultaneously. For them, combination therapy with biologics may offer a viable solution.

The literature contains few reports on the concomitant use of omalizumab with other biologic agents. One case report described a patient treated with guselkumab (anti-IL-23) for psoriasis and omalizumab for CSU for 21 months with no relevant adverse events or drug interactions.[43] Another report documented a patient who developed CSU while receiving adalimumab for psoriatic arthritis and subsequently received omalizumab concomitantly for 24 weeks. In this patient, omalizumab was discontinued after 24 weeks due to complete control of CSU.[44] Recently, a study assessed the combined use of omalizumab with 4 different biologics indicated for the treatment of psoriasis or hidradenitis suppurativa (adalimumab, ustekinumab, secukinumab, and ixekizumab) in 31 patients. No serious adverse events were observed with these combinations; only 1 patient experienced diarrhea after 9 months of combined omalizumab + secukinumab therapy, which resolved after discontinuation of secukinumab.[45]

A recently published study described 12 patients with AD receiving a combination of a Th2-axis inhibitor (dupilumab or tralokinumab) with an IL-23/Th17-axis inhibitor (guselkumab, risankizumab, or tildrakizumab) or an IL-12/IL-23 inhibitor (ustekinumab) for the treatment of psoriasis (8 patients), psoriatic arthritis (4 patients), and inflammatory bowel disease (5 patients). The mean duration of combination therapy was 560 days. Among participants, 75% (n = 9) showed clinical improvement of atopic dermatitis. In the remaining cases, one patient did not respond to treatment, another experienced worsening of arthritis after starting dupilumab, and a third lost response after an initial favorable outcome. Most patients received combination therapy to simultaneously treat psoriasis/psoriatic arthritis and AD (n = 8). Adverse events observed included ocular irritation and conjunctivitis in 17% (n = 2) of patients.[46]

Remission

Remission is a term used in health care to describe the reduction or absence of a disease's

signs and symptoms, associated with the reduction or suppression of underlying pathological mechanisms. When a patient is in remission, the signs and symptoms of their disease are under control or absent, and they are in stable health. Remission does not necessarily mean cure, but rather that the disease is not currently active. Therefore, disease remission is defined as a state or period of low or absent disease activity, which may occur spontaneously or be achieved through treatment.[47]

The concept of remission has long been used in certain malignancies, particularly hematopoietic cancers, in which treatment can induce complete remission of the disease, even after discontinuation. A similar principle applies to chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, and ulcerative colitis, in which treatment can achieve and maintain a state of remission.[48]

With the advent of new therapeutic targets with disease-modifying potential for asthma treatment over the last 2 decades, the term remission has been proposed as a goal, in addition to the traditional objectives of symptom control and reduction of future risk.[47,49]

Remission, defined as complete control of disease symptoms and biomarkers, is an emerging therapeutic goal in the management of several chronic conditions. The recent application of this concept to the management of inflammatory airway diseases has advanced the notion of clinical remission, using a "treat-to-target" or targeted treatment approach.[50,51]

Remission in asthma

Some patients with asthma may become asymptomatic spontaneously and enter a prolonged symptom-free state, whether the underlying pathophysiological process persists or not. While spontaneous remission of asthma in pediatric populations is a relatively common phenomenon, remission in adults is less frequent, and its occurrence as a treatment outcome is a relatively new and evolving concept.[48,52,53]

The use of biologics targeting different aspects of the immunopathogenesis of asthma, as well as macrolides in select cases of severe asthma, has introduced the possibility of inducing disease remission. Given the wide variability of asthma phenotypes, remission can be interpreted in various clinical contexts: spontaneous remission without treatment as part of the natural history of the disease; remission during treatment; remission achieved during treatment and persisting after discontinuation; and remission with disease relapse, which may occur in any of the previous scenarios. Figure 2 illustrates the different possible evolutionary courses of asthma.[54]

Previous studies have used a wide range of criteria to define remission, considering symptom-free periods ranging from 6 months to 3 years, with the average generally being 1 year. A minimum duration of 12 months seems to be reasonable, as it encompasses the seasonality of disease activity. The remission rate ranged from 20% to 70% in early-onset asthma and from 2% to 17% in adult-onset asthma, reaching up to 29.7% among adults with asthma included in studies, regardless of the age of onset. Factors associated with remission included lower disease severity, better lung function, younger age, earlier onset of asthma, shorter disease duration, lower bronchial hyperresponsiveness (BHR), fewer comorbidities, and absence of smoking or smoking cessation.[53] In a Tasmanian cohort of more than 8000 participants, increased BHR and elevated blood levels of tumor necrosis factor-α (TNF-α) during spontaneous remission were associated with a higher risk of asthma relapse.[52]

In 2020, a task force of experts proposed, for the first time, criteria to define remission in asthma (Figure 2). These criteria were divided into clinical remission and complete remission, both of which may occur on or off treatment.[47]

Which tool is best suited to assess asthma symptoms for the purpose of defining remission has yet to be established, since the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT) were validated for assessing symptom control in symptomatic individuals, not in those in remission. Cut-off points of ACQ < 0.75 or ACT ≥ 20 are suggested, but the thresholds used across studies vary, ranging from 0 to 1 for the ACQ and from 20 to 25 for the ACT. For now, this variation in criteria will persist until a specific instrument is validated for this purpose (Table 3).

Some authors propose including the absence of beta-agonist use for symptom relief as a criterion for clinical remission. For complete remission, they suggest defining specific thresholds for biomarkers that indicate resolution of inflammation, such as blood eosinophils < 300/mm^3, sputum eosinophils < 3%, and FeNO < 40 parts per billion (ppb).[48] However, these biomarkers are only relevant for type 2 inflammation-driven asthma, whereas for non-type 2 asthma there

are still no defined markers of complete remission, with reduction in BHR possibly serving as a measurable parameter for this inflammatory phenotype.

In 2023, a consensus statement from the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI), together with experts from the American Thoracic Society (ATS), proposed an initial definition of asthma remission on treatment comprising 6 criteria (Figure 3). All criteria must be met over a minimum period of 12 months and may be applied to patients receiving biologic therapy for asthma.[55] However, applying these criteria requires the use of three different tools to assess risk and disease control, which is not common practice in Brazil. Furthermore, it allows the use of rescue medication up to once per month, a questionable choice, given that it would not meet a strict definition of disease remission.

Recently, several real-world studies have been published evaluating the response to biologics in asthma. Sposato et al., who defined clinical remission as asthma symptom control (ACT ≥ 20), absence of exacerbations, discontinuation of oral corticosteroid use, and FEV_1% ≥ 80%, observed this condition in 21.8%, 23.6%, 35.8%, and 23.5% of patients treated with omalizumab, mepolizumab, benralizumab, and dupilumab, respectively.[56]

Patients treated with omalizumab who were older, had higher body mass index (BMI), later age of asthma onset, comorbid sinusitis/nasal polyposis, hypertension/chronic heart disease, and a higher number of exacerbations were more likely to fail to achieve asthma remission. Poorer lung function and a higher number of exacerbations were associated with failure to achieve clinical remission with mepolizumab, while higher BMI and the presence of rhinitis were associated with failure to achieve remission among patients using benralizumab. Higher FeNO levels were associated with remission in patients treated with mepolizumab and benralizumab. The small number of patients treated with dupilumab in this study prevented the identification of significant differences for these factors. In the German Severe Asthma Registry, which included 443 adult patients under treatment, 210 of whom were receiving biologics, 58% were treated with IL-5-targeted agents (benralizumab, mepolizumab, or reslizumab), 15.7% with omalizumab, and 26.6% with dupilumab. Clinical remission, defined as adequate symptom control (ACT ≥ 20), absence of systemic corticosteroid use, and absence of exacerbations for 12 months or longer, was achieved by 17.2% of patients treated without biologics and by 37.6% of those receiving biologic therapy.[57]

In conclusion, with the advent of therapies that have disease-modifying potential, albeit limited to

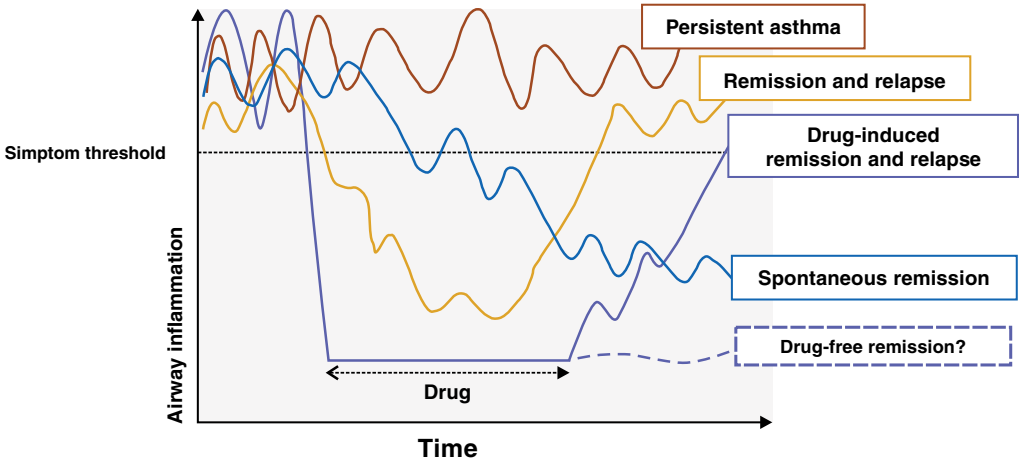

Figure 2
Possible progressions of asthma on and off treatment
Source: Cohn J.[54]

Table 3
ACAAI/AAAAI/ATS criteria for remission in treatment

1.	No exacerbations requiring a physician visit, emergency care, hospitalization, and/or systemic corticosteroids for asthma (ie, oral, injectable).
2.	No missed work or school over a 12-month period due to asthma-related symptoms.
3.	Stable and optimized pulmonary function results on all occasions, when measured over a 12-month period, with a minimum of two measurements during the year.
4.	Continued use of controllers (ICS, ICS-LABA, leukotriene receptor antagonists) ONLY at low-medium dose of ICS (or less) as defined by most recent GINA guidelines.
5.	ACT score > 20, AirQ < 2, ACQ < 0.75 on all occasions measured in the previous 12 months, with a minimum of 2 measurements during the year.
6.	Symptoms requiring reliever therapy (SABA, ICS-SABA, ICS-LABA) no more than once a month.

ACQ: Asthma Control Questionnaire; ACT: asthma control test; AirQ: Asthma Impairment and Risk Questionnaire; GINA: Global Initiative in Asthma; ICS: inhaled corticosteroid; LABA: long-acting beta-agonist; SABA: short-acting beta-agonist.
Source: Blaiss M et al.[54]

the inflammatory component of asthma and not to the structural alterations associated with bronchial remodeling, remission in asthma has become a feasible therapeutic goal, beyond mere symptom control and functional stabilization. Further studies involving the use of biologics and azithromycin in severe asthma, with larger patient populations, are needed to establish standardized criteria for clinical, functional, and complete remission. In addition, it is crucial to assess the true potential of these therapies in pursuing remission, to identify which factors or treatable characteristics predict the greatest likelihood of success with various medications, and to determine the risk factors for relapse after achieving remission.

Remission in chronic rhinosinusitis with nasal polyps

Remission in CRSwNP is defined as sustained disease control for ≥ 12 months, associated with the absence of active disease, preferably confirmed by nasal endoscopy. Remission may be achieved on or off treatment, provided there has been no use of systemic corticosteroids or surgery (within the previous 12 months). In a state of remission, patients experience no exacerbations and therefore do not require systemic corticosteroids and/or rescue surgery for nasal polyps.[58]

A Canadian consensus statement has proposed combining symptom assessment with nasal endoscopy to define successful outcomes after endoscopic sinus surgery, with outcomes considered “optimal” in the absence of symptoms combined with a normal appearance of the sinus mucosa on endoscopy.[59]

Randomized clinical trials (RCTs) of biologics in patients with CRSwNP, although not specifically designed to assess remission, have provided insights into concepts and tools that may be useful for its definition. RCTs (eg, benralizumab in the OSTRO trial; dupilumab in SINUS-24 and SINUS-52; mepolizumab in SYNAPSE; and omalizumab in POLYP-1 and POLYP-2) used several outcome measures to define clinical response. All these studies adopted as primary endpoints the change from the baseline Nasal Polyp Score (NPS) combined with the improvement in nasal congestion severity (NCS) or the Visual Analogue Scale (VAS) for nasal obstruction. Secondary endpoints included symptom improvement, quality of life assessed by SNOT-22, Lund-Mackay score on computed tomography (CT), peak nasal inspiratory flow, and the need for surgery or systemic therapy.[60-64]

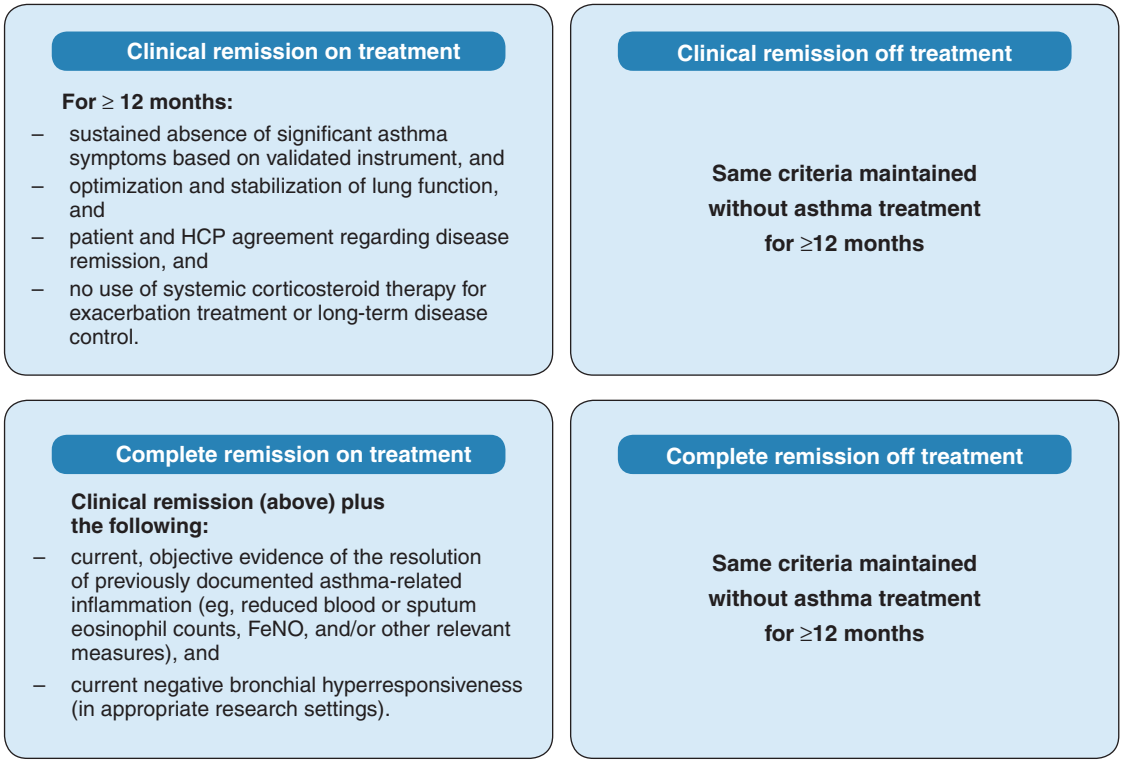

Figure 3
Suggested criteria for remission in asthma
FeNO = fractional exhaled nitric oxide.
Source: Menzies-Gow A, et al.[47]

The EPOS2020/EUFOREA expert consensus considered both patient-reported symptom control and physician assessment when defining remission. For this reason, the absence of signs of active disease, preferably confirmed through nasal endoscopy, is regarded as an important therapeutic goal. The presence of nasal discharge, edema, polypoid degeneration, and nasal polyps may be considered signs of active disease, although further research is needed to identify specific signs predictive of loss of CRSwNP control.[58]

In addition to the definition of remission in CRSwNP, the term "cure" has been proposed when remission is sustained off treatment for at least 5 years.[58] Further studies, including the identification of specific biomarkers, are needed to distinguish active from inactive nasal polyposis.

Remission in atopic dermatitis

The natural history of AD encompasses several trajectories, which can be subdivided into the following main patterns: (1) early onset transient, (2) early onset persistent, and (3) late onset persistent. Remission may occur spontaneously, particularly in pediatric patients. Analysis from the GUSTO cohort (Growing Up in Singapore Towards Healthy Outcomes), which followed 1,152 patents from three months of age to eight years, evaluated the prevalence and natural history of AD and estimated that 43% of pediatric patients exhibited the transient early-onset phenotype.[65]

There is still no established definition of remission in AD either during treatment or after discontinuation of biologics, and the available data come mostly from extension studies. Blauvelt et al. investigated

the rate of clinical remission both during and after discontinuation of dupilumab therapy in adolescents in a 52-week extension study including 102 patients, where clinical remission was defined as clear or almost clear skin sustained for 12 weeks. Among participants aged 12 to 17 years, 29.4% achieved sustained remission during therapy and stopped medication. Of these, 43.3% maintained remission without therapy, while 56.7% required reinitiation of dupilumab over a median follow-up of 18 weeks.[66]

A similar study assessing the clinical remission rate of AD in 254 children aged 6 to 11 years over a 52-week period, using comparable remission criteria, found that 28.7% achieved sustained remission while on dupilumab. Among them, 60.3% maintained clinical remission after discontinuing treatment for a median period of 15.7 weeks.[67] These data suggest a higher likelihood of sustained remission after discontinuation of treatment in children compared to adolescents. In both studies, the 12-week period used to define clinical remission was quite short, especially considering that AD alternates between periods of improvement and exacerbation in most patients. Furthermore, the follow-up period after discontinuation of treatment (ranging from 15 to 18 weeks) also seems inadequate to reliably estimate remission rates off treatment.

Miyamoto et al. conducted a study assessing sustained clinical remission in 109 adolescent and adult patients with AD after discontinuing treatment with dupilumab. The criterion for remission was defined as controlled disease for 6 months with proactive topical therapy, and documented a 20% sustained remission rate, with a mean duration of 40 weeks. Dupilumab levels declined gradually, with complete elimination in 8 to 10 weeks. When comparing baseline characteristics of patients with sustained remission versus those with recurrence of AD, the only parameter to display a significant difference was a younger age in the sustained remission group.[68]

A real-world study from Japan examined clinical remission rates during treatment with dupilumab and its maintenance after discontinuation in adults treated for up to 5 years. Fifty-eight patients were analyzed, of which 25 (43%) achieved significant control of AD after at least 12 months of treatment and discontinued therapy. Among them, 18 (31%) required reinitiation of dupilumab due to disease exacerbation, while only 7 (12%) maintained clinical remission after discontinuation. The authors conducted a comparative analysis to compare patients with sustained remission after discontinuing dupilumab and the group that required reinitiation due to exacerbation of AD. Patients with sustained remission after dupilumab discontinuation had, before treatment, lower Patient-Oriented Eczema Measure (POEM) and VAS scores for pruritus, lower serum thymus and activation-regulated chemokine (TARC) levels, and longer treatment duration (mean of 2 years) before discontinuation, compared with the group who had exacerbations after discontinuing biologics (mean of 1 year).[69]

The currently available data are still preliminary and do not allow for definitive conclusions; therefore, its is necessary standardized criteria for defining clinical remission in AD. Equally important is the identification of biomarkers of inflammatory activity that can be applied to assess treatment response as well as serve as predictors of sustained clinical remission.

Influence of biologics on the atopic march

The concept of the atopic march was proposed in 2003 to describe the axis of immune dysregulation shared by atopic diseases, the risk of developing respiratory allergies in patients with AD, and the typical progression of atopic manifestations—AD, asthma, and allergic rhinitis.[70] Subsequently, IgE-mediated food allergy was incorporated into the atopic march, as it frequently follows the onset of AD.[71] More recently, the inclusion of EoE in the atopic march has been proposed due to its strong association with atopic diseases, leading to a change in the term to “allergic march.” In most cases, EoE represents the final manifestation in this sequence.[72]

The allergic march does not always follow the classical pattern proposed initially; multiple trajectories are possible in the development of 2 or more clinical manifestations of atopic conditions, either sequentially or concurrently, depending on genetic predisposition, environmental exposures beginning in utero, and socioeconomic conditions, as illustrated in Figure 4.[73] Although there may be various trajectories, AD is the first manifestation in the majority of cases. It has been hypothesized that type 2 inflammation and epithelial barrier dysfunction in AD promote cutaneous sensitization to both food and airborne allergens.[74]

The rationale for the use of biologics in the treatment of allergic diseases includes, among other benefits, preventing the development of additional atopic comorbidities. This effect stems from the ability of biologics to act on multiple points of the type 2

inflammatory pathway, including a reduction in alarmin production in response to environmental stimuli (tezepelumab), a decrease in IgE sensitization specific to food and aeroallergens (dupilumab), and restoration of the skin barrier in AD (dupilumab).[75-77]

Given that AD is the first manifestation of atopy in nearly all cases, and that dupilumab is approved for use from 6 months of age with proven efficacy across multiple atopic comorbidities, this biologic theoretically has the greatest potential to disrupt the allergic march.

A retrospective population-based cohort study (TriNet Collaborative Network US) investigated whether dupilumab reduced the risk of developing asthma and allergic rhinitis in pediatric patients (<18 years of age) with AD and no pre-existing respiratory allergy at treatment initiation. The study included 2190 patients treated with dupilumab and 2192 patients in the control group receiving conventional AD therapy over a 3-year period. There was a 40% reduction in asthma and a 31% reduction in allergic rhinitis in the dupilumab group compared to the control group. Moreover, among patients who did develop asthma and/or allergic rhinitis, symptom severity and use of maintenance or rescue therapy were lower, suggesting a disease-modifying effect on respiratory allergy severity.[78]

A meta-analysis including 12 clinical trials and assessing 3525 patients over the age of 12 with AD (dupilumab group = 2296; control group = 1229) assessed both the risk reduction for developing new allergic diseases and the improvement in control of existing atopic comorbidities over a 52-week period. Treatment with dupilumab reduced the overall risk of developing new allergic diseases in 37% of patients. The study also found better control of concomitant allergic diseases and a significant reduction in serum IgE levels in patients treated with dupilumab compared with the control group.[79]

A prospective study conducted in the Netherlands (Dutch Bioday Registry) assessed the impact of dupilumab on the control of atopic comorbidities in patients undergoing treatment for AD. Among patients with a history of food allergy, there was a 70.5% to 82.5% reduction in food allergen-specific IgE levels (peanut, hazelnut, almond, and cashew) and a 60% reduction in allergic symptoms following accidental ingestion of these foods. In patients with allergic rhinitis and/or asthma, there was also a significant reduction in aeroallergen-specific IgE levels, ranging from 61.3% to 89.1%.[80]

Omalizumab blocks circulating IgE and the signaling through the IgE receptor, thereby inhibiting both immediate and late-phase allergic responses, and its efficacy in asthma is well established. Furthermore, it helps reduce asthma exacerbations during viral seasons and enhances interferon-α (IFN-α) release in response to rhinovirus infection, which may provide an additional protection against the development of asthma, since rhinovirus is one of the main triggers for the onset of persistent asthma in children.[81] In addition, omalizumab has been shown to raise the threshold for clinical reactivity to food allergens and was recently approved by the FDA for the treatment of patients (aged >1 year) with IgE-mediated multifood allergies, indicating potential for food allergy prevention.[7,33] Currently, the Prevention of Asthma in High-Risk Kids (PARK) study is underway, aiming to investigate the prevention of asthma development and reduction of disease severity risk in children aged 2 to 3 years at high risk for developing allergies.[82]

New biologics

Despite the significant advances achieved with the use of biologics in patients with severe allergic diseases, there are still gaps and unmet needs. The heterogeneity of allergic diseases makes it difficult to standardize treatment for all individuals. Personalizing therapies based on phenotypes and endotypes is essential to improve efficacy. Some patients do not meet the eligibility criteria for currently available biologics, while others show partial or no response to current biologics, and some have mixed phenotypes with overlapping inflammatory pathways. Moreover, adverse reactions can occur, including the development of anti-drug antibodies (ADAs). The development of innovative therapies remains essential and continues to progress as new research sheds light on the inflammatory pathways involved in allergic processes and identifies potential new therapeutic targets.[6,83-85]

Among the newly available biologics, lebrikizumab (anti-IL-13) stands out for the treatment of moderate-to-severe AD in patients aged ≥12 years, having recently been approved for use in Brazil. Lebrikizumab is a monoclonal antibody that binds to soluble IL-13, preventing the formation of the IL-13Rα1/IL-4Rα signaling complex. In pivotal studies, it showed efficacy based on the Investigator Global Assessment (IGA), with 43.1% (ADvocate1) and 33.2% (ADvocate2) of patients achieving IGA 0/1, and Eczema Area

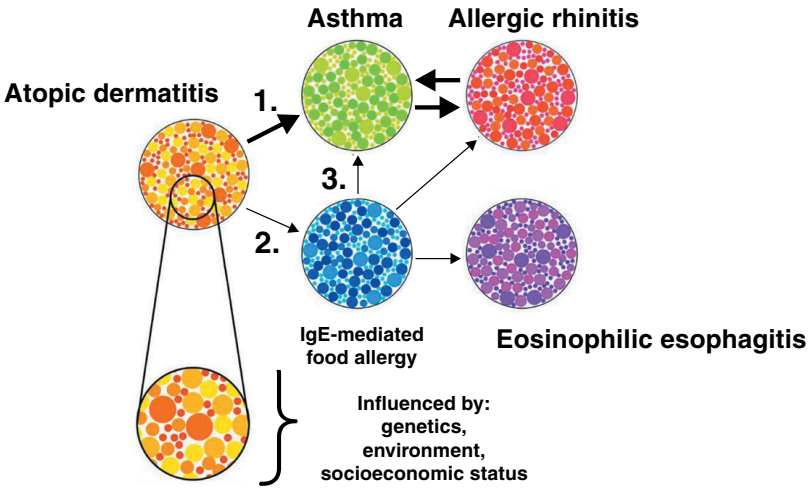

Figure 4
Atopic march trajectories
Source: Gabryszenski SJ & Hill DA.[73]

and Severity Index (EASI-75) responses in 58.8% (ADvocate1) and 52.1% (ADvocate2) of patients after 16 weeks of treatment. The most common adverse event (> 5%) was conjunctivitis, occurring in 7.4% (ADvocate1) and 7.5% (ADvocate2) of patients.[86]

As for the main biologics under investigation, there are new agents for old targets, such as anti-IL-5 (depemokimab) and anti-IL-13 (cendakimab), as well as biologics for novel targets, such as anti-IL-31R (nemolizumab), anti-IL-33 (etokimab, itepekimab, and tozorakimab), anti-OX40 (rocatinlimab, telazorlimab), and anti-OX40L (amlitelimab).[6,83]

Nemolizumab antagonizes the IL-31 receptor (IL-31RA), a key therapeutic and anti-inflammatory target in AD. IL-31 has been identified as one of the major cytokines involved in the origins of pruritus, and its serum levels correlate with AD severity. IL-31R is expressed in C-fiber nerve endings, keratinocytes, and neurons of the dorsal horn of the spinal cord. It also contributes to epidermal barrier disruption in AD, promotes nerve fiber elongation and branching, and activates pruriceptive neurons, which release neuropeptides. These neuropeptides, in turn, enhance local skin inflammation, attracting Th2 cells. Nemolizumab has been approved in Japan for patients aged ≥13 years. Clinical trials with nemolizumab found a 66% reduction in pruritus and a 78% reduction in EASI scores. The main adverse event reported was nasopharyngitis (33.9%). Additional phase 3 trials are ongoing, as well as phase 2 studies in children (aged 2-11 years) with moderate-to-severe AD.[87]

The OX40 pathway represents a promising target for therapeutic intervention in AD and bronchial asthma. OX40, a costimulatory molecule, is significantly expressed on activated T cells in patients with these conditions. The interaction of OX40 with its ligand (OX40L) drives Th2 differentiation and promotes the clonal expansion, survival, and production of memory T cells.[6] Phase 2 clinical trials of anti-OX40 antibodies

(eg, rocatinlimab and telazorlimab) and an anti-OX40L antibody (amlitelimab) have shown encouraging results in patients with moderate-to-severe AD and moderate-to-severe bronchial asthma.[88] These findings suggest that modulating the OX40 pathway may offer a novel and effective strategy for managing these conditions.

Final considerations

Biologics represent one of the most significant innovations in the treatment of allergic diseases. They have revolutionized the management of several immunoallergic conditions, such as asthma, AD, EoE, CRSwNP, and chronic urticaria. Real-world experience has confirmed the efficacy and safety of biologics in treating severe allergic diseases, substantially improving the quality of life of patients and their families.

This therapeutic modality continues to expand, with ongoing efforts to deliver broader and more effective solutions for a growing number of individuals with immunoallergic conditions. New challenges have emerged, including the combined use of biologics, the concept of clinical remission during biologic therapy, their potential influence on the atopic march, the advantages of combining biologics with allergen-specific immunotherapy, and the broadening of indications and age ranges for their use. Conducting clinical trials in children remains a challenge that research centers and the pharmaceutical industry must address to extend the benefits of biologic therapy to the pediatric population. On the other hand, for some allergic diseases multiple biologic options are available, and the challenge lies in making a judicious selection based on personalized medicine and shared decision-making. In addition, the high cost of biologic therapy limits access for a substantial share of the population, especially in low- and middle-income countries.

Research into novel therapeutic targets and the development of new biologics is rapidly expanding. Although beyond the scope of this review, in addition to biologics, small molecules also represent an important advance in the treatment of moderate-to-severe AD. Currently, new molecular classes are under investigation, such as nanobody compounds, including lunsekimig, a bispecific compound that targets the inhibition of TSLP and IL-13.[89] Fortunately, scientific progress is ongoing, and additional safe and effective treatment options for allergic diseases will become available in the near future. It is essential that specialists in Allergy and Immunology stay informed and up to date on the latest developments in their field.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Decreasing vaccination coverage in Brazil: causes, impacts, and intervention strategies

Queda da cobertura vacinal no Brasil: causas, consequências e estratégias de enfrentamento

Denise Salotti Augusto Pizani[1], Márcio Antônio Francisco Dearo[1], Aline Ferreira de Oliveira Pereira[1]

ABSTRACT

Immunization is a highly effective strategy, widely adopted worldwide, for the control and eradication of various diseases. However, in recent years, a significant decline in vaccination coverage has been recorded in Brazil. In this context, the present study aimed to highlight this decline by examining its causes and consequences for public health through a literature review. Sources included news reports, government websites, and national and international scientific articles published between 2014 and 2025, retrieved from the Google Scholar, PubMed, and SciELO databases. After a rigorous selection process, 51 publications were included to support this article. Among the main factors associated with declining vaccination coverage are the spread of misinformation (fake news) and the rise of anti-vaccine movements. These factors contribute to the resurgence of previously eradicated diseases, posing a serious threat to public health. In response, the Brazilian government has implemented several measures, including the distribution of educational materials and the intensification of vaccination programs. Considering that vaccination is one of the most important tools for disease prevention in public health, and in view of the possible reemergence of diseases such as poliomyelitis, strategies to increase vaccination coverage must be effective both in expanding access and in disseminating reliable information to the population.

Keywords: Immunization, mass vaccination, communicable diseases, vaccines, health strategies.

RESUMO

O processo de imunização representa uma estratégia altamente efetiva, adotada mundialmente para controle e erradicação de diversas doenças. Entretanto, nos últimos anos, tem sido registrada uma significativa diminuição na taxa de cobertura vacinal no Brasil. Diante disso, o presente estudo tem como objetivo evidenciar essa queda, abordando suas causas e consequências para a saúde pública, através de uma revisão da literatura. Para tanto, foram utilizadas como fontes: notícias, *sites* governamentais e artigos científicos nacionais e internacionais publicados entre os anos de 2014 e 2025, disponíveis nas bases de dados Google Acadêmico, PubMed e SciELO. Após análise criteriosa, 51 publicações foram selecionadas para embasar a redação deste artigo. Dentre os principais fatores associados à redução da cobertura vacinal, destacam-se a disseminação de informações falsas (*fake news*) e o avanço de movimentos antivacinas. Essas condições favorecem o ressurgimento de doenças anteriormente erradicadas, representando uma ameaça à saúde coletiva. Como resposta a esse cenário, o governo brasileiro tem implementado diversas medidas, como a distribuição de materiais informativos e a intensificação das campanhas de vacinação. Considerando a vacina como um dos principais instrumentos de prevenção em saúde pública e diante da possibilidade de reemergência de doenças como a poliomielite, conclui-se que as estratégias voltadas ao aumento da cobertura vacinal devem ser eficazes tanto na ampliação do acesso quanto na disseminação de informações confiáveis à população.

Descritores: Imunização, vacinação em massa, doenças transmissíveis, vacinas, estratégias de saúde.

Introduction

Vaccination, one of the main strategies for preventing infectious diseases, has played a fundamental role in the control and eradication of various pathologies, as well as in reducing infant mortality.[1] The Brazilian National Immunization Program has been internationally recognized for the

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wide range of vaccines it provides and its history of achieving high vaccination coverage rates.[2,3]

However, Brazil has seen a marked reduction in immunization adherence in recent years, which can be attributed to multiple factors. One is related to the success of the vaccination campaigns, which has led to the disappearance of many diseases, creating the false notion that these diseases are no longer a threat.[3,4] Added to this is the growth of anti-vaccine movements, fueled by the spread of false information about the safety, efficacy, and possible adverse effects of vaccines.[3,5] Social distancing measures during the COVID-19 pandemic, coupled with the fear of contagion, also significantly reduced vaccination rates in 2019 and 2020.[6,7]

Due to vaccine hesitancy, previously controlled diseases, such as measles, have resurged. Now there is even a real risk of polio, which, in its most severe form, can cause infantile paralysis, and immunization is the only form of prevention against it.[8,9] Thus, although vaccination is essential for public health, its rejection by the population challenges both individual and collective health, requiring effective action through public policy.[3,10]

Given this scenario, we investigated the decline of vaccination coverage in Brazil, identifying its main causes and consequences, in addition to reviewing government strategies to reverse the trend.

Methods

This study was based on immunization data published online by the Oswaldo Cruz Foundation (Fiocruz), UNICEF, and Brazilian universities, in addition to current immunization data from government platforms, such as DATASUS and the Ministry of Health. We focused on vaccine-preventable diseases, particularly polio and measles. For the literature review, the Google Scholar, PubMed, and SciELO databases were searched for articles published between 2014 and 2025 in national and international English-language journals. The following descriptors were used collectively and separately: “Immunization”; “Mass Vaccination”; “Communicable Diseases”; “Vaccines”; and “Health Strategies”. The search was conducted between 2022 and 2025, initially resulting in 98 publications. After careful analysis, 47 were excluded because they did not specifically address vaccine hesitancy or because they presented redundant content, resulting in a total of 51 publications.

Literature review and discussion

In 1973, the Ministry of Health established the National Immunization Program to coordinate and organize vaccination efforts in Brazil, which until then were characterized by low coverage and irregular implementation.[11-13] This program is responsible for setting standards related to the acquisition, storage, and distribution of vaccines at the municipal, state, and federal levels. Its actions are based on a vaccination schedule regulated by the Ministry of Health that can be altered according to the country’s epidemiological needs.[13] Table 1 presents the 2024 National Vaccination Calendar for children based on Ministry of Health guidelines, including priority vaccines provided free of charge by the public health system.[11]

The vaccination coverage rate represents the proportion of vaccinated people in relation to the target population, multiplied by 100. The National Immunization Program uses this indicator to monitor vaccination progress and the achievement of its goals, such as reaching 95% vaccination coverage in all municipalities and vaccinating 100% of newborns.[13,14] Vaccination campaigns, a primary strategy for achieving these goals, are conducted during pandemics, epidemics, and outbreaks, as well as on other occasions to ensure that certain vaccine-preventable diseases remain eradicated.[13] Table 2 presents the vaccination campaigns performed in 2024 in Brazil.

In addition to being a primary preventive measure, vaccination is an effective, low-cost intervention that promotes significant changes in global epidemiology by reducing the impact of vaccine-preventable diseases. Vaccination coverage of 95% establishes what is called “herd immunity,” guaranteeing protection even for unvaccinated individuals due to the reduced concentration of circulating pathogens.[14,15] However, despite historical progress, formerly high immunization rates have been declining in recent years, as shown in Table 3 and Figure 1.

Several factors have contributed to these decreasing immunization rates, of which the following stand out: the spread of anti-vaccine movements, the dissemination of false information about vaccination, a false sense of security due to the disappearance of diseases, social distancing measures used during the COVID-19 pandemic, fear of adverse effects after vaccination, as well as technical aspects, such as logistical failures in distribution and insufficient

Table 1
The 2024 National Childhood Vaccination Calendar – vaccines provided by the Brazilian Unified Health System

Vaccine	Target diseases	Recommended age
Bacillus Calmette-Guérin	Tuberculosis (meningeal and miliary)	At birth: single dose
Recombinant hepatitis B	Hepatitis B	At birth
Inactivated polio	Polio	1st dose: 2 months/ 2nd dose: 4 months/ 3rd dose: 6 months
Attenuated oral polio [a]	Polio	1st booster: 15 months/ 2º booster: 4 years
Attenuated human rotavirus	Rotavirus diarrhea	1st dose: 2 months/ 2nd dose: 4 months
DTP HBV HIB	Diphtheria, tetanus, whooping cough, *Haemophilus influenzae* type B infections, hepatitis B	1st dose: 2 months 2nd dose: 4 months 3rd dose: 6 months
10-valent pneumococcal	Pneumonia, meningitis, ear infections, Sinusitis caused by the serotypes that make up the vaccine.	1st dose: 2 months 2nd dose: 4 months Booster: 12 months
Meningococcal C conjugate	Meningococcal meningitis type C	1st dose: 3 months Booster: 12 months
COVID-19	Severe COVID-19 cases and deaths due to SARS-CoV-2	1st dose: 6 months 2nd dose: 7 months
Attenuated yellow fever	Yellow fever	Dose: 9 months Booster: 4 years
Attenuated measles, mumps and rubella	Measles, mumps and rubella	12 months
Attenuated measles, mumps, rubella, and varicella	Measles, mumps, rubella and chickenpox	15 months (2nd dose of MMR vaccine and 1st dose of chickenpox vaccine)
Hepatitis A (inactivated)	Hepatitis A	15 months
Diphtheria, tetanus, and pertussis	Diphtheria, tetanus, and whooping cough	1st booster: 15 months 2nd booster: 4 years
Diphtheria and tetanus	Diphtheria and tetanus	Beginning at 7 years
Human papillomavirus quadrivalent recombinant	Human papillomavirus 6, 11, 16 and 18	9 or 10 years: single dose (boys and girls)
23-valent pneumococcal polysaccharide vaccine	Bacterial meningitis, pneumonia, and sinusitis, among others	Beginning at 5 years for Indigenous peoples. The 2nd dose should be administered 5 years after the 1st dose
Attenuated varicella	Chickenpox	4 years

[a] The oral polio vaccine was removed from the Brazilian Ministry of Health's National Immunization Schedule for children in October 2024.
DTP-HBV-HIB: diphtheria, tetanus, and pertussis/hepatitis B virus/*Haemophilus influenzae* type b.
Source: Brazilian Ministry of Health.[11]

Table 2
Brazilian vaccination campaigns in 2024

Campaign	Target population
Flu	Children aged 6 months to < 6 years; adults aged ≥ 60 years; pregnant women; truck drivers; Indigenous people; people with disabilities; teachers; health care workers; postpartum women; Quilombola communities; homeless individuals; people with chronic non-communicable diseases or other special clinical conditions; port workers; security, rescue and armed forces personnel; public transportation workers
Flu in northern Brazil	In addition to the above mentioned groups, the following were added: young offenders aged 12 to 21 years; prison inmates; prison system employees
COVID-19	Children aged 6 months to < 5 years; people aged ≥ 60 years; people with permanent disabilities; staff and residents of long-term care facilities; immunocompromised individuals; Indigenous people living on and off Indigenous lands; Ribeirinho communities; Quilombola communities; pregnant and postpartum women; health care workers; people with comorbidities; young offenders; homeless individuals
Polio	Children aged < 5 years
School vaccinations	Children and adolescents aged < 15 years

Source: Ministry of Health - National Vaccination Movement .[41]

effort by family health services during the vaccination process.[3-7,15,16]

Anti-vaccine movements are strongly associated with the spread of misinformation, a phenomenon that has intensified with the advent and expansion of social media. A prime example of such misinformation is an article published by British gastroenterologist Andrew Wakefield in The Lancet, which suggested a link between the MMR vaccine and the development of autism in children. However, after serious flaws were identified in the study, including conflicts of interest and data manipulation, the journal itself retracted the publication. As a consequence, Wakefield's medical license was revoked, and the article was officially removed from the journal's archives. Since then, numerous rigorous studies have failed to substantiate the relationship Wakefield described.[3,6,16-18]

Similarly, with the virtual disappearance of many vaccine-preventable diseases, segments of the population have begun to question the benefits of vaccination, including the mistaken perception that the rare adverse effects caused by vaccines are more harmful than the diseases they prevent.[19,20] This distrust was evident in the results of a 2022 survey, which revealed that many Brazilians consider the potential adverse effects a serious health risk, in addition to their suspicion of pharmaceutical companies, believing that they conceal information about the dangers of vaccines.[21] Furthermore, the need for protective measures during the COVID-19 pandemic in 2020 and 2021, such as social distancing and the partial interruption of transportation services, reduced demand for routine basic vaccinations, which helps explain the decrease in vaccination coverage rates during this period.[6,7,22]

Technical factors, such as failures in the production and distribution of vaccines, have also contributed to declining vaccination rates. A 2022 study in *Cadernos de Saúde Pública* highlighted the low availability of vaccines in Brazil, including significant regional inequality.[6,23] In 2023, for example, the Brazilian National Health Surveillance Agency (Anvisa) suspended distribution of the measles, mumps, rubella, and varicella (MMRV) vaccine after detecting changes in its manufacturing process. This interruption

Table 3
Vaccination coverage in Brazil from 2015 to 2024 (percentage)

Immunobiological	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024[a]
BCG	105.08[b]	95.55	97.98	99.72	86.67	77.14	74.97	90.06	81.46	83.92
Hepatitis B (age < 30 days)	90.93	81.75	85.88	88.40	78.57	65.77	67.03	82.73	77.69	86.95
Hepatitis B	97.74	105.19	84.40	88.53	70.77	77.86	71.53	77.24	85.53	85.48
Human rotavirus	95.35	88.98	85.12	91.33	85.40	77.94	71.80	76.60	85.76	84.95
Meningococcal C	98.19	91.68	87.44	88.49	87.41	79.23	72.17	78.63	88.23	97.04
DTP HBV HIB	96.30	89.27	84.24	88.49	70.76	77.86	71.53	77.24	85.51	85.46
Pneumococcus	94.23	95.00	92.15	95.25	89.07	82.04	74.84	81.51	88.40	85.31
Polio	98.29	84.43	84.74	89.54	84.19	76.79	71.04	77.20	86.49	85.31
Polio (4 years)	0.00	0.00	62.26	63.62	68.45	67.58	54.61	67.56	*	*
Yellow fever	46.31	44.59	47.37	59.50	62.41	57.64	58.19	60.67	73.41	76.72
Hepatitis A	97.07	71.58	78.94	82.69	85.02	75.90	67.54	72.99	82.80	84.02
Pneumococcal (1st booster)	88.35	84.10	76.31	81.99	83.47	72.14	66.14	71.54	83.23	87.70
Pneumococcal C (1st booster)	87.85	93.86	78.56	80.22	85.78	75.96	68.01	75.34	86.58	98.14
Polio (1st booster)	84.52	74.36	73.57	72.83	74.62	69.30	60.50	67.71	78.09	83.54
MMR dose 1	96.07	95.41	86.24	92.61	93.12	80.88	74.94	80.70	88.39	91.72
MMR dose 2	79.94	76.71	72.94	76.89	81.55	64.27	53.20	57.64	65.62	77.55
MMRV	77.37	79.04	35.44	33.26	34.24	21.01	6.27	10.43	*	*
DTP	96.90	89.53	84.45	88.70	70.94	77.99	71.59	77.25	85.61	85.52
DTP (booster at 4 and 6 years)	0.00	2.73	66.08	68.52	53.74	73.49	57.99	66.97	*	*
DTP (1st booster)	85.78	64.28	72.40	73.27	57.08	77.21	63.65	67.45	78.11	81.95
Adult diphtheria and tetanus and DTaP for pregnant women	45.57	31.53	34.73	44.99	45.02	22.89	18.97	20.33	75.35	58.51
Chickenpox (varicella)	0.00	0.00	0.00	0.00	0.00	74.43	67.05	73.32	71.03	72.42

BCG: Bacillus Calmette-Guérin; DTaP: acellular DTP vaccine; DTP HBV HIB: diphtheria, tetanus, and pertussis/hepatitis B virus/ Haemophilus influenzae type b; MMR: measles/mumps/rubella; MMRV: MMR+varicella.

[a] Preliminary data, updated on September 15, 2024.

[b] Vaccination coverage above 100% may be related to the use of underestimated population figures, generating higher results than the actual vaccination coverage rates in the evaluated location. The formula for calculating coverage is the number of final doses administered divided by the target population, multiplied by 100.[51]

* Data unavailable from DATASUS.

Source: National Immunization Program Information System (SIPNI – http://sipni.datasus.gov.br).

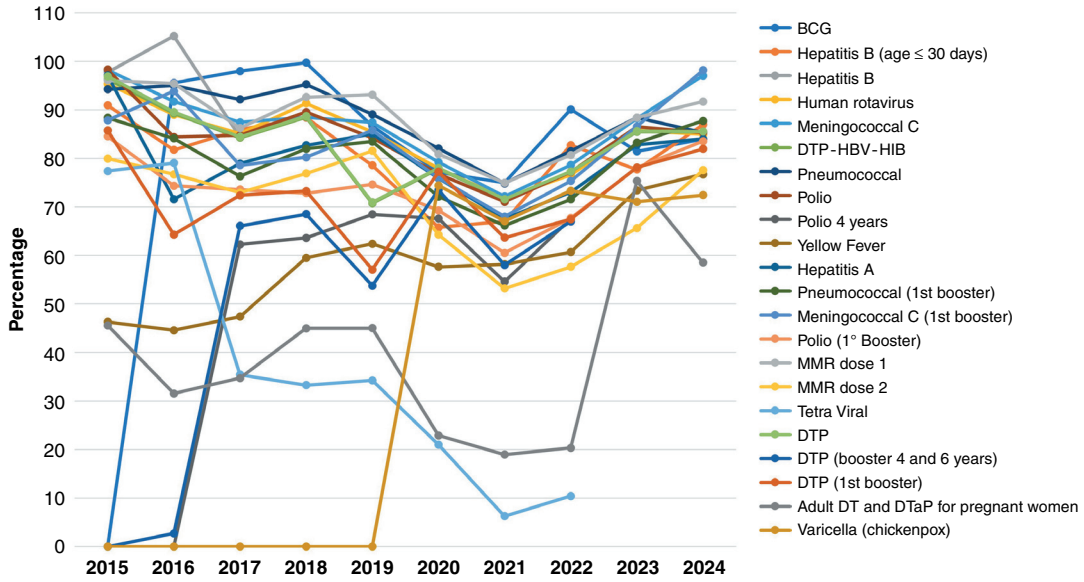

Figure 1

Vaccination coverage in Brazil between 2015 and 2024

BCG: Bacillus Calmette-Guérin; DTP-HBV HIB: diphtheria, tetanus, and pertussis/hepatitis B virus/*Haemophilus influenzae* type b; MMR: measles/mumps/rubella.

Source: National Immunization Program Information System (SIPNI - http://sipni.datasus.gov.br). Preliminary data, updated on Sept. 15, 2024.

could explain the lack of vaccination coverage data for this product in 2023 and 2024 (Table 3). It should also be noted that administration of this vaccine had already been weak in previous years due to distribution irregularities. For example, the state of Alagoas has not received a shipment of this vaccine since 2018.[24,25]

Furthermore, the Family Health Strategy, whose activities include vaccine administration, is directly associated with factors that influence the effectiveness of vaccination coverage, such as health unit infrastructure, geographic location, vaccination room operating hours, and the quality of interpersonal relationships between health professionals and service users.[15,23,26]

Vaccine hesitancy has significantly contributed to the reappearance of diseases previously considered eradicated. A prime example is the resurgence of measles in Brazil in 2018, just two years after the Pan American Health Organization had certified that the virus had been eliminated. Factors that contributed to its return include low measles, mumps, and rubella vaccination coverage in 2017, which only reached 86.24%. This scenario had a greater impact in northern Brazil, especially due to the intense migration of citizens from Venezuela, where a measles outbreak had occurred in 2017.[27,28] In subsequent years, vaccination rates remained below the ideal level: 92.61% in 2018 and 93.12% in 2019. From 2020 onwards, the decline was even sharper due to the COVID-19 pandemic, with rates of 80.88% in 2020 and 74.94% in 2021. Although the vaccination rates recovered slightly in 2022 (80.70%) and 2023 (88.39%), they were still below those of the pre-pandemic period, being insufficient to ensure collective protection.[6,7,22] Figure 2 shows measles vaccination coverage in Brazil between 2015 and 2024.

According to recent data, COVID-19 vaccination coverage in Brazil remains less than ideal, with particularly low adherence in certain age groups. It is estimated that 86.64% of the population received 2 doses of the monovalent vaccine, 56.44% received 3 doses, and only 19.69% completed the 4-dose schedule. There was a significant discrepancy between age groups, especially among children, whose vaccination schedule includes 2 doses administered at 6 and 7 months of age. Coverage was

only 36.5% among children 6 months to 2 years of age and 31.4% among 3- to 4-year olds.[11,29,30]

Among those aged ≥ 5 years, vaccination was recommended exclusively for priority groups, such as pregnant women, postpartum women, immunocompromised individuals, and health care workers, with annual boosters or, in the case of those aged ≥ 60 years, a booster every 6 months. Among children aged 5 to 11 years, 60.7% received 2 doses and 24.1% received a single dose. Among individuals aged 12 to 59 years, 2-dose vaccination coverage ranged from 85% to 92%; 3-dose coverage ranged from 40% to 70%; and 4-dose coverage ranged from 30% to 44% (in the 40- to 59-year age group). The best rates were among older adults: more than 95% received 2 doses, 80% received 3 doses, and 56.2% received 4 doses.[11,29,30]

The renewed risk of polio has led health authorities to issue warnings about low vaccination coverage. Although the disease has been eradicated in the Americas, it is still endemic in some regions of the world, and population mobility increases the possibility of reintroduction into areas where it had previously been eradicated. During the COVID-19 pandemic in Brazil, polio vaccination rates declined significantly (to 76.79% in 2020 and 71.04% in 2021), as shown in Table 3, Figure 1, and Figure 3.[3,31-33] In response, the National Immunization Program announced that the bivalent oral polio vaccine would be replaced with the inactivated polio vaccine by October 2024, in alignment with World Health Organization guidelines. However, this transition is contingent upon maintaining high vaccination coverage with inactivated polio vaccine.[34]

Meanwhile, since 2023 Brazil has seen a significant increase in pertussis (whooping cough) cases, of which the last endemic incidence had occurred in 2014. For example, in the city of São Paulo between January and June 2024, 139 cases of the disease were reported, a 768.7% increase compared to the same period in 2023.[35] This reinforces the fact that, although vaccination is mandatory in Brazil and is freely available through the public health system, adherence has declined alarmingly, which has contributed to the resurgence of preventable diseases, compromising both individual health and collective protection.[26,36] Such a situation also raises bioethical issues, especially the conflict between justice, ie, promoting the common good through universal vaccine provision, and autonomy, ie, ensuring an individual's right to choose.[37]

In this context, aiming to address the factors associated with vaccine rejection, in 2019 the Ministry of Health published a leaflet entitled "Ten Steps to Expand Vaccination Coverage in Primary Care". The following stand out among its guidelines: ensuring that vaccination rooms are in operation at all times during the health unit's opening hours, if not after hours as well; combating the dissemination of false information; and ensuring the supply of vaccines in adequate quantity and quality.[6,38]

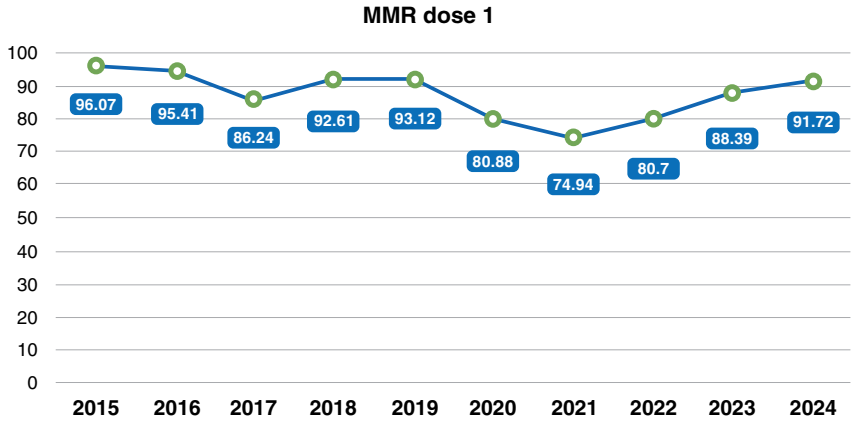

Figure 2
Measles vaccination coverage rate in Brazil between 2015 and 2024 (percentage)
Source: National Immunization Program Information System (SIPNI - http://sipni.datasus.gov.br). Preliminary data, updated on 09/15/2024.

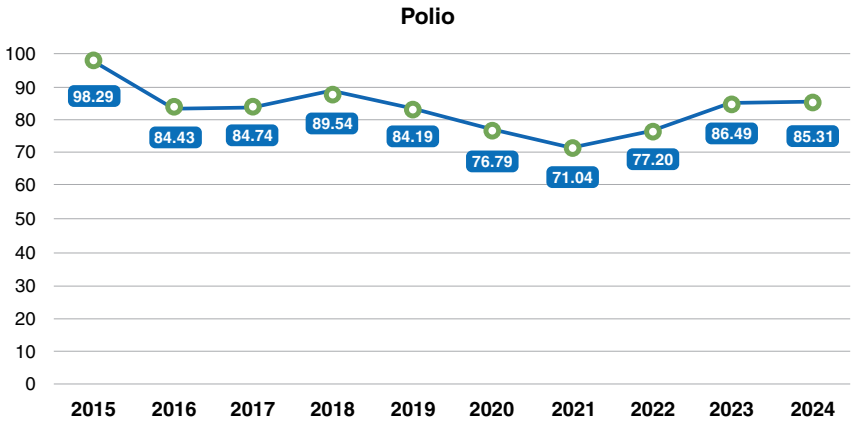

Figure 3
Polio vaccination coverage rate in Brazil between 2015 and 2024 (in percentage)

Source: National Immunization Program Information System (SIPNI - http://sipni.datasus.gov.br). Preliminary data, updated on 09/15/2024.

Additionally, in 2021, through its Institute of Immunobiological Technology (Bio-Manguinhos), Fiocruz launched its High Vaccination Rate Recovery Project, developed in partnership with the Brazilian Immunization Society and the National Immunization Program. The project aims to achieve high and homogeneous levels of vaccination coverage nationwide by 2025.[39] Moreover, in June 2022, the National Health Council began the "Vaccinate More" campaign to expand access to information about immunization through free distribution of communication materials to public establishments.[40] In 2023, the Ministry of Health also established its own national vaccination movement to recover high vaccination coverage rates, including COVID-19 and other vaccines of the national vaccination calendar.[41] As a result of these institutional efforts, vaccination coverage rates increased considerably in 2022 and 2023 (Table 3 and Figure 1). However, the established targets for most vaccines have not been fully met.[42]

The COVID-19 pandemic significantly reduced vaccination coverage rates globally, not just in Brazil. It is estimated that at least 68 countries were affected, compromising the vaccination of approximately 80 million children. During the first 5 months of the pandemic, a number of countries canceled their immunization campaigns, contributing to the resurgence of previously controlled diseases. There were reports of diphtheria cases in Venezuela, Pakistan, Nepal, Bangladesh, and Yemen, as well as cholera outbreaks in Bangladesh, Cameroon, Mozambique, South Sudan, and Yemen. Furthermore, a total of 46 polio vaccination campaigns were postponed in 38 countries, mainly in Africa, resulting in a 2021 outbreak in Niger. Childhood vaccination coverage was significantly reduced in the United States during the same period, decreasing 63% in New York, 40% in California, and 45% in Ohio.[43]

In 2023, global vaccination coverage remained stagnant and below pre-pandemic rates. A complete schedule of the diphtheria, tetanus, and pertussis vaccine, considered one of the main indicators of vaccination performance, was administered to only 108 million children. Meanwhile, the number of unvaccinated children increased from 13.9 million in 2022 to 14.5 million in 2023, and the final dose was not administered in another 6.5 million.[44,45] Measles vaccine coverage was also insufficient, with global rates of 83% for the first dose and 74% for the second dose both below the 95% recommended by the World Health Organization to prevent outbreaks. As a consequence, 103 countries have reported measles outbreaks in the last 5 years.[44,45]

Similar challenges have occurred for COVID-19 vaccination. By December 2023, primary vaccination was complete in only 67% of the world's population, which had only increased modestly (to 70.7%) by August 2024, highlighting the slow pace of global immunization progress.[46] Disparities between countries with different income levels were also evident: those with low gross domestic products had up to 70% lower vaccination coverage than high-income countries.[47] In Peru, for example, there was a direct correlation between vaccination coverage and human development index, reflecting regional inequalities within developing countries.[48]

Unequal vaccine distribution throughout the world has further exacerbated this situation. It is estimated that, in February 2021, 75% of the 191 million administered doses were concentrated in just 10 high-income countries, which together represent only 16% of the world's population.[49,50] To mitigate these disparities, initiatives such as the COVAX consortium were created to promote more equitable vaccine distribution. However, by January 2022, only 61% of the planned doses had actually been delivered.[46]

Thus, vaccination coverage has not declined due to the pandemic alone; it has been decreasing for a number of years. This compromises public health, facilitating the return of previously controlled diseases and risking the reintroduction of serious pathologies that have already been eradicated. Despite government efforts to reverse this decline, current rates remain below recommended levels.

Conclusions

Vaccination is widely recognized as one of the most effective interventions to prevent infectious diseases. Therefore, vaccine hesitancy must be addressed assertively by disseminating empirical evidence, creating educational campaigns, answering the public's questions, and promoting government initiatives to ensure adequate vaccine distribution and access for all citizens.

The imminent return of previously eradicated diseases, such as polio, reinforces the urgent need for stronger public policies to increase vaccination coverage. However, studies assessing the effectiveness of these strategies are also needed to guarantee that established goals are met and that the population is adequately protected.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Epinephrine nasal spray in the treatment of severe type I hypersensitivity reactions

Spray nasal de adrenalina no tratamento de reações alérgicas de tipo I graves

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ABSTRACT

Anaphylaxis is the most severe clinical manifestation of systemic allergic reactions and carries a potential risk of death. Most episodes of anaphylaxis occur outside the hospital setting and, to ensure immediate treatment, alternative epinephrine devices, such as epinephrine autoinjectors, have been developed. However, these devices are not widely available across the world, and there is reluctance to use them, especially among children, who are often needle-phobic. In this context, the development of an epinephrine nasal spray (ENS) represents an interesting alternative for the treatment of anaphylaxis, with favorable results. This study provides a narrative review of ENS in the management of anaphylaxis, addressing its pharmacokinetics, pharmacodynamics, and adverse events across different age groups. Comparative studies between intramuscular and intranasal administration have demonstrated comparable results, supporting the use of ENS as an alternative for the treatment of severe type I hypersensitivity reactions, especially anaphylaxis.

Keywords: Epinephrine, anaphylaxis, adolescent, children, adult.

RESUMO

Anafilaxia é a manifestação clínica mais grave das reações alérgicas sistêmicas e apresenta um risco potencial de morte. A maioria dos episódios de anafilaxia ocorre fora de ambiente hospitalar, e para que haja tratamento imediato, dispositivos alternativos de administração de adrenalina, como os autoinjetores de adrenalina, foram desenvolvidos. Todavia, estes não são disponíveis em boa parte do mundo e há relutância com o seu uso, sobretudo por crianças, geralmente fóbicas por agulha. Assim o desenvolvimento de um *spray* nasal de adrenalina (SNA) representa alternativa interessante no tratamento das anafilaxias, com bons resultados. O presente estudo tem por objetivo realizar revisão narrativa sobre o SNA no tratamento da anafilaxia com relação à sua farmacocinética e farmacodinâmica, assim como os eventos adversos nas diferentes faixas etárias. Estudos comparativos entre a administração de adrenalina intramuscular e por SNA demonstram resultados comparáveis e reforçam a sua utilização como mais uma alternativa para o tratamento de reações alérgicas graves de tipo I, especialmente a anafilaxia.

Descritores: Epinefrina, anafilaxia, adolescente, criança, adulto.

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Introduction

Anaphylaxis is the most severe clinical manifestation of systemic allergic reactions and carries a potential risk of death. International guidelines for the management of anaphylaxis recommend intramuscular (IM) administration of epinephrine (adrenaline) as the first-line treatment, with a well-established safety profile.[1-7]

Despite this, some researchers have recommended alternative routes of administration, many of which contradict current guidelines (Table 1). Epinephrine autoinjectors (EAIs) are an effective, safe, and efficient alternative for treating anaphylaxis, replacing the traditional epinephrine ampule.[1-7]

However, EAIs have significant limitations that may hinder the adequate use of IM epinephrine during anaphylaxis. As a result, innovations involving alternative administration routes may improve treatment use rates and effectiveness. These new devices, which deliver epinephrine via intranasal, sublingual, or transcutaneous routes, are currently in different stages of development and investigation.[8]

In this study, we present a narrative review of the pharmacokinetic (PK), pharmacodynamic (PD), and safety profiles of epinephrine delivered via an epinephrine nasal spray (ENS) in patients experiencing severe type I hypersensitivity reactions, including anaphylaxis. For ethical reasons, double-blind, placebo-controlled studies are not feasible in the treatment of anaphylaxis. Therefore, we reviewed studies published in English, French, Spanish, and German over the past 15 years that evaluated ENS in comparison with injectable products (IM ampules, EAIs). The search terms used were “neffy” OR “epinephrine” OR “anaphylaxis” OR “adrenaline” AND “children” OR “adults.”

EAIs are typically prescribed to individuals at ongoing risk of anaphylaxis in community settings. However, an online survey assessing anaphylaxis management across 66 countries reported that only 60% had access to EAIs, primarily high-income nations.[5] Many countries in South America, Africa/Middle East, and the Asia-Pacific region do not have EAIs available or depend on individual importation. Even in countries where EAIs are commercially available, national policies supporting their availability in public settings are limited, with only 16% of countries permitting such access.[9] Furthermore, because of differences in device design, EAIs are not interchangeable.[10]

Epinephrine is also available as a prefilled syringe (Symjepi), which is FDA-approved but not available in Brazil (Table 1). This option requires individuals

Table 1
Examples of epinephrine delivery devices

Product	Form	Children (15-30 kg)	Adults (>30 kg)
EpiPen	Autoinjector	0.15 mg IM or SC	0.3 mg IM or SC
Amneal*	Autoinjector	0.15 mg IM or SC	0.3 mg IM or SC
AUVI-Q	Autoinjector	0.15 mg IM or SC	0.3 mg IM or SC
Symjepi	Prefilled syringe	0.15 mg IM or SC	0.3 mg IM or SC
Neffy	Nasal spray	1 mg/nostril	2 mg/nostril

IM: intramuscular; SC: subcutaneous.
*Generic product.
Adapted from The Medical Letter on Drugs and Therapeutics.[10,12]

to manually insert the needle and press the plunger, which may be challenging for some, particularly children.[11]

Recently, both the European Medicines Agency (EMA) and the U.S. FDA approved an ENS (*neffy*) as the first noninjectable epinephrine option for the emergency treatment of type I hypersensitivity reactions, including anaphylaxis, in patients aged ≥ 4 years weighing more than 15 kg.[10,12,13]

To whom should preventive epinephrine be prescribed?

Despite significant advances in the management of allergic diseases, important questions remain, as, for obvious ethical reasons, no randomized clinical trials have evaluated the treatment of acute allergic reactions with epinephrine.[14]

Nevertheless, reasonable evidence from observational studies supports the use of epinephrine in the treatment of anaphylaxis. Moreover, large cohort studies indicate that in at least 80% of anaphylaxis episodes, the allergic reaction resolves despite no treatment with epinephrine.[15,16]

According to anaphylaxis guidelines, epinephrine should be prescribed for emergency treatment of a severe exacerbation by the patient/caregiver (particularly via EAI) to any patient with a history of anaphylaxis who cannot easily avoid re-exposure to the causative allergen, especially foods and *Hymenoptera* stings.[1-7,14,17] The guidelines also recommended that EAI be prescribed to patients without prior history of anaphylaxis but with risk factors considered to raise their risk of anaphylaxis, such as a diagnosis of asthma or a prior reaction to trace amounts of allergen.[1-7,14,18]

Although EAIs are commonly prescribed for the immediate treatment of anaphylaxis, fewer than half of patients at risk for severe allergic reactions (including anaphylaxis) carry the products with them, and those who do often delay use during a severe type I hypersensitivity reaction.[19] This delay, often due to needle phobia, can lead to ineffective or late treatment and is associated with significantly increased risks of biphasic reactions, hospitalization, and death.[20-23]

Low utilization rates, especially in the setting of serious adverse outcomes associated with unsuccessful or delayed treatment, represent a significant unmet medical need among patients at risk for severe allergic reactions, including anaphylaxis.[19]

Epinephrine nasal spray

Most severe type I hypersensitivity reactions occur in out-of-hospital settings, and the immediate administration of epinephrine is the only universally recommended first-line treatment.[1-7,19] Needle-free epinephrine delivery options are particularly beneficial for children, among whom needle phobia is especially common. Several medications, including midazolam, diazepam, fentanyl, naloxone, ketamine, and dexmedetomidine, among others, are routinely administered intranasally for a variety of indications.[24]

The ENS consists of 3 key components: (1) epinephrine, the active ingredient; (2) Intravail (dodecylmaltoside), a proprietary absorption-enhancing agent developed to increase the bioavailability of intranasally delivered medications; and (3) a Unit Dose Spray (UDS) device designed to generate an optimal spray pattern and droplet size that maximizes medication delivery to the nasal turbinates.[24]

Epinephrine

Epinephrine is a nonselective agonist of both α- and β-adrenergic receptors, which are all G-protein-coupled. It acts through direct agonism at α- and β-adrenergic receptors, resulting in adenylyl cyclase activation and increased intracellular cyclic adenosine monophosphate production.[25] It stabilizes mast cells by preventing their degranulation and the rapid release of allergic mediators, and directly counteracts nearly all immune mediators of anaphylaxis at end-organs. While anaphylaxis leads to loss of intravascular fluid volume and hypotension, activation of α-adrenergic receptors reduces vasodilation and increases vascular permeability. β-Adrenergic receptors relax bronchial smooth muscle, helping to relieve bronchospasm, wheezing, and dyspnea that may occur during anaphylaxis. Heart rate (HR) and contractility increase via β-adrenergic receptors to maintain blood pressure (BP). In addition, epinephrine can help relax the smooth muscle of the stomach, intestines, uterus, and urinary bladder; improve symptoms such as pruritus, urticaria, and angioedema; and relieve gastrointestinal and genitourinary symptoms associated with anaphylaxis.[25,26]

Intravail

Intravail is a safe alkylsaccharide that alters mucosal viscosity and membrane fluidity to loosen cell-cell junctions, facilitating mucosal absorption.[27] It is soluble in both water and oil and does not cause mucosal irritation or damage.[28]

The combination of epinephrine with Intravail allows greater pharmacologic efficiency while using the lowest effective dose. There are some concerns that the potential vasoconstrictive effect of epinephrine could impair its absorption via nasal spray, but this effect was not observed.[24]

Increased vascular permeability during an allergic reaction could increase epinephrine absorption and increase the risk of overdose. The inclusion of Intravail in the ENS formulation prevents this by enhancing efficacy at lower doses, thereby minimizing the risk of overdose. These factors also contribute to reducing adverse reactions.[24]

Device

Epinephrine is delivered via a UDS device similar to those used in other widely adopted pharmaceutical products. It is easy to use, reliable, and has a very low failure rate (<1 in 100,000 uses). The device delivers 80% of the medication in droplets measuring between 20 and 120 µm, almost all of which are captured on the nasal turbinates.[20]

Pharmacokinetic and pharmacodynamic clinical studies

To date, the conduct of randomized clinical trials to evaluate the efficacy of epinephrine products for the treatment of severe type I hypersensitivity reactions (including anaphylaxis) is considered unethical and impractical; therefore, no such trials have been conducted.[24] Therefore, approval of the ENS was based on multiple clinical trials comparing its PK (mean maximum plasma concentration [C_{max}], time to C_{max} [T_{max}], maximum effect [E_{max}], and time to E_{max} [TE_{max}]) and PD (BP, systolic BP [SBP], diastolic BP [DBP], and HR) with those of approved injectable products. These studies demonstrated that the ENS has a PK profile that is comparable to or better than that of injectable products.[29-32]

An integrated analysis was performed including 4 randomized, crossover trials comparing the PK and PD profiles of manual epinephrine IM injection (0.3 mg), 2 EAIs (EpiPen and Symjepi, both 0.3 mg), and ENS (1 mg) in healthy individuals and individuals with a history of type I allergies (not active) aged 19 to 55 years.[33] It showed that although the ENS resulted in a C_{max} (258 pg/mL) that was lower than but comparable to IM injection (254 pg/mL), Symjepi (438 pg/mL), and EpiPen (503 pg/mL), it led to comparable increases in SBP (E_{max}, 16.9, 10.9, 14.9, and 18.1 mm Hg, respectively). The effect of the ENS on DBP was also markedly more pronounced than that of other products (E_{max}, 9.32, 5.51, 5.78, and 5.93 mm Hg, respectively). According to the authors, the PD profile of the ENS is comparable to that of EpiPen and superior to that of IM injection.[33]

Conversely, Casale et al. conducted a similar study in healthy individuals in which the ENS dose was increased to 2 mg, followed by a repeat dose 10 minutes later. The highest mean epinephrine C_{max} was observed after EpiPen administration (753 pg/mL), and this level remained elevated for 20 minutes, followed by ENS (481 pg/mL) and IM injection (339 pg/mL). [29]

All treatment regimens resulted in an increase from baseline SBP, with the greatest increase occurring after ENS. EpiPen was associated with a faster but less pronounced SBP increase compared with ENS. For all treatments, SBP returned to baseline values within 120 minutes. Mean SBP increase was greater following ENS than IM injection, but not significantly different from EpiPen. Following repeated doses, change from baseline SBP was also greater for ENS compared with EpiPen.[29,30]

Anatomical or structural nasal abnormalities may interfere with the absorption of epinephrine administered via nasal spray. A similar effect might be expected in patients with rhinitis. However, Oppenheimer et al. compared the PD and PK profiles of epinephrine delivered via IM injection and nasal spray in individuals with seasonal allergic rhinitis (SAR), both before and after a nasal allergen challenge. The PD and PK profiles of the ENS were comparable to or better than IM injection, regardless of whether one or two doses were administered, and consistent with findings previously reported in individuals without SAR.[31]

In children and adolescents, PK/PD studies have been conducted with reference to adult data, while reinforcing the presence of age-related differences in these parameters. As children grow, well-recognized physiological increases in BP and HR occur, and

these age-dependent changes must be considered when interpreting PK/PD responses.[25,32,33]

Fleisher et al. conducted a phase 1, multicenter, single-dose PK/PD study of 42 pediatric patients (aged 4-18 years) who were dosed with 1 mg (for body weight 15-30 kg) or 2 mg (for body weight > 30 kg) of ENS. The results were compared with those from 42 healthy adults (aged 22-54 years) who received a single 2-mg dose.[28]

Among pediatric participants who received 1 mg, the mean C_{max} was slightly lower than that of those who received 2 mg (651 vs. 690 pg/mL), and both values were higher than those observed in adults (481 pg/mL).

Both ENS doses resulted in an overall mean increase from baseline SBP; however, transient decreases in DBP were also observed, occurring at 5 minutes for the 1 mg dose and at 10 minutes for the 2 mg dose. No differences were observed between the 2 pediatric doses in terms of HR elevation or mean SBP and DBP values. Adults experienced significantly greater increases in SBP than children, while DBP differences were minimal. HR changes were similar between both children and adults.[28] These increases occur due to activation of adrenergic receptors, which is the main mechanism of action through which epinephrine reverses severe allergic reactions and anaphylaxis.[33] Interestingly, despite the higher epinephrine C_{max} observed in children and adolescents, the maximal increase in mean SBP was significantly lower than that seen in adults. Could this difference be the result of age-related physiological variations?[28] Unlike adults, children demonstrated an initial decrease from baseline DBP with both ENS doses (1 mg and 2 mg), in an age-dependent pattern.[28] This decrease is presumed to result from activation of high-affinity β2-adrenergic receptors, resulting in transient vasodilation. β2-mediated vasodilation subsequently reduces venous return, followed by a decrease in cardiac output, which can potentially lower both SBP and DBP.[29,33] Redistribution of blood flow continues until epinephrine levels rise sufficiently to activate lower-affinity α-adrenergic receptors, resulting in a plasma concentration-dependent shift from vasodilation to vasoconstriction.[34-37]

The relatively high vascular elasticity in children likely makes them more sensitive to this transient β2-mediated vasodilation and the associated transitory decrease in DBP. This effect tends to be more pronounced and to occur earlier with higher ENS doses, and it may also be reflected in SBP changes.[34,36]

Regarding changes in HR, although children showed higher epinephrine concentrations, their HR responses were comparable to those observed in adults. These physiological differences are also likely age-related. Two mechanisms help explain this: (a) a decrease in chronotropic responses to β1-adrenergic stimulation with age, with downregulation and reduced agonist binding of β1-receptors,[35] resulting in a less pronounced HR response in older adults; and (b) reduced baroreflex sensitivity with age,[35] leading to decreased HR modulation (less decrease in HR) in response to rapid increases in BP. Together, the reduced response to β1-adrenergic stimulation and the decreased HR regulation due to a less sensitive baroreflex may minimize differences in cardiac responses to epinephrine in older individuals,[37] resulting in HR responses similar to those observed in pediatric patients, whose HR was reduced by a more sensitive baroreflex with higher epinephrine concentrations.

Hypotension is frequently associated with severe allergic reactions. Therefore, it is important to evaluate how this condition might affect the absorption of intranasally administered epinephrine.[38] A study in anesthetized beagle dogs, assessed under both normal conditions and hypotension associated with anaphylaxis, investigated this question. After being dosed with 1 mg of ENS, the dogs demonstrated significantly higher mean C_{max} of epinephrine during anaphylaxis than under normal conditions (2670 ± 2150 pg/mL vs. 1330 ± 739 pg/mL, $p < 0.05$). The same occurred with the area under the curve (0 to 45 minutes). These findings demonstrate that epinephrine absorption was not impaired by anaphylaxis-associated hypotension.[38]

Overall, when administered to children and adolescents, the ENS demonstrated absorption comparable to or greater than that observed in adults, with increases in SBP and HR consistent with activation of relevant adrenergic receptors at pediatric doses. Regarding DBP, differences in patient responses are largely attributable to normal age-related physiological differences rather than to epinephrine's pharmacologic effect. When compared with data from more than 700 adults, pediatric doses of the ENS performed as expected.[28]

Safety

Epinephrine is the first-line treatment for anaphylaxis and is associated with a well-established safety profile. Effective resolution of anaphylaxis symptoms depends largely on its immediate administration by the patient/caregiver. However, the potential for overdose and serious cardiac adverse effects exists with any route of administration, although this risk is lower with IM injection compared with intravenous administration.[39]

Epinephrine should be administered with caution in pregnant women, older adults, and patients with underlying heart disease or those taking cardiac glycosides, diuretics, or antiarrhythmics, as it may worsen angina or precipitate ventricular arrhythmias (including fatal ventricular fibrillation). Individuals taking antidepressants or those with thyroid disorders, diabetes, or hypertension may be at increased risk for adverse reactions. Epinephrine may temporarily exacerbate underlying conditions and/or worsen symptoms in patients with hyperthyroidism, Parkinson's disease, diabetes, and renal insufficiency.[6,8]

Although the ENS contains metabisulfite in its formulation, this should not preclude its use in patients with sulfite sensitivity.[6,8] Mucosal changes may persist for up to 2 weeks following ENS use and may potentially increase the systemic absorption of medications applied intranasally, including epinephrine itself.[6,8]

The ENS is supplied as a single-dose (1 mg or 2 mg) spray to be administered as follows: 1 mg for children aged ≥ 4 years weighing 15-30 kg; and 2 mg for patients weighing ≥ 30 kg.[6,8] The recommended regimen is one spray administered into one nostril. If symptoms do not improve after 5 minutes, a second dose may be applied to the same nostril using a new nasal spray.[6,8]

Correct use of the device is essential, even by untrained individuals relying solely on written instructions. Hernandez-Trujillo et al. conducted a human factor study of ENS in adults, juveniles, caregivers, and patients. All participants were able to carry the case containing 2 devices, open it during a simulated allergic emergency, and successfully administer the product both once and twice (10 minutes apart) in the same nostril.[9]

Adverse events occur in approximately 7%-19% of cases and are generally mild. Common reactions include nasal discomfort, headache, rhinorrhea, dizziness, nausea, vomiting, throat irritation or dryness, paresthesia, sneezing, upper airway congestion, epistaxis, nasal dryness, fatigue, and nervousness.[6,8]

Fleischer et al. reported adverse events in 52.4% of patients who received ENS 1 mg and 66.7% of those who received 2 mg. In the 1 mg group, the most common events were nasal congestion (19%), upper respiratory tract congestion (14.3%), dry throat, nasal dryness, and paresthesia (9.5%). In the 2 mg group, the most common were nasal discomfort, rhinorrhea, and intranasal paresthesia (19%), sneezing (14.3%), rhinalgia, epistaxis, paresthesia, fatigue, and feeling jittery (9.5%). No gastrointestinal adverse events (nausea or vomiting) were reported. Most events were mild and resolved quickly. No serious adverse reactions or study withdrawals occurred.[28]

According to the manufacturer, the ENS should be stored at room temperature, with excursions permitted up to 50 °C. At temperatures below –15 °C, the solution freezes and the device fails to release epinephrine. The shelf-life of the ENS (*neffy*) is 30 months, longer than that of injectable products, which typically have a shelf-life of 12 to 18 months.[6,8]

Conclusion

To date, PK and PD studies of ENS have demonstrated clinical efficacy comparable to IM epinephrine (ampule or EAI) in both adults and children.[31,40] The ENS represents an innovative and promising alternative, particularly for patients who face barriers to using injectable devices.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Original Article

Analysis of polio vaccination coverage in the context of the anti-vaccine movement and the onset of the COVID-19 pandemic in the municipality of Piracicaba compared to Brazil

Análise da cobertura vacinal contra poliomielite no contexto do movimento antivacina e do início da pandemia de COVID-19, no município de Piracicaba em comparação com o Brasil

Beatriz Caroline Câmara[1], Talita Bonato de Almeida[1]

ABSTRACT

Introduction: The Brazilian National Immunization Program is one of the most important preventive tools within the Brazilian Unified Health System. Poliomyelitis is a notifiable disease that was eliminated in Brazil through vaccination efforts that began in 1961, with the country being certified, in 1994, as wild poliovirus-free. However, the emergence and rise of the anti-vaccine movement in the country, combined with periods of governments adopting neoliberal policies that restricted health expenditures, pose a threat to vaccination coverage nationwide. **Objective:** The aim of this article was to compare polio vaccination data from Piracicaba with national data and to discuss the possible impacts of the anti-vaccine movement, misinformation (fake news), and the COVID-19 pandemic on local and national vaccination coverage. Methods: We conducted a retrospective longitudinal study through the analysis of secondary data on vaccination coverage in the city of Piracicaba, state of São Paulo, and Brazil between 2017 and 2022, obtained from the databases of the Regional Health Department of Piracicaba, the Information Technology Department of the Brazilian Unified Health System, and DATASUS. **Results:** Between 2017 and 2020, the Piracicaba region reported 3 suspected (but unconfirmed) cases of poliomyelitis and vaccination coverage ranging from 91.19% to 103.46% between 2017 and 2021. In contrast, southeastern Brazil recorded coverage rates between 73.11% and 90.04% during the same period. **Discussion:** Beginning in 2024, the Brazilian Ministry of Health gradually replaced the oral polio vaccine with the

RESUMO

Introdução: O Programa Nacional de Imunizações é uma das ferramentas de maior impacto no setor preventivo da medicina integrativa do Sistema Único de Saúde. A poliomielite é um dos componentes da lista de doenças de notificação compulsória, a qual foi extinta no Brasil devido à vacinação iniciada em 1961, obtendo em 1994 o certificado de área livre de circulação do vírus selvagem. Porém, o surgimento e crescimento do movimento antivacina no país, associado a um período de governos de políticas neoliberais com controle de gastos da área da saúde, mostram-se uma ameaça à cobertura vacinal em território nacional. **Objetivo:** Comparar dados vacinais da poliomielite de Piracicaba, SP, com os nacionais e discutir os possíveis impactos do movimento antivacina, das *fake news* e da pandemia de COVID-19 na cobertura vacinal local e federal. **Métodos:** Estudo longitudinal retrospectivo realizado por meio da análise de dados secundários de cobertura vacinal do município de Piracicaba, SP, e do Brasil entre os anos de 2017 a 2022 obtidos nas bases de dados do Departamento Regional de Saúde de Piracicaba, Departamento de Informática do Sistema Único de Saúde do Brasil e DATASUS. **Resultados:** A região de Piracicaba registrou entre 2017 e 2020, 3 casos notificados (mas não confirmados) de poliomielite e uma cobertura vacinal variando entre 91,19 e 103,46% entre os anos de 2017 e 2021; enquanto o Sudeste do Brasil registrou uma variação entre 73,11 e 90,04%, nesse mesmo período. **Discussão:** A partir de 2024, o Ministério da Saúde substituiu gradualmente a Vacina Oral Poliomielite pela versão inativada do imunizante,

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inactivated polio vaccine, based on new scientific evidence. These changes aimed to improve the effectiveness of the immunization schedule in light of epidemiological evidence. **Conclusion:** The influence and consequences of persistent misinformation against vaccination can be observed in both the pre- and post-COVID-19 pandemic periods.

Keywords: Poliomyelitis, anti-vaccination movement, COVID-19, vaccination coverage.

considerando novas evidências científicas. O objetivo dessas mudanças visa melhorar a eficácia do esquema vacinal frente aos índicios epidemiológicos. **Conclusão:** É possível perceber a interferência e as consequências das *fake news* persistentes contra a vacinação no período pré e pós-pandemia de COVID-19.

Descritores: Poliomielite, movimento contra vacinação, COVID-19, cobertura vacinal.

Introduction

One of the requirements of primary health care is comprehensiveness, which is also one of the directives of the Brazilian Unified Health System (SUS).[1] Its premise is ensuring the provision of comprehensive health care to all individuals, in alignment with the current World Health Organization (WHO) definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." This enables SUS to ensure full treatment for patients in all their human complexity, more than just their biology, not reducing them to an isolated complaint.[2] In addition, comprehensiveness expands in the chronology of disease trajectory, encompassing prevention at all levels of care.[3]

The Brazilian National Immunization Program is one of the most important preventive tools within the SUS, coordinating and organizing national vaccination policy in its entirety, from immunization campaigns to vaccine cold chain management and adverse event reporting.[4] The program operates in conjunction with the Brazilian Ministry of Health, as well as state and local health departments, overseeing the logistics of procurement and distribution of immunobiologicals as well as the collection of all immunization-related data.[5] This data collection process is conducted through the National Immunization Program Information System, which includes doses administered and missed, movement of immunobiologicals, and adverse event reports.[4] This gives Brazil a highly interconnected health system with access to information from across the country, since it integrates the different municipal health systems.

This preventive framework includes notifiable diseases, defined as conditions that may pose risks to public health, such as diseases with the potential to cause outbreaks or epidemics, illnesses or conditions of unknown cause, or diseases that lead to changes in the usual clinical-epidemiological pattern of known diseases, taking into account their potential for dissemination, magnitude, severity, prevalence, and vulnerability in the population. Mandatory reporting of these diseases to health authorities is required whenever a suspected or confirmed case, condition, or public health event is identified. This reporting is conducted through the Information System for Notifiable Diseases (Sinan), which compiles all notifications, performs dynamic analyses of the occurrence of a given event in the observed population, and generates data for the development of its epidemiological profile. These data further inform the establishment of intervention priorities and the evaluation of their impact. Thus, its systematic and decentralized use contributes to the democratization of information, allowing all health care professionals to access and share data with the broader community.[6]

Poliomyelitis is a notifiable disease. It is a highly contagious disease caused by wild poliovirus, which destroys parts of the nervous system leading to permanent limb paralysis.[7] Both children and adults can be infected, and transmission occurs through direct contact with the feces or oral secretions of infected individuals, making basic sanitation, housing conditions, and personal hygiene key factors in the spread of the virus. In general, symptoms include fever, malaise, headache, sore throat, body pain, vomiting, diarrhea, constipation, muscle spasms, neck stiffness, and in some cases, meningitis. In severe forms, it can cause flaccid paralysis, typically affecting one of the lower limbs, representing one of the main sequelae of poliomyelitis. There is no specific treatment for poliomyelitis; hospitalization and symptomatic management are recommended for all affected individuals.

Vaccination remains the most effective strategy to prevent poliomyelitis. The immunization schedule

consists of 3 doses of the inactivated poliovirus vaccine (IPV; types 1, 2, and 3) administered at 2, 4, and 6 months of age, followed by a booster dose at 15 months.[8] With the introduction of polio vaccination in the 1950s, many countries have drastically reduced, or even completely interrupted, disease transmission,[9] as was the case in Brazil, where the last confirmed case was reported in 1989. The Americas were declared polio-free in the 1990s.[10]

However, the emergence and rise of the anti-vaccine movement in Brazil, coupled with neoliberal policy agendas that restricted public health expenditures and reduced federal investment in health care,[11] pose a threat to polio vaccination coverage nationwide. In addition to substantially reducing investment in the SUS and, consequently, in the National Immunization Program,[10] these administrations also created space for the proliferation of fake news about vaccines. Although the anti-vaccination movement has a centuries-long history, it has evolved and persisted over time. Records date back to 18th-century England, when Reverend Edmund Massey described vaccines as "diabolical operations," and branded the practice of inoculation as sinful. In the 19th century, the National Anti-Vaccination League was established in London in strong opposition to compulsory vaccination on the grounds of personal liberty. In the 20th century, the movement gained further momentum following the publication of an article in The Lancet by former British physician and researcher Andrew Wakefield, which suggested an association between the measles, mumps, and rubella (MMR) vaccine and the onset of autism in young children.[12] Brazil has not escaped this long and persistent global history unscathed, experiencing a decline in overall vaccination coverage beginning in 2015. Following a nationwide mobilization effort in 2018, Brazil briefly regained protective immunization levels, but this progress was short-lived. In 2019, vaccination coverage declined sharply once again, and the situation worsened with the onset of the COVID-19 pandemic,[10] a period marked by widespread dissemination of vaccine-related misinformation, amplified even by statements from the country's then president, which contributed to legitimizing vaccine hesitancy.[13]

Given this context, the collection, quantification, and comparison of vaccination data from before and during the pandemic are essential for planning strategies and coordinated actions across all levels of government in order to restore previous levels of vaccination coverage.

Therefore, the aim of this study was to compare polio vaccination data from Piracicaba, São Paulo, with national data and to discuss the potential impacts of the anti-vaccine movement, misinformation (fake news), and the COVID-19 pandemic on both local and national vaccination coverage.

Methods

This retrospective longitudinal study analyzed secondary data on vaccination coverage in the city of Piracicaba, state of São Paulo, and in Brazil as a whole between 2017 and 2022. Data were obtained from the databases of SUS Regional Health Department of Piracicaba and the SUS Information Technology Department (DATASUS).

Data extracted from these databases included vaccination coverage rates, the completion of the vaccination schedule, region, and the number of reported poliomyelitis cases, when available.

From the Regional Health Department of Piracicaba, information was obtained from an Excel spreadsheet titled "DADOS_BOLETIMSE1A52_2021.xlsx." The "Casos Pólio" tab utilizes the Brazilian Institute of Geography and Statistics (IBGE) codes 352690 and 353870, both referring to the municipality of Piracicaba; the first corresponds to notifications made in the city of Limeira, the second to notifications in Piracicaba itself. The spreadsheet also includes the number of reported cases for the years 2019, 2020, 2021, and 2022.

In the "Cobertura Vacinal Polio" tab, the IBGE code 353870 was used, corresponding to the same municipality and to polio vaccination coverage with the oral poliovirus vaccines 1 and 3 (OPVb) and IPV types 1, 2, and 3 in children under 2 years of age who had completed the full vaccination schedule (3 doses plus 1 booster) between 2017 and 2021. These correspond to the data extracted on March 9, 2022, while those for 2020 and 2021 are marked as "subject to change."

Polio vaccination coverage in Piracicaba was analyzed starting from 2017 to provide a benchmark preceding 2019 and the onset of the COVID-19 pandemic, both moments associated with intense dissemination of misinformation about vaccination.

From DATASUS, within the "Assistência à Saúde" ("Health Care") tab, the "Imunizações — desde 1994 — Cobetura" ("Immunizations — since 1994 — Coverage") path was selected. The following parameters were applied: Linha: Ano; Coluna: Região;

Medidas: Imuno - Poliomielite, poliomielite 4 anos, and poliomielite (1° reforço); Períodos disponíveis: De 2010 a 2022; Seleção disponível: Nenhuma seleção; Gráfico: Coluna (Row: Year; Column: Region; Measures: Immunization – Poliomyelitis, poliomyelitis (age 4), and poliomyelitis [1st booster]; Available periods: 2010 to 2022; Selection: None; Graph type: Column chart).

The period from 2017 to 2022 was chosen to assess the impact of the growing anti-vaccination movement in Brazil, which, as discussed in the Introduction, began to have a significant influence around 2014–2015.

Results

The data collected from the Regional Health Department of Piracicaba are shown in Table 1. The incidence by reported case in the municipalities of Piracicaba and Limeira was low, totaling 3 cases over a 6-year period. Although reported, these cases were investigated and categorized as acute flaccid paralysis, not as poliomyelitis caused by wild poliovirus.

Table 2 presents data collected from IBGE, under code 353870, showing variations in vaccination coverage in Piracicaba over the study period. Decreases were observed in 2017, 2019, and 2021, with the lowest coverage rate in the most recent of these 3 years.

Table 1
Reported poliomyelitis cases in the municipality of Piracicaba, São Paulo, between 2017 and 2022

IBGE code	Reporting GVE	Reporting municipality	Number of reported cases					
			2017	2018	2019	2020	2021	2022
352690	Piracicaba	Limeira			1	1		
353870	Piracicaba	Piracicaba			1			

GVE: Grupo de Vigilância Epidemiológica (Epidemiological Surveillance Group).
Source: Regional Health Department of Piracicaba, São Paulo.

Tabela 2
Polio vaccination coverage (oral poliovirus vaccine types 1 and 3 [attenuated] [OPVb] and inactivated poliovirus vaccine types 1, 2, and 3 [IPV]) in the municipality of Piracicaba, São Paulo, between 2017 and 2021, in percentage

IBGE code	City	2017	2018	2019	2020[a]	2021[a]
353870	Piracicaba	93.75	103.46[b]	95.55	98.87	91.19

[a] Data subject to changes.
[b] The target population for vaccination is estimated annually, and the vaccination target is set at 95%. However, population mobility, especially in tourist cities such as Piracicaba, can affect the accuracy of these estimates, sometimes exceeding 100%, as seen in this case.
Source: IBGE.

From DATASUS, using the parameters described in the Methods section, the study collected the data shown in Figure 1 and Table 3, indicating that Brazil's overall vaccination coverage, including all states, declined progressively over the years until 2021, and began increasing again in 2022.

Discussion

The data presented in this study indicate that polio vaccination coverage in Brazil remained steady, with only minor fluctuations between 2010 and 2015. However, beginning in 2016, a gradual decline in coverage was observed, coinciding with periods of greater dissemination of misinformation about vaccines and health more broadly, as well as the onset and peak of the COVID-19 pandemic.

According to the WHO, the pandemic was accompanied by a wave of excess information, not always accurate, making it increasingly difficult to identify reliable sources and trustworthy guidance. This vulnerable environment was also characterized by the widespread dissemination of fake news and misinformation,[14] fostering fear and vaccine hesitancy in the population.[15] Additional factors contributing to the decline in vaccination coverage during this period included limited access to vaccination services during lockdowns,[16] logistical challenges in vaccine production, transportation, and distribution across the country,[17] and the psychological impact of the pandemic, which led many individuals to deprioritize vaccination.[18]

These events were associated with disruptions in a long-standing pattern of vaccination coverage that had served for years as a global benchmark. This trend is especially evident at the regional and municipal level, as observed in Piracicaba, a municipality located in one of Brazil's most economically developed regions, characterized by highest levels of investment in health, technology, infrastructure, and sanitation. Despite these favorable conditions, suspected poliomyelitis cases were reported in 2019 and 2020, and vaccination coverage reached 91.19% in 2021; while high, this rate is still considered insufficient for population-level protection. Polio vaccination coverage data from 2023 and January–September 2024 show a continued downward trend, with alarming rates of 86.48% and 86.95%, respectively.

The reemergence of a dangerous disease once eradicated at the national level, accompanied by new cases and even deaths, underscores the paradox of a modern era defined by unprecedented access to scientific and public health knowledge, yet undermined by a barrage of exaggerations and the proliferation of fake news.

In 2024, the Brazilian Ministry of Health initiated the gradual replacement of the OPV with the IPV, in line with emerging scientific evidence. This change

Table 3
Polio vaccination coverage (oral poliovirus vaccine types 1 and 3 [attenuated] [OPVb] and inactivated poliovirus vaccine types 1, 2, and 3 [IPV]) by Brazilian region over 6 years, in absolute numbers (data updated as of June 29, 2023)

Region	2017	2018	2019	2020	2021	2022	Total
Total	84.74	89.54	84.19	76.79	71.04	77.20	80.64
North Region	75.67	77.06	79.59	65.69	62.29	71.23	71.92
Northeast Region	81.92	90.04	82.73	73.11	68.53	78.50	79.13
Southeast Region	87.56	92.66	84.54	78.28	71.53	75.14	81.77
South Region	89.82	89.91	89.04	86.50	79.98	83.10	86.44
Central-West Region	84.44	88.59	85.40	80.47	74.22	80.50	82.26

Source: DATASUS.

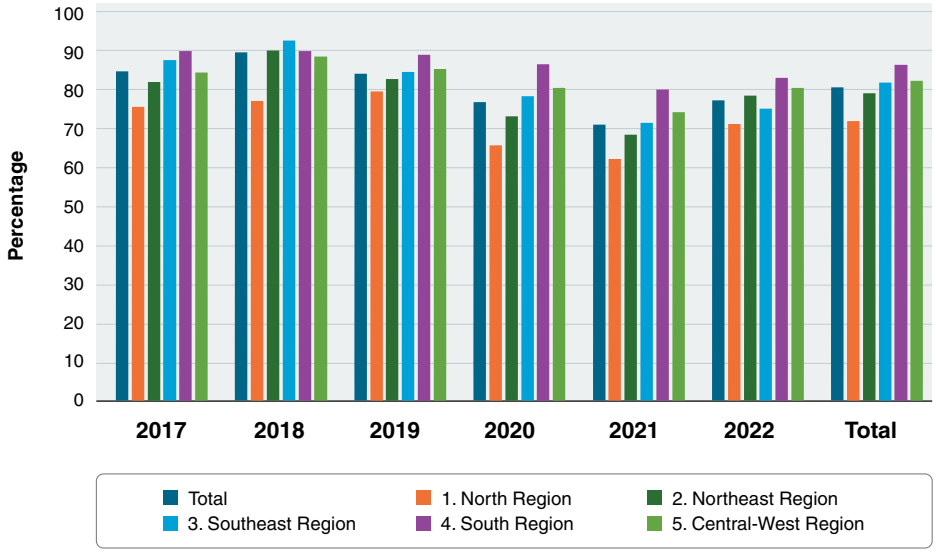

Figure 1
Polio vaccination coverage by Brazilian region over 6 years (data updated on 06/29/2023)
Source: DATASUS.

was discussed in a meeting of the Technical Advisory Committee on Immunization, which brought together representatives from all regions of Brazil with the goal of restoring national vaccination coverage to high levels.[19] Since the first half of 2024, Brazil has adopted IPV exclusively for the booster dose administered at 15 months of age, replacing the oral formulation. Injectable IPV is already part of the national vaccination schedule at 2, 4, and 6 months of age. The booster dose currently administered at 4 years of age will be discontinued, as the 4-dose schedule ensures full protection against poliomyelitis.[19]

Although the OPV has been extremely effective in controlling poliomyelitis for decades, the evolution of vaccination strategies recommended by the WHO[20] and concerns related to safety and maintenance of disease eradication[21] have justified the Brazilian Ministry of Health's decision to adopt IPV as the primary vaccine in the country.

Conclusion

A clear association emerges between the infodemic and the dissemination of misinformation, particularly through the spread of fake news during the pre- and post-pandemic periods, and the decline in vaccination coverage, particularly for diseases previously eradicated in Brazil, such as poliomyelitis. Consequently, this has increased the population's vulnerability to preventable diseases.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Allergic fungal rhinosinusitis – case series and literature review

Rinossinusite fúngica alérgica – série de casos e revisão da literatura

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ABSTRACT

Allergic fungal rhinosinusitis is a noninvasive subtype of chronic rhinosinusitis with nasal polyps associated with type 2 inflammation. It is characterized by immunoglobulin E-mediated fungal sensitization, the presence of allergic mucin, and typical computed tomography and magnetic resonance imaging findings in paranasal sinuses. Diagnosis is classically established using the Bent & Kuhn criteria; however, recent studies have indicated a lack of specificity for some of the major criteria. Treatment almost always requires surgery, and adjunctive therapy mainly consists of oral and/or topical corticosteroids. Omalizumab, dupilumab, and mepolizumab are currently approved for the treatment of chronic rhinosinusitis with nasal polyps in general, but clinical trials with these biologics have not included patients with allergic fungal rhinosinusitis. Here, we describe the main characteristics of patients diagnosed with allergic fungal rhinosinusitis treated in a university hospital, along with a literature review of published data.

Keywords: Sinusitis, allergic fungal sinusitis, respiratory hypersensitivity, biological products.

RESUMO

A rinossinusite fúngica alérgica é um subtipo não invasivo de rinossinusite crônica com pólipos nasais com inflamação do tipo 2. É caracterizada por sensibilização a fungos IgE mediada, mucina alérgica e achados característicos de tomografia computadorizada e ressonância magnética nos seios paranasais. O diagnóstico é classicamente feito usando os critérios de Bent & Kuhn. No entanto, estudos recentes indicaram a falta de especificidade de alguns critérios importantes. O tratamento na maioria das vezes é cirúrgico, e a terapia adjuvante consiste principalmente no uso de esteroides orais e/ou tópicos. O omalizumabe, dupilumabe e mepolizumabe estão atualmente aprovados para o tratamento da rinossinusite crônica com pólipos nasais em geral, mas os ensaios clínicos até o momento com esses produtos biológicos não envolveram pacientes com rinossinusite fúngica alérgica. Descrevemos as principais características dos pacientes diagnosticados com rinossinusite fúngica alérgica de um hospital universitário e revisamos os dados atuais da literatura sobre o tema.

Descritores: Sinusite, sinusite fúngica alérgica, hipersensibilidade respiratória, produtos biológicos.

Introduction

Allergic fungal rhinosinusitis (AFRS) is a noninvasive subtype of chronic rhinosinusitis with nasal polyps (CRSwNP) that typically develops in immunocompetent atopic individuals.[1,2] It is characterized by antifungal immunoglobulin E (IgE) sensitivity, eosinophil-rich mucus (allergic mucin), and characteristic findings on computed tomography (CT) and magnetic resonance imaging (MRI) of the paranasal sinuses.[2] AFRS occurs predominantly in geographic regions with warm and humid climates, which favor a higher environmental

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fungal burden.[1,3] The molecular pathways and immune responses in the pathophysiology of AFRS are still being elucidated. Dysfunction of the epithelial barrier and the presence of fungi within the sinus cavities can upregulate type 2 immune responses, leading to type I hypersensitivity, eosinophilic inflammation, and type 2 cytokine production.[1,4,5] The first description of AFRS as a distinct clinical entity was published in 1976 by Safirstein, who reported the case of a 24-year-old patient presenting with recurrent nasal obstruction, nasal polyps, thick secretions within the nose, and sinus cultures positive for *Aspergillus* species.[6] Since then, this condition has been increasingly investigated, and several studies are published annually to better understand its mechanisms. Diagnosis is based on the criteria defined by Bent and Kuhn.[7] Treatment of AFRS almost always requires surgical debridement of the affected sinuses combined with topical and oral corticosteroids, which reduce postoperative recurrence.[5,6,8] Biologic agents appear to be a promising option; however, more studies are required.[1,3-5,8,9] The objective of this study was to describe the main clinical characteristics of patients diagnosed with AFRS and followed in the chronic rhinosinusitis (CRS) outpatient clinics of the Immunology and Otorhinolaryngology Services of the Hospital Universitário Clementino Fraga Filho (HUCFF-UFRJ), in Rio de Janeiro, Brazil, and to review the current literature to support a better understanding of this condition.

Methods

A retrospective cross-sectional study was conducted based on a review of the medical records of patients with AFRS. Demographic characteristics, comorbidities, and laboratory findings were described, in addition to a review of the current literature on AFRS.

Results

A total of 5 patients with AFRS were included, 3 men and 2 women. The median age was 44 years (range, 12-54 years). Associated comorbidities included allergic rhinitis (n=2), arterial hypertension (n=2), type 2 diabetes (n=2), asthma (n=1), thyroid nodule (n=1), obesity (n=1), and gastroesophageal reflux disease (n=1). Mean total serum IgE level was 1419.5 IU/mL. All patients demonstrated sensitization to at least one fungus: *A. fumigatus* (n=4), *C. albicans* (n=3), *C. herbarum* (n=3), and *P. notatum* (n=1). Sensitization to other aeroallergens was also observed: *B. tropicalis* (n=3), *D. pteronyssinus* (n=3), *D. farinae* (n=3), and staphylococcal enterotoxins (n=2). The most common CT findings were expansile changes with thinning of bony structures. Regarding fungal cultures, only 2 patients had positive results, with *Aspergillus sp.* and *Curvularia sp.* identified. In 1 patient, direct mycological examination revealed numerous hyaline, septate, and branched hyphae and round, pigmented conidia (Table 1).

Review of the literature

The incidence of AFRS appears to be influenced by geographic factors, as most reported cases occur in regions with temperate climates and relatively high humidity.[1,3] Studies have shown that AFRS primarily affects men between 21 and 33 years of age, an age range significantly younger than that observed in patients with CRS without nasal polyps and CRSwNP.[10,11] The incidence of AFRS has been estimated to range from 1.3% to 10% of all patients with CRS undergoing surgery.[5,12] The most commonly affected sinuses include the ethmoid sinuses (71%-92%), maxillary sinuses (7%-76%), sphenoid sinuses (58%-86%), and frontal sinuses (29%-65%).[3] The most common fungi involved are dematiaceous fungi (*Bipolaris*, *Curvularia*, and *Exserohilum*) and *Aspergillus*, a hyaline mold.[13]

In this study, we identified several comorbidities, including allergic rhinitis and asthma. Previous reports indicate that up to 24% of patients with AFRS also have asthma.[4]

AFRS has a complex and not yet fully defined pathogenesis. The most established mechanism is an exaggerated type 2 inflammatory response. Additional contributing factors include bacterial colonization and superantigen expression, the direct effects of pathogenic fungi, and epithelial barrier dysfunction.[2,4,5] Activation of T helper 2 (Th2) cells leads to the release of interleukin (IL)-4, IL-5, and IL-13, which promote B-cell differentiation, IgE production, mast cell degranulation, and eosinophilia, resulting in elevated IgE, eosinophilic mucin, and fungal hypersensitivity.[2,4] *Staphylococcus aureus* is a common colonizer of the nasal cavities and has been shown to coexist with fungi within eosinophilic mucin in patients. With superantigen expression, *S. aureus* can amplify fungal-induced Th2 activation, contributing to the elevated total serum IgE levels characteristic of AFRS.[4,14] Environmental exposure

to fungal spores can facilitate their germination into immunogenic fungal hyphae within the sinus cavities, leading to epithelial barrier cell dysfunction and the release of epithelial-derived cytokines IL-25, IL-33, and thymic stromal lymphopoietin.[4,5,15] This triggers compensatory overstimulation of the type 2 immune response, with the ensuing inflammatory cascade driving eosinophilia, nasal polyposis, and mucus production. Mucosal swelling and mucin can trap additional fungal material, perpetually stimulating the dysfunctional response in a vicious cycle that clinically manifests as AFRS.[4]

Patients with AFRS typically present with nasal obstruction secondary to nasal polyposis, along with complaints of hyposmia or anosmia.[4,5] The mucin has a thick consistency often described as "peanut-butter-like," with its color varying from light tan to brown.[1,2,5] The affected nasal sinuses often undergo expansile changes that may lead to erosion of bony boundaries. In some individuals, these changes become sufficiently pronounced to result in orbital or facial deformities.[4]

In 1994, Bent and Kuhn established a set of major and minor criteria for the diagnosis of AFRS that remain in use today. The major criteria include: (1) type I hypersensitivity to fungi confirmed by history, skin testing, or serology; (2) nasal polyposis; (3) characteristic CT findings; (4) eosinophilic mucin

Table 1
Clinical and laboratory characteristics of patients with AFRS from the Immunology and Otorhinolaryngology Services of the Hospital Universitário Clementino Fraga Filho (HUCFF-UFRJ) , Rio de Janeiro, Brazil

Patient	Sex	Age, y	Comorbidities	Total IgE	Positive specific IgE	Culture
1	M	34	Thyroid nodule	2540	*B. tropicalis*, *A. fumigatus*, *P. notatum*, Staphylococcal enterotoxins	*Aspergillus sp.*
2	M	12	Allergic rhinitis	1963	*D. pteronyssinus*, *D. farinae*, *B. tropicalis*, *A. fumigatus*, *C. albicans*, *C. herbarum*	*Curvularia sp.*
3	F	44	Diabetes Hypertension	726	*D. pteronyssinus*, *D. farinae*, *A. fumigatus*, *C. albicans*, *C. herbarum*, Staphylococcal enterotoxins	Negative
4	M	45	Asthma	449	*D. pteronyssinus*, *D. farinae*, *B. tropicalis*, *A. fumigatus*	Negative
5	F	54	Obesity, allergic rhinitis, GERD, diabetes, hypertension	NA	*C. albicans*, *C. herbarum*	Direct mycological examination: numerous hyaline, septate, and branched hyphae and round, pigmented conidia

A. fumigatus: Aspergillus fumigatus; *B. tropicalis: Blomia tropicalis*; *C. albicans: Candida albicans*; *C. herbarum: Cladosporium herbarum*; *D. farinae: Dermatophagoide farinae*; *D. pteronyssinus: Dermatophagoide pteronyssinus*; GERD: gastroesophageal reflux disease; NA: not available (test not performed); *P. notatum: Penicillium notatum*.

without fungal invasion of sinus tissue; and (5) a positive fungal stain of sinus contents removed during surgery. Minor criteria include: (1) bone erosion on radiography; (2) positive fungal cultures; (3) unilateral predominance of disease; (4) Charcot-Leyden crystals; and (5) peripheral eosinophilia. For diagnosis, all five major criteria must be fulfilled.[1,4,5,7,8] However, these diagnostic criteria require reassessment, as several inconsistencies with clinical findings have been reported.[4]

IgE-mediated hypersensitivity to fungi is very common in AFRS, with *A. fumigatus* being the most frequent antigen, as seen in our case series.[4,9]

Radiologic evaluation typically includes radiography of the paranasal sinus, CT, and MRI. Findings can help identify nasal polyps, the extent of disease, bony expansion, and erosive changes. As observed in our cohort, expansile changes with thinning of bony structures are common. CT imaging of the nasal sinuses in patients with AFRS typically shows near complete opacification with heterogenous radiodensity of the soft tissue of the sinuses.[1,2,5,17] More than 30% of patients with AFRS have skull-base or orbital expansion or erosion that is extensive enough to cause local anatomic distortion (including the orbital and cranial cavities) and visual disturbances.[1] MRI is highly valuable for assessing soft tissue extension, orbital pathology, and intracranial involvement.[2,16,17]

As first described by Millar et al., Lamb et al., and Katzenstein et al., histologic examination of allergic mucin shows characteristic findings. Branching, noninvasive fungal hyphae are observed surrounding layers of eosinophils and Charcot-Leyden crystals. H&E staining is typically complemented by Gomori methenamine silver staining to better identify fungi.[18-20] Fungal cultures obtained from allergic mucin may provide supportive evidence in the evaluation of AFRS; however, their results must be interpreted with caution. It is important to emphasize that a diagnosis cannot be confirmed or excluded solely on the basis of culture findings, since a positive culture may simply represent saprophytic fungal growth.[4,21]

In the management of AFRS, surgery combined with topical and oral corticosteroids remains the standard of care. Endoscopic sinus surgery allows removal of nasal polyps and eosinophilic mucin, which harbors the fungi responsible for triggering and perpetuating sinonasal inflammation. It also improves drainage and ventilation of the affected sinuses, thereby increasing the penetration of topical medications postoperatively.[1,2,4,8,9,15]

According to the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS2020), systemic corticosteroids improve short-term postoperative outcomes and reduce long-term recurrence of AFRS.[12] However, their use should be limited to short courses due to the risk of adverse effects. Topical corticosteroids are also a key component of AFRS therapy and are essential for maintenance treatment, offering the advantages of minimal systemic absorption and low rates of adverse events.[3,4,12] Nonstandard, off-label topical steroid therapy, such as high-volume budesonide sinonasal irrigation, may provide higher steroid concentrations to the sinonasal mucosa depending on the mode of delivery.[22]

Currently, omalizumab, dupilumab, and mepolizumab are approved for the treatment of CRSwNP; however, patients with AFRS were excluded from those trials.[1,4,5,8] These biologic agents target type 2 inflammatory mediators: IgE, IL-4, IL-5, and IL-13.[8] Dupilumab inhibits signaling of both IL-4 and IL-13 and is currently being evaluated in phase III clinical trials for AFRS (NCT04684524).[4,8] Biologic agents appear to be a promising option, but more studies are required.[1,3-5,8,9]

Because AFRS is characterized by type I hypersensitivity to fungi, immunotherapy has been proposed as a potential strategy to attenuate the immune response to fungi and reduce disease burden.[1,15] However, to date, the only systematic review examining immunotherapy in AFRS found insufficient evidence to recommend for or against its use, due to methodological limitations such as small sample sizes, adjunctive use of other treatments, and lack of standardized control groups.[5] EPOS2020 describes immunotherapy as an adjunctive option that may reduce symptoms and the need for revision surgery.[3,12] Due to the limited number of published studies, immunotherapy is currently regarded as an adjunctive therapy.[5,23]

Topical antifungals have shown inconsistent activity and limited ability to access all affected mucosa, even in surgically opened sinus cavities. Regarding oral antifungals, most clinical trials have demonstrated limited treatment benefit.[4] A Cochrane review concluded that topical and oral antifungals in patients with any CRS phenotype did not demonstrate any clinical benefit.[1,2,4,24]

Conclusion

Our findings provide an updated account of AFRS cases followed in our center. It is important to consider this diagnosis in immunocompetent patients with CRSwNP who present with bilateral expansile changes and characteristic allergic mucin. In addition, we highlight the need to reevaluate the currently used diagnostic criteria, representing a potential area for future research.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Recurrent septicemia in secondary immunodeficiency induced by nasal steroid abuse

Sepse recorrente induzida por abuso de corticoide nasal em paciente com imunodeficiência secundária

Bruna Giavina-Bianchi[1], Adriana Pitchon[2], André Luiz Oliveira Feodrippe[2], Pedro Giavina-Bianchi[1,2]

ABSTRACT

Nasal corticosteroids are recommended as first-line therapy for patients with moderate-to-severe allergic rhinitis. We report a case of a patient with secondary immunodeficiency who presented with recurrent septicemia induced by the 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

Os corticosteroides nasais são recomendados como terapia de primeira linha para pacientes com rinite alérgica moderada a grave. Relatamos o caso de um paciente com imunodeficiência secundária que apresentou sepse recorrente induzida pelo uso inadequado de corticosteroides nasais, destacando os riscos associados ao uso incorreto desse medicamento.

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

Sepsis is a clinical syndrome defined as a life-threatening organ dysfunction caused by a dysregulated or aberrant host response to infection.[1] Recurrent episodes of sepsis are frequently associated with underlying anatomic abnormalities, functional disorders, and primary or secondary causes of immunosuppression. Secondary immunodeficiencies are substantially more common than primary immunodeficiencies and should be considered in the presence of underlying diseases, such as diabetes mellitus, HIV infection, nephrotic syndrome, and chronic renal failure, or in patients receiving immunosuppressive therapy, such as chemotherapeutic agents and corticosteroids.[1]

We report the case of a 39-year-old man admitted to the intensive care unit with a 1-day history of progressive fever, malaise, cough, dyspnea, and hemodynamic instability. His medical history included 3 prior hospitalizations: pneumonia at 7 years of age; pulmonary embolism of unclear etiology 8 years earlier; and an episode of sepsis associated with pneumonia 3 years earlier. Comorbidities included arterial hypertension, hypercholesterolemia, depression, ocular hypertension, and a rib fracture without antecedent trauma. He also reported a history of allergic rhinitis and asthma, both in remission without maintenance therapy. The patient had previously used low-dose inhaled corticosteroid/long-acting bronchodilator therapy intermittently but had been free of asthma medications for the past 5 years. No systemic corticosteroid use was reported during this period.

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On hospital admission, broad-spectrum antibiotic therapy was initiated. Due to respiratory failure, the patient required mechanical ventilation. Cardiocirculatory instability developed, necessitating vasoactive drug support to maintain blood pressure. The patient deteriorated rapidly, requiring extracorporeal membrane oxygenation (ECMO) within 24 hours of admission. Multiple COVID-19 tests were consistently negative.

Blood cultures were positive for multisensitive *Streptococcus pneumoniae*. The patient improved with antibiotics and systemic corticosteroid therapy (methylprednisolone, 0.75 mg/kg), ECMO was discontinued after 3 days, and extubation occurred on day 6 of hospitalization. Thirteen days later, the patient developed recurrent dyspnea. Imaging revealed a saddle pulmonary embolism, which was managed surgically with subsequent improvement. He was discharged after 28 days of hospitalization.

On the day of hospital admission, the patient's serum immunoglobulin G level was 601 mg/dL (reference range: 600-1500 mg/dL), with progressive increase during hospitalization. Other immunoglobulins were within the normal range (Table 1). HIV serology was negative. After discharge, he was referred to an immunologist for outpatient evaluation of recurrent sepsis.

The patient denied diabetes or any known causes of secondary immunodeficiency. There was no family history of consanguinity, adrenal insufficiency, recurrent infection, or inborn errors of immunity.

Review of the patient's medical records showed serum cortisol and adrenocorticotropic hormone (ACTH) levels below the reference range 2 years earlier (Table 2). At that time, the patient was unaware of the rationale for the testing, and no further actions were taken based on the results. Bone densitometry confirmed osteoporosis (lumbar spine T-score of –2.6 SD). During follow-up, persistently low serum cortisol and aldosterone levels were documented (Table 2). When further asked about exogenous corticosteroid use, the patient disclosed long-term daily use of an over-the-counter topical nasal preparation available in Brazil under the brand name Decadron Nasal® (dexamethasone disodium phosphate 0.5 mg/mL, neomycin sulfate 3.5 mg/mL, phenylephrine hydrochloride 5.0 mg/mL). He had used approximately 1 mL daily for 21 years. The patient did not consider this formulation to be a medication. He stated that he began using the preparation, which was borrowed from his father, for rhinitis symptoms, found it highly effective, and subsequently developed a long-standing dependence on its daily use.

Follow-up testing of immunoglobulins and their subclasses, lymphocyte immunophenotyping, complement system testing, and assessment of pneumococcal vaccine response yielded normal results (Table 1). As the conjugated pneumococcal vaccine had been administered after the 2 episodes of septicemia and before patient presentation at our service, only post-vaccination antibody titers could be assessed. Final diagnoses included septicemia, secondary immunodeficiency due to long-term intranasal corticosteroid use, Cushing's syndrome, and adrenocortical insufficiency (AI). The patient responded well to treatment with daily hydrocortisone replacement until recovery of adrenal gland function. At present, 4 years after the initial consultation, the patient has discontinued continuous exogenous systemic corticosteroid use and has remained free of new episodes of immunodeficiency or adrenal insufficiency. However, during infections or other stress-related conditions, he still requires supplemental doses of systemic corticosteroids.

Corticosteroids are essential hormones for life as they regulate physiological and developmental processes. Human endogenous glucocorticoid (cortisol) is synthesized in the adrenal cortex under the control of hypothalamic corticotropin-releasing hormone (CRH) and pituitary ACTH, constituting the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol, through a negative feedback loop, inhibits CRH and ACTH release. Likewise, exogenous corticosteroids suppress HPA axis activity, and persistent exposure can reduce endogenous ACTH, leading to AI and adrenal hypoplasia or atrophy.[2,3]

AI may occur even with physiologic doses of exogenous corticosteroids, although the risk is higher with supraphysiologic doses and prolonged use. The increased risk of developing AI has also been associated with specific aspects of the treatment regimen, such as splitting daytime and nighttime doses, as well as with the pharmacokinetics/pharmacodynamics properties of the involved corticosteroid and its administration route. Even the intranasal route should not be disregarded.[3] We hypothesize that the initial drop in blood pressure observed in our patient on hospital admission may be attributed not only to septic shock but also to AI. Subsequently, during hospital stay, the patient received methylprednisolone in combination with antibiotic therapy, leading to improvement.

Table 1
Patient's immunological assessment during and after hospitalization

Test	Day of hospital admission	Day 21 of hospitalization	2 weeks after discharge	18 months after discharge	Reference range
Leukocytes (cells/mm^3)	16,310	8260	8290	5940	4000–11,000
Neutrophils (cells/mm^3; %)	11,920 73.1%	3760 45.5%	3460 41.7%	3470 58.4%	2500–7500 (40%-75%)
Lymphocytes (cells/mm^3; %)	1660 10.2%	2710 32.8%	3440 41.5%	1750 29.5%	1500–3500 (20%-45%)
CD4 T cells (cells/mm^3; %)	–	–	1577 46.4%	– –	507–1496 (31.0%-56.0%)
CD8 T cells (cells/mm^3; %)	–	–	1483 43.6%	–	303–1008 (17.0%-41.0%)
CD4/CD8	–	–	1.1	–	0.9-2.6
CD19 cells (cells/mm^3; %)	–	–	165 12.0%	–	140–950 (<5%)
Eosinophil (number; %)	470 2.9%	630 7.6%	430 5.2%	260 4.4%	50–500 (8.0%–18.0%)
IgG	601	1084	1107	729	600-1500
IgG1	–	545	523	–	490-1140
IgG2	–	316	321	–	150-640
IgG3	–	31	26	–	22-176
IgG4	–	85	82	–	8-140
Antipneumococcal antibodies: positive serotypes (values in µg/mL)	–	–	6B (1.5); 9V (5.1); 14 (>20); 18C (4.6); 19F (12.6); 23F (4.5)	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 (units/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

Ig = immunoglobulin.

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

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

Besides the induction of AI, long-term use of supraphysiologic doses of corticosteroids is associated with several local and systemic adverse effects characteristic of Cushing's syndrome, including cataract, glaucoma, gastric ulcers, skin thinning and striae, hirsutism, acne, growth retardation, osteoporosis, weakness, fatigue, myopathy, hypertension, glucose elevation, obesity, and immunosuppression.[2,3] Our patient presented with arterial hypertension, ocular hypertension, osteoporosis with vertebral fracture, and thromboembolic events, clinical manifestations consistent with Cushing's syndrome.

Corticosteroids exert significant immunomodulatory effects primarily due to their anti-inflammatory and immunosuppressive properties. They suppress the production of pro-inflammatory substances, such as cytokines, chemokines, and prostaglandins, and inhibit several pathways of innate and adaptive immune responses, including the function of immune cells such as T cells and B cells, decreasing antibody production.[2]

Intranasal corticosteroids are recommended as first-line therapy for moderate-to-severe allergic rhinitis. The major advantage of intranasal corticosteroid administration is that high concentrations of the drug, with rapid onset of action, can be delivered directly into the target organ, so that systemic effects are avoided or minimized. The drug has a good efficacy and safety profile.[4]

The preparation used by our patient was inappropriate for maintenance therapy in allergic rhinitis because it combined vasoconstrictors, antibiotics, and dexamethasone, a high-potency long-lasting corticosteroid with high systemic bioavailability. A recent case report described a 19-year-old man, for whom dexamethasone nasal drops were prescribed for an episode of nasal obstruction, who developed Cushing's syndrome with panhypopituitarism, growth retardation, osteoporosis, and hypertension after more than 5 years of daily dexamethasone nasal drop use (0.7-1.0 mg/day).[5]

The diagnosis of secondary immunodeficiency is classically based on the exclusion of other potential causes. In the current case, the likelihood of secondary immunodeficiency arising from intranasal corticosteroid abuse is supported by the patient's medical history, laboratory investigations, and clinical evolution.

Although intranasal corticosteroids have been previously described as a cause of AI, they have not been associated with systemic immunosuppression or septicemia. To our knowledge, this is the first reported case of recurrent septicemia associated with intranasal corticosteroid use, underscoring the risks of abusive use of this medication.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Why should physicians value sexual issues in patients with atopic dermatitis?

Por que os médicos devem valorizar as questões sexuais em pacientes com dermatite atópica?

Aline Lopes Bressa[1], Natalia Torres Troncoso[1], Priscilla Filippo A. M. Santos[1,2], Sueli Carneiro[3]

ABSTRACT

Sexual health is a crucial but underrecognized component of quality of life in patients with eczematous conditions such as atopic dermatitis (AD). This cross-sectional study evaluated 452 adults attending a dermatology referral clinic in Brazil between 2022 and 2023. Sexual impact was assessed through item 9 of the Dermatology Life Quality Index (DLQI). Overall, 23% reported sexual difficulties, most frequently among women. AD (n=195) and psoriasis (n=140) predominated, with 47 patients with AD and 29 with psoriasis reporting impairment. The majority of affected individuals described moderate to very serious quality-of-life compromise. Findings highlight that AD, beyond its cutaneous and systemic manifestations, substantially affects intimacy and well-being. Despite its relevance, sexual health is rarely discussed in dermatological practice. The potential utility of the traditional DLQI, beyond its overall score, can serve as an opportunity to reach the patient´s suffering in sensitive topics.

Keywords: Atopic dermatitis, sexual dysfunction, skin diseases, quality of life.

RESUMO

A saúde sexual é um componente crucial, porém pouco reconhecido, da qualidade de vida em pacientes com condições eczematosas, como a dermatite atópica (DA). Este estudo transversal avaliou 452 adultos atendidos em uma clínica de referência em dermatologia no Brasil entre 2022 e 2023. O impacto sexual foi avaliado por meio do item 9 do Índice de Qualidade de Vida em Dermatologia (DLQI). No geral, 23% relataram dificuldades sexuais, mais frequentemente entre mulheres. DA (n=195) e psoríase (n=140) predominaram, com 47 pacientes com DA e 29 com psoríase relatando comprometimento. A maioria dos indivíduos afetados descreveu comprometimento moderado a muito grave da qualidade de vida. Os resultados destacam que a DA, além de suas manifestações cutâneas e sistêmicas, afeta substancialmente a intimidade e o bem-estar. Apesar de sua relevância, a saúde sexual raramente é discutida na prática dermatológica. A potencial utilidade do DLQI tradicional, além de sua pontuação geral, pode servir como uma oportunidade para abordar o sofrimento do paciente em tópicos delicados.

Descritores: Dermatite atópica, disfunção sexual, doenças de pele, qualidade de vida.

Introduction

The impact of cutaneous diseases on patients' sexual life has increasingly attracted attention from the scientific community in recent years. However, the available evidence is insufficient, particularly concerning eczematous conditions such as atopic dermatitis (AD). Multiple disease-related factors may compromise sexual function, including alterations in appearance, odor, pruritus, cutaneous exudation, and genital lesions, as well as extracutaneous manifestations such as sleep disturbance, depression, and the financial burden of treatment. Moreover, partners of patients with chronic dermatologic conditions may also face adjustments to daily activities and psychosocial challenges.[1]

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Male sexual dysfunction is mainly represented by erectile dysfunction. Globally, its prevalence approaches 50% in later adulthood and shares several risk factors with cardiovascular disease. The European Urological Association defines erectile dysfunction as "the persistent inability to achieve and maintain an erection sufficient to permit satisfactory sexual performance."[2] Erection depends on the convergence of psychological and neurovascular processes, both of which may be affected in AD.[3] Systemic inflammation in AD has been implicated in neurovascular changes that prevent erection in erectile dysfunction.[4] Also, reduced testosterone levels observed in patients with AD may provide a causal link with erectile dysfunction.[5]

Female sexual dysfunction encompasses 6 domains: desire, arousal, lubrication, orgasm, pain, and satisfaction. Its prevalence exceeds 40% and is higher in postmenopausal women.[2] AD has been shown to disrupt sexual function and negatively influence reproductive intentions.[6]

Male and female sexual dysfunction are not diseases per se. They represent symptoms reflecting broader impairments in physical, psychological, and social well-being.[7]

Recognizing sexuality as an external expression of well-being, this study aimed to highlight sexual health complaints among adult patients attending a dermatology referral service, compare findings with the existing literature, and examine differences between AD and other dermatoses.

Methods

This cross-sectional study was conducted by administering a questionnaire to patients followed up from January 2022 to December 2023 at the dermatology outpatient clinic of Hospital Universitário Pedro Ernesto, Rio de Janeiro, Brazil. The study was approved by the institution's research ethics committee.

Eligible participants were all patients aged ≥18 years who were able to read and write in the local language (Brazilian Portuguese) and had no severe psychiatric disorders. All patients were examined by a dermatologist who recorded the diagnosis. Patients aged <18 years or those who did not provide informed consent were excluded from the study.

Epidemiological data such as age, sex, race, type of dermatosis, and personal/family history of atopy were collected during clinic visits and from electronic medical records.

AD severity was assessed using the Scoring Atopic Dermatitis (SCORAD) index and classified as mild (<25), moderate (25-50), or severe (>50).

Quality of life and sexual function were assessed using the Dermatology Life Quality Index (DLQI), validated for Brazilian Portuguese. The questionnaire consists of 10 items assessing impairment over the preceding week in domains such as symptoms, feelings, leisure, work, personal relationships, sleep, and treatment. Each item is scored from 0 to 3, and the final DLQI score is calculated by summing the score of each question, resulting in a maximum of 30 and a minimum of 0. Higher scores indicate greater impairment in quality of life. The sexual impact of skin conditions was specifically assessed through item 9 of the DLQI:[8] "Over the last week, how much has your skin caused any sexual difficulties?" Response options included "very much" (3), "a lot" (2), "a little" (1), and "not at all/not relevant" (0). For analysis, responses were dichotomized into "yes" (scores 1-3) and "no" (score 0). Data were compiled and analyzed using Microsoft Excel 2019. AD received special attention and was analyzed in comparison with other dermatoses.

Results

Of a total of 452 patients evaluated, 104 (23.01%) reported sexual difficulties, as indicated by selecting any of the DLQI item 9 response options corresponding to an impact on sexual life ("a little," "a lot," or "very much"). Patients who responded "not at all" were considered to have no impact and were excluded from further analysis. Of those reporting sexual difficulties, 60.58% were women and 39.42% were men. Given the specific nature of our outpatient clinic, the most frequently assessed dermatoses were AD (n=195) and psoriasis (n=140), followed by scleroderma, prurigo, and vitiligo. Based on responses to DLQI item 9, 47 of 195 patients with AD reported a negative impact of their condition on sexual life, as did 29 of 140 patients with psoriasis, 5 of 11 with scleroderma, 2 of 3 with prurigo, and 2 of 7 with vitiligo (Figure 1).

Analysis of final DLQI scores in patients reporting sexual difficulties revealed the following dermatosis-related impact on quality of life: 0.96% reported no impact; 5.77%, slight impact; 21.15%, moderate impact; 52.88%, serious impact; and 19.23%, very serious impact.

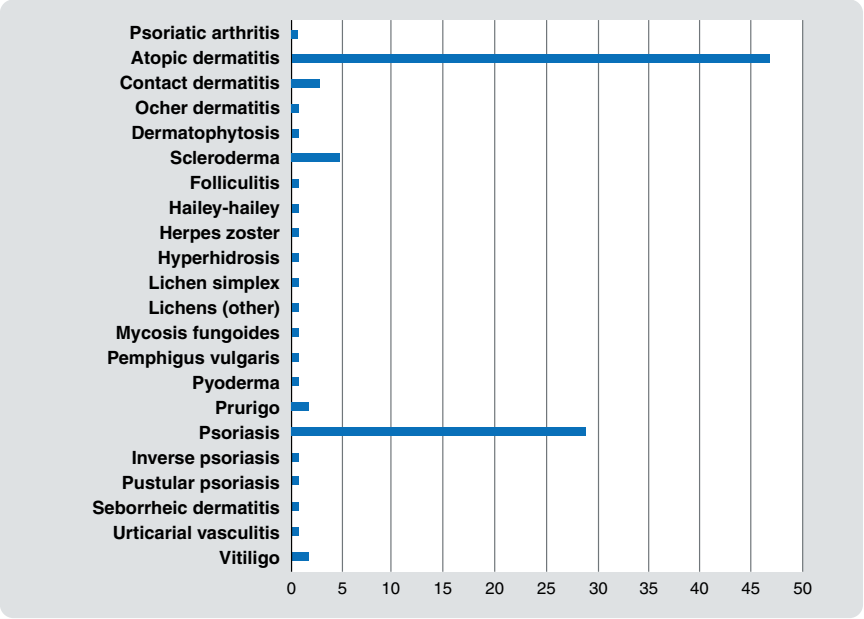

Figure 1
Dermatoses associated with impact on sexual life, identified through item 9 of the Dermatology Life Quality Index

Discussion

Sexual function is a broad concept that includes physical, psychological, sociocultural, and relational factors, all of which may directly or indirectly influence sexual activity, libido, and performance.[8] Sexuality is fundamental to human well-being, closely connected to mental health, and an integral component of quality of life. Chronic diseases can negatively impact sexual health, particularly those with visible manifestations such as cutaneous disorders.[9] In addition to physical discomfort, visible lesions may cause embarrassment or self-consciousness, especially if patients perceive that their partners view these manifestations as unattractive. The use of emollients and topical medications may discourage intimacy, either because of their texture, odor, or the possibility of transferring products to partners. Furthermore, physical touch can increase discomfort associated with dermatoses such as AD, urticaria, and mastocytosis.[10]

The negative impact of dermatoses on quality of life and the correlation of disease severity with sexual function have been demonstrated in previous studies.[11] A European multicenter study assessing impairment of sexual life, with DLQI item 9 score used as an indicator of the sexual impact of skin conditions, reported that 23% of patients experienced sexual problems, with higher impairment in patients with hidradenitis suppurativa (66.7%); other diagnoses with a prevalence greater than one-third were prurigo (41.7%), blistering disorders (34.9%), and psoriasis (34.8%).[12] In the setting of AD, accumulating evidence suggests that both patients and their partners experience compromised sexual health, which may occur due to reduced libido associated with disease severity, increased risk of erectile dysfunction in men with AD, or the localization of lesions in sensitive anatomic areas such as the hands and nipples.[13]

Addressing patients' sexual health concerns depends on the clinician's ability to communicate this sensitive issue, which may not be adequately broached for many reasons. First, dermatology residency programs rarely provide structured training on how to address sexual health concerns. Second, sexual dysfunction has traditionally remained under the umbrella of gynecology and urology, although in recent years other medical specialties have demonstrated

interest in the topic. Rheumatology was one of the first specialties to study sexual dysfunction, extending the studies to psoriasis, hidradenitis suppurativa, and eczema. Dermatology is advancing, but there remain a myriad of dermatoses with no visibility of their actual impact on patients' lives. Third, but perhaps not least, dermatology practice is at a fast pace, and it can be challenging for both patients and clinicians to directly discuss sexual health during the limited time dedicated to consultations.

The use of validated questionnaires such as the DLQI can facilitate identification and serve as a guide to address this topic, or another topic covered by other questions, which may be highlighted by the patient through a higher score that will demonstrate a negative impact. If a point of weakness or suffering is identified, dermatologists can further explore the complaint with more specific questionnaires, such as the Female Sexual Function Index or the Female Sexual Quotient for women and the International Index of Erectile Function or the Male Sexual Quotient for men. These tools can also be used to substantiate the need for further specialist advice, including psychiatrists, urologists, and gynecologists.

Future studies should focus on identifying patients who are at increased risk of sexual health impairment and explore the link between disease severity, sexual functioning, and overall quality of life across common dermatoses. However, in order to do so, it is necessary to arouse the interest of dermatologists by emphasizing the clinical importance of sexual health and showing them how to approach the topic. That was the primary reason for this study.

Study limitations

A control group was not included. Marital status, a variable that can influence sexual function, was not assessed. Furthermore, reliance on DLQI item 9 as a measure of sexual dysfunction represents a constraint, as it was not designed or validated specifically for this purpose. The inclusion of other validated sexual dysfunction questionnaires would provide a more comprehensive assessment.

Conclusion

Pioneer study in Brazil to highlight the impact of common dermatoses on sexual function and to address this complaint in the setting of AD. This study also underscores the potential utility of the traditional DLQI beyond its overall score, demonstrating that specific items can be used for different analyses, thus serving as a guide or an opportunity to reach the patient´s suffering in sensitive topics.

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ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

The role and impact of tissue-resident memory T cells in allergic contact dermatitis

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Dear Editor,

Allergic contact dermatitis (ACD) is a type IV (delayed-type) hypersensitivity reaction, mediated by the host immune response to small molecules (< 500 Daltons), known as haptens, that contact the skin of sensitized individuals. The process is divided into 2 main phases: the induction phase and the elicitation phase. During induction, the hapten binds to a skin protein to form a complex recognized by the immune system. This complex activates and expands allergen-specific T cells, a process known as sensitization. After sensitization, during elicitation, re-exposure to the allergen leads to an intense immune response, resulting in the onset of dermatitis. ACD accounts for approximately 20% of contact dermatoses, and allergens differ greatly based on geographical region, personal habits, and hobbies.[1]

The discovery of tissue-resident memory T cells (TRM) in mice has transformed our understanding of skin immunity. These cells are not merely part of immune surveillance, they also form long-lived sentinels in the epidermal and dermal compartments, acting as central mediators of human skin health and disease. TRM cells play a key role in the defense against pathogens, cancer, and inflammatory skin diseases. They can arise from circulating memory T cells or from pre-existing cell populations in the skin, acting as the first line of defense against invading antigens in non-lymphoid peripheral tissues, including the skin, respiratory tract, and intestines. TRM plasticity enables them to differentiate into central memory T cells, depending on tissue microenvironment, which is regulated by local cytokines. The transcription factors HOBIT and BLIMP-1 are essential for their resident phenotype. In addition, TRM cells develop in response to skin infection and play a critical role in inflammatory response, contributing to the diverse pool of local memory T cells. TRM differentiation and maintenance are guided by signals such as IL-7, IL-15, and TGF-β, ensuring long-lasting defense without displacement of pre-existing populations.[2]

Recent studies have highlighted the pivotal contribution of TRM cells to the modulation of adaptive immune responses in allergic disorders such as rhinitis, asthma, atopic dermatitis, and contact dermatitis, with profound implications for prevention and treatment.[3]

TRM cells have a dual role in allergic diseases, acting as mediators and regulators. They coordinate allergic responses through the release of pro-inflammatory and chemotactic factors, activating tissues at the affected sites and recruiting immune cells to amplify the response. These cells also express ligands that attract resting memory T cells from the circulation, maintaining a feedback loop in the allergic response. In addition, they can reactivate $CD4^+$ and $CD8^+$ T cells in the presence of allergens and enhance antigen presentation by dendritic cells (DCs). Recent studies have shown that, upon allergen re-exposure, $CD4^+$ TRM cells produce cytokines such as IL-4, IL-5, and IL-13 (Th2 profile), IL-17 (Th17), and IFN-γ and TNF-α (Th1). IFN-γ, in particular, activates epithelial tissues and recruits immune cells, inducing the expression of CXCR3, CXCL9, and CXCL10. In the lungs, TRM cells reactivate $CD4^+$ and $CD8^+$ T cells, attracting eosinophils and $CD11c^+$ DCs to the inflamed site. However, TRM cells also express inhibitory checkpoints such as PD-1 and TIM-3, which attenuate allergic reactions, and their blockade may exacerbate these reactions. Whereas earlier studies associated $CD8^+$ TRM cells with the intensification of allergic conditions, recent evidence reveals their dual function in both the induction and regulation of allergic reactions.[3]

In ACD, TRM cells accumulate at the site of allergen contact during sensitization and trigger rapid and intense responses to re-exposure. They also play a key role in disease flare-ups, chronicity, and severity, positioning them as promising therapeutic targets.[4]

Active ACD lesions contain a mixed $CD4^+$/$CD8^+$ lymphocytic infiltrate, predominantly composed of $CD4^+$ cells expressing CCR10. Murine hapten-induced ACD studies have shown that long-term immunological

memory is mediated by CD4+ TRM cells, initially confined to sensitized areas until re-exposure to the allergen. Recent studies suggest that the severity of flare-ups is related to the density of epidermal CD8+ TRM cells. In mice, depletion of CD4+ TRM cells resulted in increased inflammatory response, suggesting a potential regulatory role, whereas CD8+ TRM cells appear to contribute to persistent inflammatory responses through rapid reactivation after allergen re-exposure. Although murine models have provided valuable insights into TRM functions, there are still significant differences compared to human immune responses. Additional translational studies will be required to determine how TRM cells interact with other cell populations in the skin and how their metabolism and functional profile may be modulated in order to develop new therapeutic approaches to ACD.[2]

Using various mouse models and cell depletion protocols, Gadsbøll et al. investigated the role of TRM cells in ACD flare-ups induced by the experimental allergen 1-fluoro-2,4-dinitrobenzene. The study demonstrated that CD8+ TRM cells promote massive neutrophil infiltration into the epidermis within 12 hours of re-exposure to the allergen. Neutrophil depletion before allergen re-exposure resulted in rapid resolution of flare-ups. In addition, CD8+ TRM cells were responsible for mediating neutrophil recruitment, inducing CXCL1 and CXCL2 production in the skin. Blocking the receptors of these chemokines inhibited both neutrophil infiltration and inflammatory reactions, suggesting that CD8+ TRM cells play a crucial role in flare-ups, facilitating neutrophil recruitment to the epidermis. Regarding the dynamics of skin-resident T cells, allergen exposure led to an accumulation of CD8+ TRM cells and displacement of dendritic epidermal T cells (DETCs), which are Tγδ cells specialized in epidermal immune surveillance. DETCs play a vital role in detecting pathogens or allergens and modulating local inflammatory response. DETC displacement after allergen exposure was mediated by the requirement for CD8+ T cells, as their absence prevented DETC migration. Compared with DETCs, CD8+ TRM cells exhibited a more robust inflammatory response and greater proliferative capacity, suggesting a metabolic advantage. These findings indicate that the metabolism of CD8+ TRM cells may be a promising therapeutic target for the treatment of ACD, since the magnitude of allergic reactions is directly related to the number of these cells in the skin.[5]

Future research should focus on unraveling the complex mechanisms underlying the longevity of TRM cells, their tissue-specific functions, and their dual role in flare-ups and regulation of allergic reactions. This will pave the way for innovative, targeted therapies, making allergy management more efficient and personalized. Ongoing efforts into integrating molecular, immunological, and clinical studies are essential for translating these insights into practical applications in allergy treatment.[3] We must remain attentive to these developments.

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