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Allergy to *Alternaria alternata*: Comprehensive review from the origin to the therapeutic approach

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Abstract
Alternaria alternata is an ubiquitous mold commonly found in both outdoor and indoor environments. It is a common airborne mold recognized as a significant aeroallergen linked to pediatric allergic rhinitis and asthma. Although sensitization rates in children vary regionally, evidence suggests that *A. alternata* allergy significantly impacts pediatric respiratory health and as its exposure worsens, respiratory outcomes in susceptible pediatric populations *Alternaria*. Children are especially vulnerable due to their developing immune and respiratory systems and greater exposure to environmental allergens. This narrative review aims to summarize current knowledge on *A. alternata* as an allergenic source in children, including its biology, allergenic components (especially Alt a 1), interactions with immune system, airway epithelium interacting with other allergens, and clinical relevance. We also discuss the allergen-specific immunotherapy strategies with standardized extracts that are effective and safe in pediatric patients. Understanding the role of *Alternaria* in allergic disease is essential for early and accurate diagnosis (including component-resolved methods), effective intervention, and improving long-term outcomes in affected children. Future research should focus on novel vaccine technologies and standardized pediatric-specific treatment protocols.

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Introduction

Fungi are complex living organisms belonging to a kingdom of their own as they do not meet the characteristics of the animal and plant kingdoms. Like plants, they have a cell wall and do not move, but they do not photosynthesize and are heterotrophic (they obtain nutrients after secreting their digestive enzymes on plant or animal remains, usually in decomposition).

It is estimated that between 2 and 11 million fungal species exist,[1] yet just over 150,000 have been formally described,[2] of which 112 genera contain allergens.[3] The ones that are frequently implicated in respiratory allergic pathology are *Alternaria alternata, Cladosporium, Aspergillus,* and *Penicillium*.

A. alternata is a common saprophytic fungus in our environment, especially abundant in agricultural areas. It has a significant impact on the respiratory health of children, especially in those with asthma, representing an important diagnostic and therapeutic challenge, as it is associated with severe forms of asthma. These require more follow-ups with an increased risk of emergency room visits, admissions, and even death.

Aspergillus and *Penicillium* are thermotolerant filamentous fungi, which enables them to act not only as pneumoallergens but also to germinate in the lower respiratory tract causing infection and lung damage. The genera *Cladosporium* and *A. alternata* do not share these characteristics but are frequently associated with respiratory allergic diseases, with *A. alternata* as the main sensitizing source in humans.[4] Less frequently, *A. alternata* can cause hypersensitivity pneumonitis (farmer's lung), subcutaneous (phaeohyphomycosis), and systemic infections (alternariosis), especially in immunocompromised individuals.[5]

It is noteworthy that the vast majority of patients allergic to *A. alternata* are polysensitized, mainly in the pediatric age group. Due to its presence in both outdoor and indoor environments, avoidance of this allergen is particularly difficult. Therefore, symptomatic treatment, especially immunotherapy, is the fundamental pillar in the management of these patients. As *A. alternata* sensitization seems to be more prevalent in the pediatric age, indication of an early allergen-specific immunotherapy helps in preventing the development of asthma and therefore improve the evolution to adulthood.

This review considers, among others, aspects such as aerobiological dynamics, geographical distribution, epidemiology of allergic sensitization in the pediatric population, immunological mechanisms underlying the interaction with the organism and therapeutic strategies against *A. alternata*, and finally the evolution of patients over time is revised.

Frequency of sensitization to A. alternata*— magnitude of the problem*

The prevalence of fungal sensitization is not clearly defined, varying according to the geographical area, the population studied, and the diagnostic methods used. In the general population, it ranges from 3% to 10% and then increasing from 10% to 20% in patients with asthma and/or rhinitis,[3] and more than 66% among patients with severe asthma.[6,7] A Spanish multicenter study revealed that 20.2% out of a total of 1156 patients with asthma and/or rhinoconjunctivitis were sensitized to fungi, of which 94% were sensitized to *A. alternata* and/or Alt a 1, their major allergen.[8]

Sensitization to *A. alternata* has been identified as a risk factor for the development and persistence of asthma, being associated with severe asthma, increased risk of emergency room visits, hospitalizations,[9] (9), intensive care unit (ICU) admissions, and deaths.[10-12]

Aerobiological dynamics of A. alternata

A multitude of microscopic particles of different origins are suspended in the air that make up the atmospheric aerosol. The fraction of biological origin, called bioaerosol, is composed mainly of viruses, bacteria, pollen, and fungal spores,[13] with *A. alternata* being one of the most prevalent and best studied sources.[3,14]

Fungi have traditionally been divided into four main groups: chytridiomycetes, zygomycetes, basidiomycetes, and ascomycetes. *A. alternata, Aspergillus, Cladosporium*, and *Penicillium*, the most prevalent species involved in allergic diseases, belong to the latter.[15]

Fungi can reproduce sexually (teleomorphic phase) and asexually (anamorphic phase), and *A. alternata* represents the anamorph (asexual state) while *Lewia* constitutes the teleomorph (sexual state) of the same fungal species. In the ascomycetes, sexual reproduction generates meiotic spores (ascospores) inside a sporangium called *asca*, while asexual reproduction gives rise to long chains of mitotic spores called conidia, which constitute one of the largest sources of bioaerosol in our environment,[16,17] as they make up a significant portion of the spores found in the air that multiply the concentration of pollen grains by more than 1000 times.[18]

A. alternata is a widespread fungal genus comprising of more than 300 species,[19] including saprobic, endophytic, and pathogenic types that colonize a wide variety of substrates,[20] with a particular affinity for agricultural crops.[21] Although humidity is essential for their growth and for the production of spores,[22] it is heat, dryness, and wind that favor the release and dissemination of spores/conidia into the atmosphere. It can behave as a saprophytic (feeding on decomposing organic matter), symbiotic (establishing close relationships with other organisms and depending on them for nutrition but not cause injury), and opportunistic parasite with endophytic growth, creating infection in the tissues of leaves, seeds, and viable fruits[23] in the field and during storage causing significant damage to agriculture.

The intensity and duration of exposure, measured by temporal averages, are responsible for sensitization, but from the patients' point of view it is the peaks that produce symptoms. Threshold concentrations of airborne *Alternaria* that can induce respiratory symptoms in sensitized patients are controversial, oscillating between 10 spores/m^3 and 100 spores/m^3[24,25]; however, the simultaneous presence of floating fungal spores and pollen may trigger sensitization and symptoms even below these established thresholds,[26] exerting a kind of reciprocal priming effect. As with

pollens, the concentration of specific allergens is better associated with the respiratory allergy symptoms than the environmental concentration of spores. During mechanized harvesting of cereals, the peak levels of conidia from 10^6 to $10^7/m^3$ of air are observed,[27] which break[28] and release the airborne submicron particles,[21] and can access the bronchial tree; so, they not only cause allergic rhinitis but also asthma symptoms, which are characterized by their special severity, especially in children.[29] Epidemic episodes of asthma associated with high percentages of broken *A. alternata* conidia in the environment during thunderstorms have been documented.[30] Another aspect is that germinated conidia releases a greater amount of allergens,[25] which could also influence respiratory morbidity.

The main spore season (MSS) refers to the period during which spores are present in the atmosphere at a given location in significant concentrations.[31] While definitions may vary, one of the most widely accepted characterizations defines it as the time span during which the central 90% of all spores of a given type are recorded, excluding the first and last 5%. In warmer climates, this period tends to be longer. There are different patterns of environmental dispersion depending on geographical and climatic characteristics, with a marked dependence on temperature[32] and low relative humidity.[33] The optimal range of average temperatures that favors the production and release of *A. alternata* conidia into the environment is from 18.9°C to 25.2°C.[22] This explains why in central and northern Europe an annual unimodal distribution of *A. alternata* conidia records is observed *in* the environment, with their highest values during the summer,[34] while in southern Europe they frequently present bimodal distributions, with maximum concentration in late spring and early autumn.[35]

For this double peak, the maximum temperatures in summer must exceed 32.6°C, and for the autumn peak, more likely the minimum temperatures in autumn must exceed 11.4°C, conditions that are reached twice in southern Spain, but only once in the north. The distribution of annual rainfall is another determining factor in the presence of *A. alternata*, since water is essential for its growth and to produce spores.[22]

Although *A. alternata* is mainly an outdoor allergen, if the right conditions are given it can be found indoors too. The clinical relevance of *A. alternata* as an indoor allergen is not well understood, because its concentrations indoors have (as with *Cladosporium*) a strong influence of outdoor concentrations, which explains the difficulty in analyzing its contribution to symptoms independently. In a prospective cohort of 499 Boston infants, Behbod et al.[36] demonstrated a significant correlation, even after adjusting for outdoor air concentrations, between indoor exposure to *A. alternata* at 2–3 months of age and frequency of wheezing at one year, especially if the mothers were sensitized to *A. alternata*.

In addition, children who live in houses with *A. alternata* present have higher levels of specific immunoglobulin E (IgE) against it,[37] its concentration being directly proportional to the prevalence of asthma in its occupants.[38] This should be taken into account when establishing primary prevention measures to decrease the growth of fungi indoors, such as the use of fans and air purifiers, or simply ventilating rooms frequently.[37]

Characteristics, allergens and relevant components of Alternaria

The dimensions of the fungal spores of *A. alternata* (20–60 μm)[30] cause them to be retained in the nasal cavity, causing rhinitis. The breakage of the conidia (mechanized harvesting, osmotic changes) generates smaller unquantified fractions in the material obtained by conventional collectors, which are rich in allergens that access the bronchial tree.[39] This explains why respiratory allergy to *A. alternata* is associated with greater bronchial inflammation and worse lung function,[40] and that these patients have a higher risk of developing asthma attacks,[41] hospitalizations,[37] and death from asthma.[42] As with pollens, the concentration of specific allergens is better associated with respiratory allergy symptoms than with the concentration of spores.[43]

Between 70% and 95% of patients sensitized to *A. alternata* whole extract are specifically sensitized to Alt a1,[3,8,44] which makes it its main allergen. Alt a1 is a 30 Kd acidic glycoprotein, exclusive to fungi, composed of two subunits of 16.4 kD and 15.3 kD linked by disulfide bridges. It is a very stable protein, whose conformation and IgE epitopes resist exposure to temperatures of 95°C. It has an unknown biological function, although being expressed predominantly in the cell walls of the spores, it seems to be related to germination processes.[45] It has been suggested that the spores produce Alt a1 even before germinating, with an accelerating role in the decomposition of plant matter, inducing the plant to produce PR-5 defense proteins to bind to them and then inhibit each other, favoring infection.[46] The rest of the minor allergens are listed in Table 1.[47-49]

Alt a6 and Alt a14 show homology with their latex equivalents and could be responsible for cross-reaction; it has been suggested to include these two allergens in diagnostic panels.[44]

Among the nonallergenic components of the fungi responsible for asthma morbidity are beta-glucans and chitin that can activate innate responses without the need for prior sensitization.[51]

The walls of fungi, like many invertebrates, contain chitin, a polysaccharide not present in mammals that acts as a pathogen-associated molecular pattern (PAMP). Respiratory epithelial cells produce alarms that activate innate immune cells (eosinophils,[52] macrophages) and adaptive immune cells (Th2 lymphocytes expressing IL-4/IL-13),[53] as part of the "antiparasitic" response. These epithelial cells are rich in chitinase, which could constitute a biomarker of the response to fungi.[53]

β-Glucans are polysaccharides with a molecular weight greater than 100 kDa, nonexistent in mammals, which represent 50–60% of the dry weight of the cell wall of fungi.[47-49] When ingested, they have benefits on immune function and cholesterol reduction.

These molecules, which are not allergenic per se, are not considered determinants of cross-reactive carbohydrates (CCDs), do not induce IgE production, and are therefore not responsible for false positives in allergy tests. Their immunological importance is due to the fact that they behave as PAMPs, inducing the humoral response in helminth infection and therefore activate innate responses without the need for prior sensitization to *Alternaria*. They act as adjuvants in the activation of dendritic cells,

Table 1 Allergens of *A. alternata*

	Protein type (function)	molecular weight (kD)
Alt a 1	Unknown, associated with pathogenicity in plants	30 (15,3 + 16,4)
Alt a 3	Heat shock protein (HSP70), cellular protective function against heat and oxidative stress	85
Alt a4	Disulfide isomerase, involved in protein synthesis	57
Alt a5	P2 ribosomal acid protein, involved in protein synthesis	11
Alt a6	Enolase. Thermostable panallergen involved in glycolysis. Present in fish, birds, crustaceans, insects, fungi, plants and latex. It can sensitize by contact, ingestion or inhalation.[48] It sensitizes 22% of people allergic to *A. alternata* .	45
Alt a 7	Flavodoxin	22
Alt a8	Mannitol Dehydrogenase	29
Alt a10	Aldehyde dehydrogenase	53
Alt a12	P1 Helping Ribosomal Protein	11
Alt a13	Glutation-transferase	26
Alt a14	Manganese SO dismutase[49]	24
Alt a15	Vacuole Serin-protease[50]	58

intensifying T helper (Th)2 responses and decreasing the Th1 response,[54] as occurs in the case of peanut allergy.[55] Fungal β-glucans have also been observed to promote Th17 responses, when combined with Th2 responses are responsible for progression to a severe corticosteroid-resistant type of asthma.[56]

Interaction of A. alternata *with the respiratory epithelium*

A. alternata is rich in proteases, used in degrading organic matter, capable of breaking the intercellular *tight junctions* and causing structural changes in the epithelium of the bronchial epithelium,[57] which makes it more permeable (facilitated transport) to other allergens and also to pathogens and irritants. This effect, well known to mites, could act as an "enhancer" of sensitization to other allergens and of nonspecific bronchial hyperresponse to bronchial irritants and pathogens. Proteolytic attack on the epithelium induces an alarming release of tissue damage, such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, cytokine production, and Th2 inflammatory responses, mediated by both eosinophils[52] and IgE.[57,58] IL-33 has been proposed as a specific biomarker and possible therapeutic target in children with severe asthma due to fungal sensitization, with resistance to corticosteroids.[59]

Interaction with viruses

In addition to proteolytic damage to the epithelium, which increases permeability to pathogens, *A. alternata* is able to reduce innate responses to viral infections. Kobayashi et al.,[54] discovered in a murine model that *A. alternata* represses the production of interferons (IFN)-(54)γ, tumor necrosis factor (TNF)-α, and IL-12 (in turn, inducers of IFN-synthesisγ), key pieces in the immune response against viruses. It has also been observed to inhibit the production by dendritic cells of IFN-β and other cytokines important in the defense against viruses by inhibiting toll-like receptors 3 (TLR3).[60]

Percopo et al.[61] showed that mice exposed to influenza viruses after being sensitized intranasally to *A. alternata* had survival inversely proportional to the dose of the fungus supplied. Influenza morbidity and mortality was independent of the viral load (both groups with/without previous exposure to *A. alternata* had the same number of copies of influenza in bronchoalveolar lavage) due to the amplification of Th2 inflammatory responses (increase in eosinophils, IL-5, IL-13, and eotaxin-1) and the decrease in alveolar macrophages and Th1 responses,[62] which produced an increase in morbidity and mortality predisposed to bacterial superinfection.

On the one hand, innate cellular antiviral responses are defective in allergic patients due to IgE/virus cross-linking, which highlights the link between viral infections and exacerbations of atopic disease. For example, stimulation of the high-affinity IgE receptor (FcεRI) on plasmacytoid dendritic cells inhibits Th1 responses such as influenza-induced IFN-α secretion.[63] These findings suggest that patients sensitized to *A. alternata* may have greater frequency and severity of virus-induced asthma attacks. Whereas, on the other hand, it is known that respiratory virus infections in patients sensitized to pneumoallergens produce hyperresponse and bronchial inflammation that is longer and more intense, which reinforces the importance of virus-allergen immune system interactions.

Polysensitization

Those sensitized to *A. alternata* are usually also sensitized to other fungi, usually due to cross-reactivity between fungal proteins.[64] The Spanish multicenter study PREVAL found that the majority (77.7%) of those sensitized to fungi had polysensitization to other nonfungal allergenic sources.[8] *A. alternata* could perform as an "initiator" of new sensitizations[65] due to the above-mentioned interactions with the respiratory epithelium and the immune system, which could enhance allergic inflammation caused by pollens and mites, acting as an inducer of Th2 responses,[49] and secreting substances that promote the activation and degranulation of eosinophils.[52]

Recently, Kalyniuc et al.[66] reviewed the sensitization profile of 3349 Ukrainian patients hypersensitive to fungal allergenic components. This study highlights the role of Alt a1 in promoting sensitization to other allergens such as pollen, outlining that 31.86% of patients were co-sensitized to Alt a1 and Phl p2, of which 83.22% were children. We can speculate about possible reasons why co-sensitization to Alt a 1 and Phl p 2 is more frequent in children:

1. Increased exposure and developing immune system that may be prone to sensitization to new allergens. In addition, it is common for children to spend more time outdoors, being early and repetitively exposed to elevated concentrations of both grass pollen and *Alternaria* spores during the peak seasons for both allergens (May through September).
2. It is possible that sensitization to Alt a 1 is an early step in the atopic march, facilitating sensitization to other respiratory allergens such as grass pollen.
3. Immaturity of the skin and/or respiratory barrier could facilitate allergen entry and the attainment of new sensitizations over time.

Interaction with pollens

Kobayashi et al.[54] showed in a murine model that in the presence of *Alternaria*, there is a greater capacity for sensitization to *Ambrosia artemisifolia*, with a greater response of specific IgE and immunoglobulin G (IgG)1 after exposure to this pollen and a marked increase in eosinophils and IL-13 in the Lymphocyte B compared to a minimal response in mice exposed only to pollen (without previous *A. alternata* exposition).

In an interesting article, Feo Brito et al.[43] observed that patients monoallergic to grass presented symptoms attributable to them in the absence of detection by the collectors as they were outside their pollination period. The authors suggest that *A. alternata* spores contaminate the stems of wild or cultivated grass remain integrated into the plants during summer. In this way, the spores could incorporate the grass allergens, acting as Trojan horses that, when dispersed in autumn into the atmosphere, would release their own allergens and also those of grass, such as Phl p1. It is a possibility to be considered in patients with extemporaneous respiratory symptoms, inconsistent with their allergic sensitization and not attributable to other triggers (virus, exercise, cold) or to the appearance of new allergic sensitizations. This reaffirms the importance of scavengers not only measuring pollen grains or fungal spores but should also quantify allergens, which correlate better with patients' symptoms, and that should be reflected in clinical research studies.

Interaction with food

Fungi usually behave in a saprophytic way, invading the fruit in senescence (ripe), in which they develop and decompose it. Gómez-Casado et al.[67] deposited *A. alternata* spores on the skin of a non-senescent kiwi fruit (which is not their usual host). They observed that the spores remain silent until ripening without developing hyphae in the pulp, but that there was an increase in the expression of Alt a 1 fused with the kiwi protein PR5, a thaumatin-like plant defense protein that limits the development of the fungus. Alt a1, whose function was unknown, induces the plant to produce PR-5, both inhibiting each other. In this way, *Alternaria* could behave in some patients as a food allergen by ingestion or inhalation.

Interaction with mites

Inside built structures, especially in a humid environment, there are conditions conducive to the development of mites and fungi that interact in a perpetual feedback loop, in which the fungus digests the organic particles that make up house dust and later ingested by mites; it survives its digestion and then goes outside with its feces where it digests more dust particles and becomes food for the mites again.

Specific immunotherapy in patients allergic to A. alternata: *a targeted and modifying intervention*

AIT is the only intervention capable of modifying the natural course of respiratory allergic disease, inducing a state of immunological tolerance or, at the very least, a desensitization. It has been shown to be effective in improving symptoms of rhinitis and asthma as well as reducing the use of symptomatic treatment.[68] While native extracts have demonstrated efficacy, their use has been limited by safety and standardization concerns. At present, molecular immunotherapy with Alt a1 and polymerized extracts offers safer and more effective treatments tailored to the individual needs of patients

Ensuring the success of the AIT requires adequate patient selection and demonstration of the clinical relevance to sensitization. It is also essential to have standardized and high-quality allergenic extracts. The development of fungus-specific immunotherapy, in particular *Alternaria*, has faced multiple difficulties, especially in relation to the standardization of extracts due to their variability in potency and allergenic content, although this situation has improved significantly in recent years.

Native extracts

Although immunotherapy with native *A. alternata* extracts has demonstrated real-life efficacy, availability of evidence remains limited. There are few controlled studies evaluating the efficacy and safety of these extracts, and many have important methodological limitations, such as open design, absence of a placebo group, poor long-term follow-up, and lack of standardization.

A systematic review conducted by Bona et al.[69] analyzed seven clinical trials involving *A. alternata* extracts and two trials with *Cladosporium* extracts in a total of 268 patients (99 adults and 169 children). The authors concluded that, although some findings suggest potential efficacy, the overall quality of the evidence was low due to inconsistent results, small sample sizes, and a moderate to high risk of bias.[69]

In a randomized, double-blind, placebo-controlled trial, 50 children aged 5–18 years with *A. alternata*-induced allergic rhinitis and/or asthma received either active treatment with a standardized extract or placebo over a 3-year period. Significant reductions in combined symptom-medication score were observed in the active group during the second and third years of treatment (38.7% and 63.5% vs. placebo, respectively; $p < 0.001$). Immunologic assessment revealed a significant increase in specific IgG4 and a moderate decrease in IgE levels.[70]

In 2008, a double-blind, placebo-controlled trial using an *A. alternata* extract in 28 patients over 12 years of age with respiratory allergy demonstrated symptom improvement and reduced medication use at 6 months.[71]

A 2011 multicenter, prospective, open-label study evaluated the clinical evolution of 99 children with respiratory allergy sensitized to *A. alternata* treated with subcutaneous immunotherapy (SCIT). After a year, the treatment led to reduced medication use, improved symptom control, better asthma management, and enhanced quality of life.[72] Finally, a study published in 2007 showed an improvement in symptom scores and immunological modifications with a decrease in IgE and an increase in IgG4.[73]

Few studies have investigated the efficacy of sublingual immunotherapy (SLIT) with *A. alternata* extracts. In a randomized, double-blind, placebo-controlled trial, 27 patients aged 14–42 years with confirmed *A. alternata* allergy were treated with either SLIT or placebo over a 10-month period. SLIT with a standardized extract proved to be effective and safe, leading to a significant improvement in allergic rhinitis symptoms and a reduction in the use of rescue medication.[74] Another randomized study evaluated daily SLIT over a 3-year period in patients with allergic rhinitis, with or without mild-to-moderate asthma, showing clinical improvement in 97% of SLIT-treated patients compared to 27% of controls. SLIT was well tolerated in both studies, with no serious adverse events reported.[75]

Classically, safety has been one of the main issues with native extracts of *A. Alternata*. The use of inadequately standardized extracts has led to reports of a higher rate of local and systemic reactions. A retrospective study published in 2000 reported an adverse reaction rate of 1.95% per administered dose. Reactions were more frequent in children during the initial build-up phase and in asthmatic patients with elevated IgE levels, with the authors coming to the conclusion that this extract is less well tolerated.[76] In 2005, a multicenter study conducted by the Spanish Society of Pediatric Clinical Immunology and Allergology (SEICAP) evaluated 94 children undergoing immunotherapy with *A. alternata*. The study reported a 1.9% reaction rate per dose with a conventional regimen compared to only 0.4% with a clustered regimen. Systemic reactions of grade 2–3 occurred in six patients (6.37%). These findings suggest that the clustered protocol offers better tolerability in pediatric patients.[77]

Polymerized extracts

The use of native extracts is not without risks to adverse reactions, both local and systemic. These limitations have encouraged the development of safer formulations, such as allergens or polymerized extracts. Due to their reduced allergenicity, while retaining their immunogenic capacity, they offer an effective and safer alternative to conventional native extracts, reducing the risk of adverse reactions and allowing for faster administration schedules.

Although there are still no double-blind, placebo-controlled trials with polymerized *A. alternata* extracts, some observational studies offer encouraging data. A preclinical study published in 2017 showed the favorable safety profile of a polymerized depigmented extract of *A. alternata* by showing no adverse effects in the toxicological tests carried out. In addition, it demonstrated its efficacy in inducing the production of blocking IgG antibodies and stimulating the release of IL-10, suggesting its therapeutic potential.[78]

More recently, an observational study evaluated the safety of ITA with polymerized extracts of *A. alternata* in 738 patients (435 children and 303 adults), registering a local reaction rate of 0.24% in children and 0.09% in adults and systemic reactions in only 0.09% of the total. No serious events were reported. These results suggest that polymerized *A. alternata* extracts are safe and well tolerated.[79]

Another advantage of polymerized extracts is the possibility of formulating mixtures that include allergens with proteolytic activity, as is the case with *A. alternata*. The native extracts of this mold have a high enzymatic activity that can cause the degradation of other allergens present in the mixture. Polymerization significantly reduces this protease activity, which improves the stability of mixed formulations and preserves the integrity of the combined allergens.[80]

Molecular immunotherapy

In order to solve the standardization, efficacy, and safety issues of the traditional *A. alternata* AIT, new products targeting Alt a1 and innovative vaccines, such as epitope, deoxyribonucleic acid (DNA), and messenger ribonucleic acid (mRNA) vaccines, look promising, although not all of them are a reality in clinical practice.[81] Currently, there is a purified extract of Alt a1, the main allergen of *A. alternata*, which has proven to be an effective and safe treatment.[82,83]

A multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted with the goal of evaluating the efficacy and safety of this extract in patients with *Alternaria*-induced rhinoconjunctivitis with or without asthma.[82] The study included 113 patients aged 12–65 years randomly assigned to three groups: placebo, low-dose Alt a 1 (0.2 mcg), and high-dose Alt a 1 (0.37 mcg). After 12 months of treatment, the group that received the high-dose Alt a 1 experienced a significant reduction in both symptoms and medication use compared to the placebo group. In addition, a decrease in skin reactivity and IgE levels was observed, accompanied by an increase in IgG4 levels in the treated groups. In terms of safety, no serious adverse reactions were reported; the reactions observed were mainly local and late, with no significant differences between the groups.

To investigate changes in the sensitization profile of patients treated with Alt a 1 immunotherapy, the authors analyzed serum from 64 patients enrolled in the clinical trial. At baseline, 98.4% of patients were sensitized to Alt a 1, while recognition of other allergens such as Alt a 4/6 (21.9%), Alt a 7 (12.5%), and others was much lower. Most patients (70.3%) were monosensitized to Alt a 1.

After 1 and 2 years of treatment, a reduction or even disappearance of Alt a 1-specific IgE was observed, particularly in patients receiving active immunotherapy, indicating effective desensitization. The study also revealed demographic differences: adolescents and males showed higher rates of polysensitization, whereas females and adults were more often monosensitized to Alt a 1. Patients who were initially monosensitized to Alt a1 experienced greater clinical improvement. These findings proves that Alt a 1 molecular immunotherapy is effective in desensitizing patients allergic to *A. alternata*, reducing IgE reactivity to the major allergen and improving clinical outcomes.

More recently, a polymerized molecular extract of Alt a 1 was developed. A nonrandomized study in 42 children aged 6–16 years with asthma and allergic rhinitis showed that after 24 months, the treated group had significant improvements in fractional exhaled nitric oxide (FeNO), forced expiratory volume in 1 second (FEV1), and asthma control test (ACT) score, in addition to a reduction in medication use, with no adverse effects recorded. The authors conclude that this immunotherapy represents a promising and safe strategy to modify the course of allergic disease in the pediatric population.[84]

The passing of time in pediatric patients treated with AIT: How does allergy to A. alternata *evolve?*

It has been proven that greenhouse effect increases the global mean temperature and the amounts of carbon dioxide (CO_2) in the atmosphere are responsible for the longer fungal season lengths in warmer European regions, resulting in more allergy symptom days.[85] Wolf et al. (2010)[86] showed that increased CO_2 and temperature amplified spore production and antigenic protein content, suggesting that climate change will increase fungal responsiveness by increasing sporulation rates, potentially contributing to the increasing prevalence and severity of asthma and other respiratory allergies.[87]

The component resolved diagnosis (CRD) allows not only accurate diagnosis but can also predict clinical prognosis and responses to AIT, enabling personalized treatment plans to be developed in a rapidly changing climate scenario. Hypersensitivity to fungi in polysensitized patients may be masked by sensitization to other allergenic sources, making fungal allergy difficult to diagnose.

In the PREVAL study[8] of consecutive patients diagnosed with allergic rhinitis, children were more frequently sensitized to *A. alternata* (69.8%) compared to adults (30.2%), and 63% of those patients were male with a stylistically significant difference ($p = 0.0292$). A doctoral thesis (University of Granada, Spain) found that the figures for monosensitization to *A. alternata* were higher in children under 5 years (27.4%) compared to patients aged 11–15 years (19.4%) and those older (1.6%).[88]

Conclusions

In the dynamics of *A. alternata*, the intensity and duration of exposure, measured by temporal averages, are responsible for sensitization, but it is the spore peaks (from 10 spores/m^3 to 100 spores/m^3) that produce the symptoms. The optimal range of temperatures that promote the production and release of conidia of *A. alternata* into the environment is from 18.9°C to 25.2°C. This explains why in central and northern Europe the distribution is unimodal with higher values of conidia in summer, and in southern Europe the distribution is bimodal with maximum concentration at the end of spring and the beginning of autumn.

A. alternata, if the optimal conditions are met, can also be found inside homes; so, it is an allergen both outdoors and indoors. The size of the fungal spores (20–60 um) causes them to be retained in the nasal mucosa triggering rhinitis, but the rupture of the conidia generates smaller fractions that are deposited at the airways, causing an inflammatory reaction in the bronchial mucosa and a worse lung function.

Between 70% and 95% of patients sensitized to the whole extract of *A. alternata* are specifically sensitized to Alt a1. *A. alternata* is rich in proteases that are capable of breaking the tight intercellular junctions, causing structural changes in the bronchial epithelium, which makes it more permeable, promoting sensitization to other allergens such as pollens and mites, and also interacting with the immune system to modify the innate response to viral infections.

In reference to the treatment of allergy to *A. alternata* with specific allergen immunotherapy, native extracts have demonstrated efficacy, although their use has been limited due to safety and standardization issues. Currently, treatments with AIT with polymerized and molecular extracts with Alt a1 offer safer and more effective treatments that are tailored to the needs of each patient, allowing combinations of allergens for the treatment of poly-allergic patients, positively valuing the early start of treatment of immunotherapy as the only treatment that can control the evolution of this disease in pediatric patients.

Competing Interests

The authors had no relevant financial interests to disclose.

Author Contributions

All authors contributed equally to this article.

Conflicts of Interest

The authors declare that they have no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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