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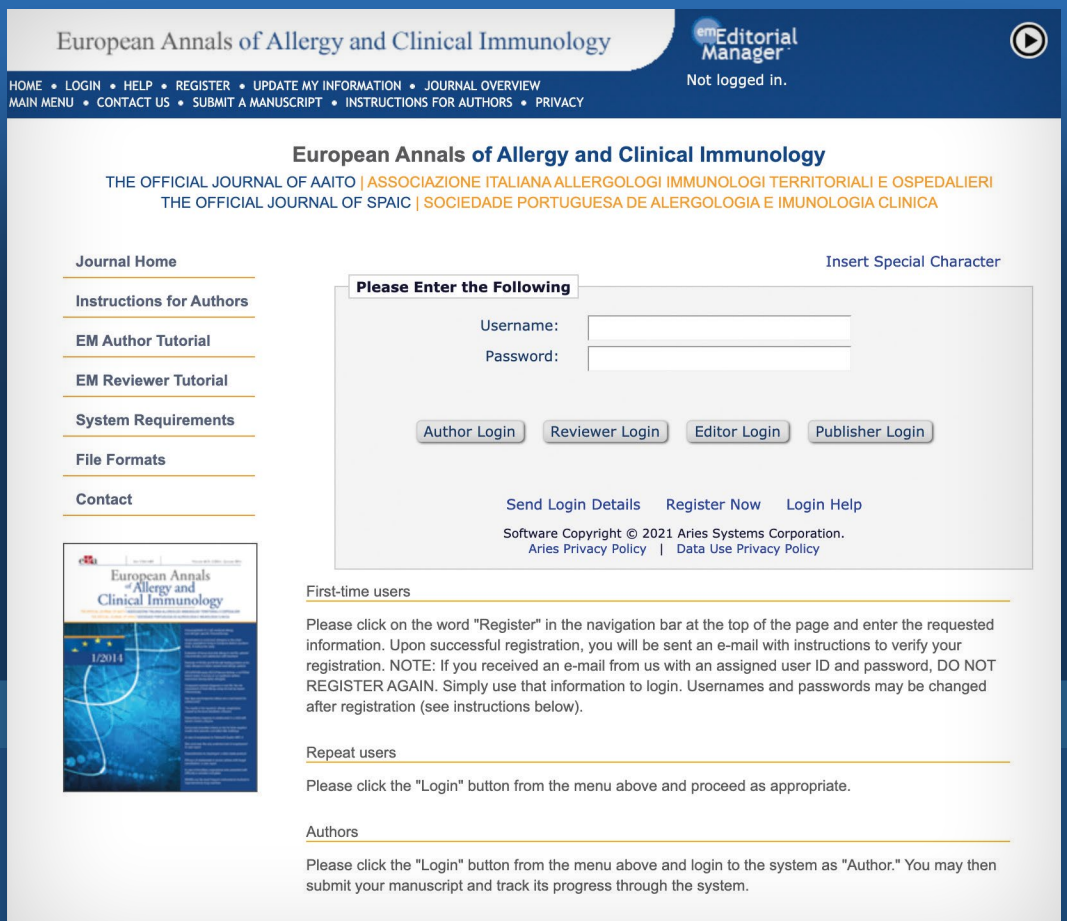
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Riccardo Asero[1], Valerio Pravettoni[2], Danilo Villalta[3], Enrico Scala[4]

Is gastrointestinal epithelial barrier dysfunction the only responsible for sensitization to food allergens?

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Key words

Epithelial barrier; epithelial damage; food allergy; allergen sensitization; immune tolerance.

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Impact statement

Evidence is accumulating that sensitization to food allergens occurs outside the intestinal tract in most instances, as if the first contact is with the intestinal it results in immune tolerance.

Summary

Epithelial barriers are crucial defenses against pathogens and allergens, and recent theories suggest that environmental factors may compromise them, leading to type 2 inflammation and conditions such as asthma, atopic dermatitis, food allergy, and rhinitis. While skin and respiratory barriers show clear dysfunctions in allergies, the role of the gut epithelium is less defined, particularly given its ability to absorb nutrients and maintain immune tolerance under normal conditions.

Research indicates that gastrointestinal barrier integrity typically remains preserved in food allergies, allowing for the development of immune tolerance to ingested food antigens through mechanisms like Treg cells and IgA. Allergies to cow's milk or hen's egg proteins often resolve with age, highlighting the gut's evolving role in allergen sensitization.

Studies like the LEAP (Learning Early About Peanut Allergy) trial demonstrate the preventive benefits of early allergen exposure against peanut allergy, supporting the dual allergen exposure hypothesis. New allergens such as alpha-Gal and gibberellin-regulated proteins (GRP) reveal distinct sensitization pathways beyond traditional ingestion routes, implicating non-dietary sources in allergen introduction.

Introduction

Epithelia constitute the primary defensive barrier against pathogens, pollutants, and allergens. There is an increasing consensus that the dysfunction of epithelial barriers may initiate the development of type 2 inflammation and, consequently, allergic diseases such as asthma, atopic dermatitis, food allergy, and rhinitis. This concept, first proposed in 2017 (1), and subsequently revisited and expanded by Akdis in 2021 (2), posits that, in the presence of a genetic predisposition, mucosal damage induced by environmental factors, including agents associated with industrialization, urbanization, and modern life, may explain the rise in allergic, autoimmune, and other chronic diseases. Indeed, epithelial barrier dysfunctions associated with type 2 inflammatory responses have been extensively documented in asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), atopic dermatitis (AD), and eosinophilic esophagitis (EoE) in both children (3) and adults (4-6). For these conditions, biologics targeting IgE, IL-5, or IL-4 and IL-13 receptors are widely used with excellent results. Unlike other epithelial barriers (*e.g.*, skin, respiratory tract, and esophagus), the gastrointestinal tract epithelium possesses unique features that may play a protective role against allergies

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and should be considered when investigating the processes leading to sensitization to food allergens. First, the intestinal epithelium is naturally structured to absorb nutrients, and it has been known for many years that, under normal conditions, about 2% of food proteins are absorbed and systemically distributed in an immunologically active form (7). Second, there is a lack of consistent evidence that gastrointestinal epithelial barrier function is impaired in food allergy in humans (8). Finally, under normal conditions, the contact between food allergens and the immune system following intestinal absorption leads to specific immune tolerance mediated by antigen-specific Treg cells, IgA, and T clonal anergy (9, 10).

In effect, hypersensitivity to cow's milk or hen's egg proteins, which is extremely common in infancy and early childhood and generally attributed to gut immaturity, is outgrown in most instances later in childhood (11, 12), persisting into adolescence or adulthood only in a minority of cases. Furthermore, *de novo* sensitization to cow's milk or hen's egg proteins in adulthood is exceptionally rare, and adult allergic individuals encountered in clinical practice have typically been allergic to these foods since childhood, with the exception of sensitization to hen's egg alpha livetin allergen, present in feathers and excrements of domestic birds (parrots or canaries), which occurs via the respiratory tract. In animal models of food allergy or asthma, mice (most commonly BALB/c) are sensitized to ovalbumin or other allergens by epicutaneous, subcutaneous, or intraperitoneal (rarely respiratory) administration of the allergens. Once sensitized, they are challenged orally or via the respiratory tract (13-17). This is because the initial sensitization via the oral route would be very difficult to achieve in the absence of adjuvants.

The idea that food allergy/sensitization may originate outside the gut, at least in adults, was suggested thirteen years ago in an article reviewing a large series of case reports and case series on sensitization to foods via the skin or respiratory tract (18). Since then, several novel types of food allergies have been described, and we have witnessed enormous progress in understanding the patho-mechanisms of sensitization to foods and other allergens. This article will critically review some of these newly described food allergies, focusing particularly on the routes of sensitization to the corresponding allergens.

Materials and methods

A PubMed search covering the last thirteen years of published scientific papers was conducted to identify novel types of food allergies and to verify whether the most recent findings in this field could support our previous hypotheses (18). The newly described food allergens in the literature were categorized by models and discussed individually, with particular emphasis on the possible modes of sensitization, since in many cases sensitization via the gut appeared highly unlikely.

Food allergy models

The LEAP study

One of the most intriguing models of food allergy development in children has been the LEAP (Learning Early About Peanut Allergy) Study. The authors of this study observed that peanut allergy developed more frequently in Jewish children living in the UK who strictly avoided peanuts compared to Jewish children from Israel who were early introduced to peanuts (19). Building on this observation, the same group conducted randomized studies on peanut consumption in infancy (20), concluding that the early introduction of peanuts significantly decreased the frequency of peanut allergy development among high-risk children and modulated immune responses to peanuts. The same group later demonstrated that the tolerance induced by oral ingestion is allergen-specific, does not prevent the development of other food allergies (21), and is long-lasting (22). Skin protein deficiencies increase the severity of eczema and risk of food allergy to peanuts (23, 24).

These findings fully confirmed the dual allergen exposure hypothesis proposed in 2008 (19), which suggested that primary exposure through the skin and/or airways leads to sensitization, whereas exposure through the gut leads to tolerance. This study has eventually led to a complete paradigm shift in clinical practice regarding food avoidance in high-risk children.

Galactose-alpha-1,3-Galactose (alpha-Gal)

The observation in 2007 of anaphylactic reactions upon the first administration of Cetuximab occurring exclusively on a regional basis (25), and of the development of delayed IgE-mediated anaphylactic reactions following the ingestion of red meat in the same areas, led to the identification of a common allergen: the oligosaccharide galactose-alpha-1,3-galactose (alpha-Gal) (26). Sensitization to this novel allergen was eventually found to follow the bite of different ticks, such as the lone star tick in the US (27), *Ixodes ricinus* in Europe (28), *Amblyomma sculptum* in South America (29), and *Haemaphysalis longicornis* in Japan (30), which inject this non-primate mammalian oligosaccharide into the human host. Alpha-Gal allergy, therefore, represents a typical example of extra-intestinal sensitization to a food allergen.

Gibberellin-Regulated Proteins (GRP)

In recent years, severe allergic reactions to peach and other plant-derived foods have been observed in specific regions of the world, particularly Japan, Southern France, and Italy, in individuals not sensitized to the well-known allergens PR-10, profilin, or lipid transfer protein. The pan-allergen responsible for these allergic reactions was eventually identified as gibberellin-regulated protein (GRP). Cross-inhibition studies indicated that the primary sensitizer is cypmaclein, a minor allergen in cypress pollen (31-34). Thus, GRP allergy represents a novel type of pollen-food syndrome.

Plant defensins

Defensins are another example of primary sensitization to molecules found in pollens (in this case, Asteraceae, specifically Art v 1 in Artemisia and Amb a 4 in Ambrosia), with cross-reactivity to homologous molecules in plant foods (such as Ara h 12 and Ara h 13 in peanut, or Api g 7 in celery), long recognized as the "Mugwort-Celery-Spice Syndrome" (35, 36). Defensins are small peptides of approximately 5 kDa in weight, rich in cysteine and therefore highly resistant to proteolytic digestion, temperature, and pH. Sensitization to plant defensins is predominantly observed in Northern Europe (0.45%) and accounts for about 6% of food-induced anaphylaxis cases in Europe linked to consumption of celery, coriander seed, fennel, cumin seeds, anise seed, *etc*. (37). The phenomenon of defensins is yet another example of food reaction triggered by sensitization to aeroallergens.

Mint pollinosis and anaphylaxis

Interesting is the case of a man who, after starting to cultivate mint plants in his backyard. developed nasal congestion, cough and wheeze while gardening during the pollen season of mint. He experienced an anaphylactic reaction within five minutes of eating a peppermint candy (38). Other systemic reactions are reported in the literature after the assumption of products containing mint (39-41).

Shrimp allergy

House dust mites (HDM) and crustaceans, as well as mollusks and other invertebrates, share many allergens in a complex interaction (42). Shrimp is the second cause of food allergy in Italy (43). It is not yet fully clear whether shrimp allergy originates as a primary phenomenon or because of airborne house dust mite allergy, as cross-inhibition studies between shrimp and mites have not been conducted thus far. However, in a study on a large group of HDM-allergic subjects, about 20% were sensitized to crustaceans, and 41% of these had never eaten crustaceans before (44). Two studies on shellfish allergies highlight occupational risks and clinical features. In a pilot study of Greenlandic snow crab workers, 40% showed positive skin prick tests for snow crab and 21% had specific IgE antibodies. Asthma symptoms were common (45%), and 11-22% of workers had probable or possible occupational asthma (45). Meanwhile, a study on shellfish hypersensitivity in 48 patients found that shrimp and squid were the most frequent allergens, causing urticaria/angioedema (81%), asthma (38%), and rhinitis (29%). Prick tests yielded better diagnostic results than CAP, with significant associations between clinical history and test results for crustaceans and cephalopods (46).

Edible insects

Edible insects are considered novel food in the European Union, as they were not consumed by humans in the EU before 1997 (47). Recently, our research group conducted a comprehensive survey involving over 2000 participants who had never previously consumed insect proteins, as these were not available in the Italian market until 2023 (48). Surprisingly, just under 10% of the study population showed sensitization to *Tenebrio molitor, Acheta domesticus, or Locusta migratoria,* despite never having consumed these protein sources before. This represents another clear example of sensitization not induced by ingestion of the culprit food, barring inadvertent exposure, which is plausible but objectively unproven.

Fish allergy

Fish allergy is particularly common in areas with a high supply of fish. A recent study demonstrated that fish allergy is often present in early childhood, with 95% of fish-allergic children also having atopic dermatitis (49). This significant proportion was corroborated by another study on fish allergy in children, which importantly observed that the median age at the first reaction was 12 months, with most children reacting upon their first exposure (50). Jellyfish is another marine animal which can sensitize humans through skin contact. Sensitization can then lead to anaphylaxis when the jellyfish is ingested cooked (a typical food of the oriental world) (51) as reported by several case reports (52, 53).

Anisakis allergy

Anisakiasis is a fish-borne parasitic disease caused by consuming raw or undercooked fish or cephalopods contaminated by third-stage larvae of Anisakis simplex or other members of this nematode family. The live larvae can elicit a parasitic infection of the digestive tract or, occasionally, other organs, causing erosive and/or hemorrhagic lesions, ascites, perforations, and allergic reactions such as anaphylaxis, acute/chronic urticaria, and angioedema (54). There is a consensus that an active infection is required to initiate allergic sensitivity to Anisakis. In other words, the immune system comes into direct contact with the Anisakis allergen only after the parasite causes mucosal damage. In effect, already in 2000 Purello D'ambrosio and co-workers noted that in a population of fishermen/fishmongers, Anisakis hypersensitivity had caused urticaria/angioedema episodes in 72% of cases and respiratory symptoms in 28% of cases (55).

The prevalence of sensitization to Anisakis was found to be higher than that to fish, with rates of 8% and 6%, respectively. Reactivity to Anisakis-specific IgE was linked to bronchial hyperreactivity and dermatitis and showed a significant increase in correlation with fish consumption. Sensitization to Anisakis is associated with cutaneous symptoms (OR 1.9), whereas sensitization to fish is correlated with rhinoconjunctivitis (OR 2.7) (56).

Cereals

There have been reports, particularly from Japan, indicating that the use of wheat-germ cosmetics, such as soaps and face scrubs, has frequently led to sensitization to wheat (57, 58). This serves

as a clear example of percutaneous sensitization to food allergens in adults. Furthermore, severe allergic reactions, including anaphylaxis, have been documented in individuals allergic to house dust mites who suffer from rhinitis and/or asthma after ingesting cereals contaminated by mites (59).

Lipid transfer protein

Lipid transfer protein and its possible ways of sensitization have been extensively reviewed in our previous paper (18). In recent years an unusual way of sensitization to this allergen has been reported via Cannabis smoke (Can s 3 is the primary sensitizing LTP in these cases) (60, 61). Albeit not always clinically expressed, this is one further example of sensitization to a food allergen through the skin and/or the respiratory tract.

α-Livetin and the Bird-egg syndrome

Gal d 5 (α-Livetin), an allergen present in egg yolk, plays a crucial role in the phenomenon known as Bird-egg syndrome. This allergen is also prevalent in the serum, feathers, meat, and excrement of birds, making it a common environmental allergen in places where birds such as parrots, pigeons, or canaries are found or bred. In adults, sensitization generally occurs initially through inhalation, leading to conditions such as asthma or rhinoconjunctivitis, and is subsequently followed by the development of an egg allergy (62).

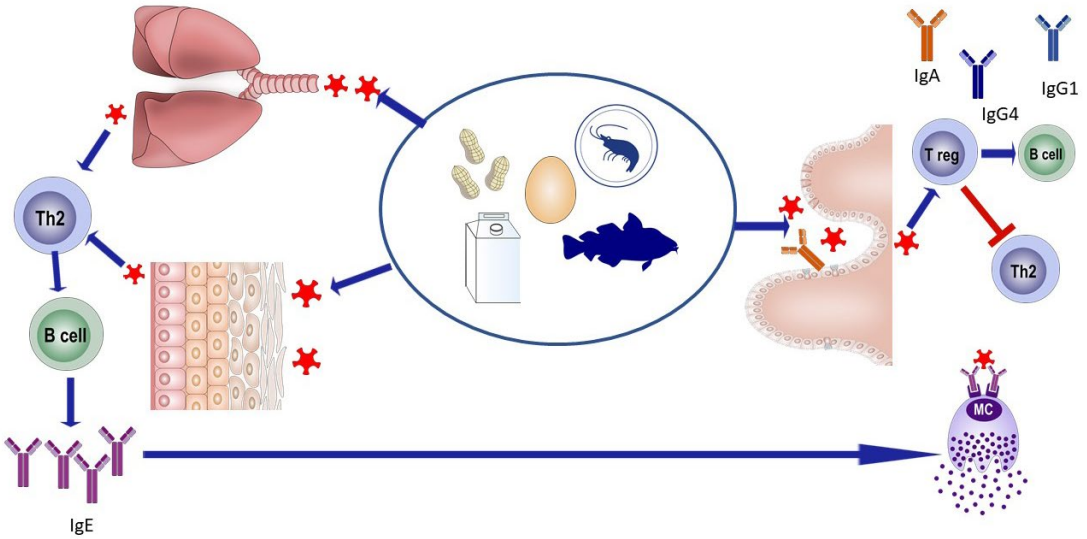
Donkey milk lysozyme allergy

Lysozyme in donkey's and horse's milk, which is suggested as a theoretically safe alternative food in cow's milk allergic children, has been identified as a potentially relevant food allergen. Interestingly, in a recent report the two patients described and thoroughly investigated got most probably sensitized through the skin by using donkey milk-based cosmetics (63).

Conclusions

Significant advancements have been achieved in understanding the development and maintenance of oral tolerance (64, 65), elucidating key mechanisms by which the immune system can discriminate between harmless food antigens and harmful pathogens. However, while the defective epithelial barrier theory is robustly supported for the skin and respiratory tract, its applicability to the gut epithelium remains less conclusive. The gut epithelium's role in food allergy pathogenesis is nuanced, with evidence suggesting that under normal conditions, allergen exposure through the oral route predominantly induces tolerance rather than sensitization (64, 65). Albeit the postulate of gastrointestinal sensitization to food allergens remains, an increasing number of studies consistently highlight that primary sensitization to food allergens often occurs via routes other than the intestinal tract, such as the skin or respiratory mucosa (**figure 1**). This phenomenon challenges traditional paradigms and underscores the complexity of allergen sensitiza-

Figure 1 *- The primary exposure of food allergens via the digestive tract leads to anergy or to the production of specific IgG1, IgG4 and/or IgA. Exposure of the immune system to food allergens via the airways or via damaged skin (in atopic dermatitis patients) leads to Th2-mediated inflammation and eventually to the production of specific IgE antibodies that spread throughout the body. The subsequent ingestion of the same food allergens causes potentially severe allergic reactions.*



tion pathways. The LEAP study exemplifies how early and controlled exposure to allergens can prevent the development of allergies, supporting the dual allergen exposure hypothesis. Conversely, novel allergens like alpha-Gal and gibberellin-regulated proteins (GRP) illustrate instances where sensitization occurs via unconventional routes, such as tick bites or exposure to plant-derived allergens, further expanding our understanding of allergic sensitization mechanisms. A recent systematic review and meta-analysis comparing the prevalence estimates of the eight big food allergies in Europe during the last decade and the previous period concluded that, with some exceptions, the prevalence of allergy/sensitization to cow's milk, egg, wheat, soy, peanut, tree nuts, fish and shellfish had not substantially changed. However, it also noted that more foods beyond the "big eight" have been studied recently, and thus that the balance between the "big eight" and emerging food allergies is probably changing in Europe (66). In clinical practice, these insights require tailored approaches to diagnose and manage food allergies effectively. Better care of atopic dermatitis may contribute to prevent sensitization to food allergens. Future researches should continue to explore the interplay between epithelial barrier function, immune tolerance, and environmental factors to refine strategies for allergy prevention and treatment, aiming to improve outcomes for individuals affected by food allergies globally.

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Contributions

RA: conceptualization. RA, VP, DV, ES: methodology, supervision, writing – original draft, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Local allergic rhinitis in children: identification and characterization in a specialty outpatient clinic

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Key words

Rhinitis; acoustic rhinometry; nasal allergen challenge; house dust mite; child.

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Impact statement

This is the first study to investigate LAR in child and adolescent subjects in Latin America, contributing to the understanding of its prevalence and characteristics in this geographic area.

Summary

Background. *Local Allergic Rhinitis (LAR) is a phenotype defined by rhinitis symptoms with negative responses to systemic sensitization tests but with an exclusively nasal allergic inflammatory response. Data on the pediatric age group is scarce, and no Latin American data has been published so far.* ***Methods.*** *Nasal Allergen Challenge (NAC) was performed with Dermatophagoides pteronyssinus and Blomia tropicalis in six- to 18-year-old patients diagnosed with rhinitis and no systemic sensitization. NAC was monitored using subjective parameters and acoustic rhinometry. The study aimed to identify LAR in child and adolescent subjects previously diagnosed with non-allergic rhinitis (NAR) in a Brazilian specialty outpatient clinic (Allergy and Immunology).* ***Results.*** *During the study period, we analyzed 758 skin prick tests (SPT). Of those, 517 (68.2%) were diagnosed with rhinitis. Among those, 18.4% (95/517) had a negative SPT, meeting the criteria for inclusion in the study. Twenty-five patients underwent NAC, and 40% (10/25) of them, previously considered to have NAR, had a positive test and were reclassified as having LAR. Based on the analyzed characteristics, clinically differentiating LAR from NAR was impossible.* ***Conclusions.*** *This study represents the first investigation of LAR in child and adolescent subjects in Latin America, contributing significantly to the understanding of its prevalence and characteristics in this geographic area. Among a subgroup of patients lacking systemic sensitization submitted to NAC, 40% (10/25) demonstrated a positive NAC with Dermatophagoides pteronyssinus and Blomia tropicalis, warranting their reclassification to LAR. NAC, with multiple allergens, has been proven safe and viable in pediatric populations, affirming its critical role in the accurate diagnosis of LAR.*

Introduction

Rhinitis is defined as inflammation of the nasal mucosa, characterized by one or more of the following symptoms: nasal congestion, rhinorrhea, sneezing, nasal pruritus, and hyposmia (1). Patients with chronic rhinitis are primarily classified into two main groups: allergic rhinitis (AR) and non-allergic rhinitis (NAR) (2). However, over the past decades, studies have indicated that numerous patients with rhinitis, despite negative responses to systemic sensitization tests, exhibit an exclusively nasal allergic inflammatory response (3). This response has been corroborated through Nasal Allergen Challenge (NAC) with pollens and/or house dust mites (4, 5). These findings have led to the conceptualization of a new rhinitis phenotype, termed local allergic rhinitis (LAR) (6). LAR appears to be a stable (7) and well-delineated phenotype in adult subjects, predominantly affecting young, eutrophic, non-

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smoking women with a family history of atopy (8). However, limited data exists on LAR in the pediatric age group. A recent systematic review (9), encompassing ten studies with a total of 1,024 patients revealed significant variation in the prevalence rates of LAR (3.7% to 83.3%) among individuals previously classified as having non-allergic rhinitis (NAR). Notably, the prevalence rates in Eastern countries (3.7% to 16.6%) were considerably lower than those in Western countries (22.3% to 83.3%). Yet, no distinct clinical features have been identified that could explain this geographical discrepancy or differentiate between the various rhinitis phenotypes in childhood (4).

In adult patients, protocols involving conducting NAC with multiple allergens sequentially on the same day have shown favorable safety and result reproducibility when compared to performing a single NAC separately (10). Utilizing multiple allergens in NAC accelerates the procedure, simplifies it, and enhances comfort for both physicians and patients, thereby facilitating the screening for LAR. The selection of allergens for NAC, whether multiple or single, should be individualized based on the relevance of the allergens involved in the pathophysiology of AR, particularly in the region where the test is conducted.

In Brazil, there is a predominance of perennial AR, primarily triggered by household allergens. The most significant of these are the mites: *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), and *Blomia tropicalis* (Bt). Other household allergens include the epithelia of domestic animals (dogs and cats), cockroaches, and fungi (11).

The primary objectives of this study were twofold: 1) to ascertain the prevalence of child subjects presenting with rhinitis without systemic sensitization, and 2) to identify LAR in child and adolescent subjects previously diagnosed as NAR in a Brazilian specialty outpatient clinic (Allergy and Immunology). This differentiation was achieved by conducting NAC with multiple allergens. Additionally, the study aimed to pinpoint any clinical or demographic features that could effectively discriminate between patients with LAR and those with NAR.

Materials and methods

This cross-sectional study involved a retrospective selection of patients aged six to 18 years diagnosed with rhinitis in accordance with the Allergic Rhinitis and its Impact on Asthma (ARIA) (2) criteria, who were attending the Allergy and Clinical Immunology outpatient clinic and showed no evidence of systemic sensitization. Systemic sensitization was determined by a positive skin prick test (SPT) and the presence of serum-specific IgE for the following allergens: *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), *Blomia tropicalis* (Bt), animal epithelia (dog and cat), fungal mix, and *Periplaneta americana* (Pa). A positive result for the SPT was defined as a wheal with a diameter > 3 mm greater than the negative control. For serum-specific IgE levels (measured using ImmunoCAP; Thermofisher), values ≥ 0.35 kUA/L were considered positive.

Patients who had other pulmonary or cardiovascular diseases, uncontrolled asthma, significant anatomical defects of the upper airway affecting nasal patency (such as deviated septum, adenoid hypertrophy, and nasal polyposis), those on systemic corticosteroids within the last 15 days, and those with a history of upper airway infection in the previous 30 days were excluded from the study. Additionally, patients with any motor or neurological inability to cooperate were also excluded.

During the study period (October 2017 to September 2022), patients were invited to the outpatient clinic to undergo voluntary NAC with Dp and Bt. Before the NAC, patients completed the total nasal symptom score (TNSS) based on the last seven days to assess the severity of AR. This assessment considered the following symptoms: runny nose, itching, nasal obstruction, and sneezing. Each symptom was scored on a scale: 0 = no symptoms, 1 = mild symptoms (when present for a short time and without impact on daily life), 2 = moderate symptoms (frequently present but without impact on daily life), and 3 = severe symptoms (when present most of the time with significant effect on daily activities or sleep). The TNSS, ranging from zero to 12 points, is categorized according to the sum of the scores for each item: mild symptoms (0-4), moderate symptoms (5-8), and severe symptoms (9-12) (13).

The present study was approved by the local Research Ethics Committee (#2.330.653).

Nasal allergen challenge with multiple aeroallergens

The NAC was conducted using extracts of Dp and Bt (FDA ALLERGENIC® - Brazil, 5,000 UBE/ml) diluted at different levels in 0.9% saline solution. The nasal response was monitored using acoustic rhinometry (A1, GM Instruments, Scotland - UK). Evaluations were conducted by the same observer (FM) in triplicate, adhering to international recommendations (14), and under standardized room conditions, including temperature and humidity. All patients were instructed to discontinue oral antihistamines, topical intranasal corticosteroids and antihistamines, chromones, leukotriene receptor antagonists, and decongestants for two weeks before the provocation test.

As noted earlier, the volume of the nasal cavity in its first five centimeters (V5) was defined as the primary parameter for monitoring by AcR in child subjects (15). This parameter was calculated by summing the values from each nostril (16). Additionally, the two smallest cross-sectional areas (MCA1 and MCA2, cm^2) in each nostril were measured. To determine the concentrations and dilutions of Dp and Bt for NAC with multiple allergens, data from previous single NAC protocols with these allergens in the same age group were utilized (17).

Baseline measurements were taken following the instillation of 0.15 mL of saline solution (0.9%) into each nostril. If the initial

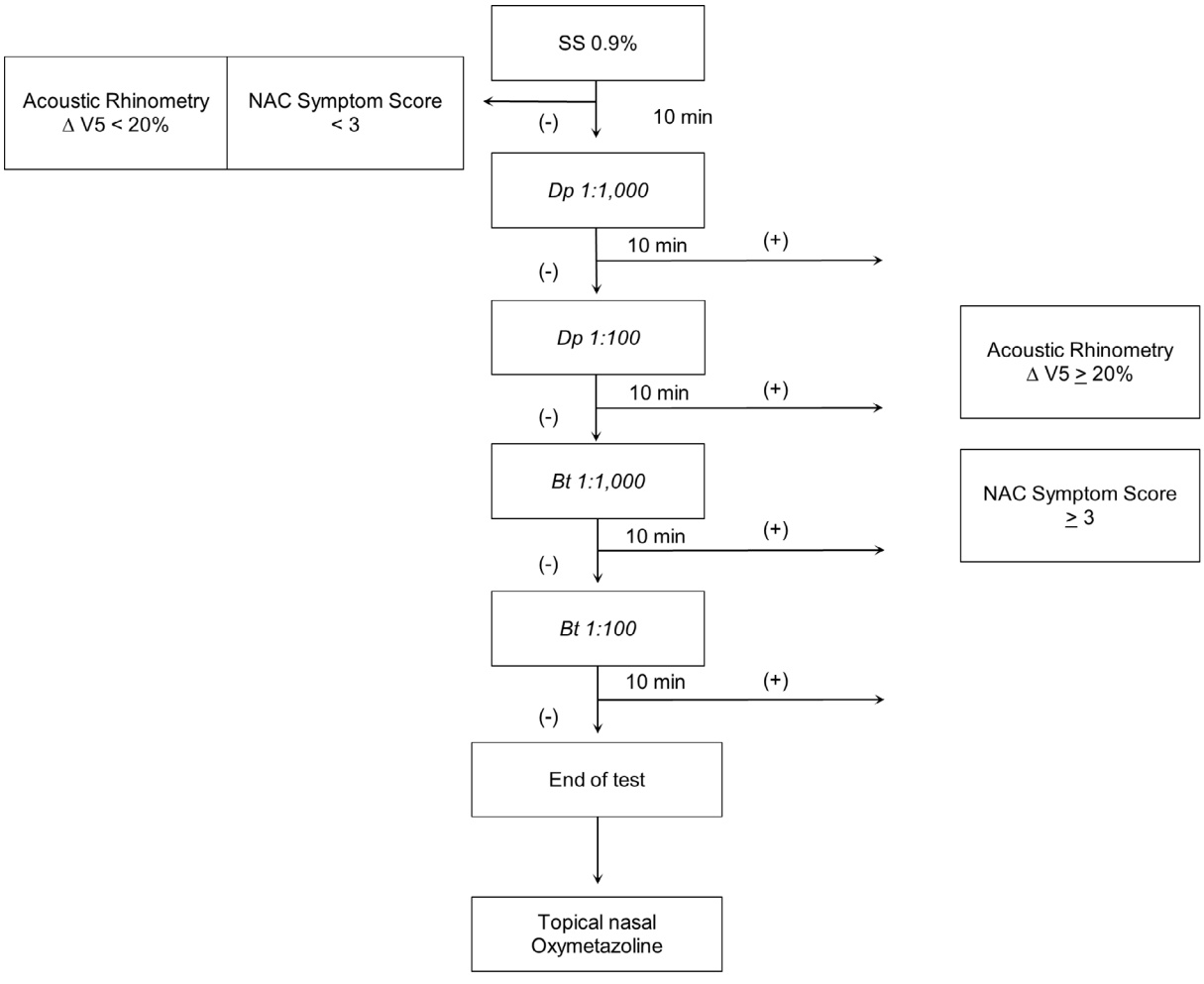
result was negative, the administration of two consecutive allergen solutions, Dp and Bt, commenced. These were provided in two increasing dilutions (1:1,000 and 1:100) for each allergen, at an average interval of ten minutes, in the aforementioned order, bilaterally using a spray device delivering 0.15 mL per nostril. AcR measurements were taken ten minutes after each instillation. Subsequently, nasal symptoms were assessed and recorded using a standardized symptom score (17, 18) (**figure 1**).

NAC symptom score

All patients were clinically evaluated on the day of the NAC, and this assessment was considered as baseline for starting NAC. To monitor the test, a NAC symptom score previously adapted to Brazilian children (17) was used, assessing the following symptoms: nasal secretion assessed by anterior rhinoscopy, amount of sneezing, and presence of extranasal symptoms (eye tearing, conjunctivitis/chemosis, urticaria, cough/dyspnea) (18). This score assigns significance to values equal to or higher than three (**table I**), the threshold for positive tests.

NAC with multiple allergens was deemed positive if a reduction equal to or greater than 20% in V5 was observed, or when the symptoms score questionnaire was > 3 points. In cases of a positive NAC result with Dp (at any dilution), the patient was required to return after seven days for an NAC with Bt only. Regardless of the final NAC result, all patients remained under observation for 30 minutes following the conclusion of the test.

Figure 1 - *NAC with Dp (5,000 UBE/mL) and Bt (5,000 UBE/mL) in children and adolescents.*



Dp: *Dermatophagoides pteronyssinus;* Bt: *Blomia tropicalis.*

Table I *- NAC symptom score carried on to monitor NAC with Dermatophagoides pteronyssinus and Blomia tropicalis.*

	Symptoms	Points
Nasal secretion at anterior rhinoscopy (examiner's judgment)	As before / normal	0
	Slight increase / minor amounts visible	1
	Pronounced	2
Irritation	0-2 sneezes	0
	3-5 sneezes	1
	> 5 sneezes	2
Distant symptoms	None	0
	Watery eyes and/or palatal itching and/or deep aural itching	1
	Conjunctivitis and/or chemosis and/or urticaria and/or cough and/or dyspnea	2

Min: 0 points; Max: 6 points; Positive NAC > 3 points.

Statistical analysis

The initial stage involved a descriptive analysis of the collected data. For categorical variables, both absolute and relative frequencies were tabulated. Numeric variables were presented in terms of averages and interquartile ranges. To compare results between groups, nonparametric tests, including the Mann-Whitney, Wilcoxon, and Fisher tests, were employed. In all instances, the threshold for rejecting the null hypothesis was established at a 5% level. Data derived from the NAC with multiple allergens was systematically encoded, transferred to a database prepared in Microsoft Excel, and subsequently subjected to statistical analysis using the Statistical Package for the Social Sciences (SPSS) - version 29.0.

Results

During the retroactive analysis period (January 2015 to December 2019), a total of 758 skin prick tests (SPTs) performed on patients attending the outpatient clinic were analyzed. Of these, 517 (68.2%) patients were diagnosed with rhinitis according to the Allergic Rhinitis and its Impact on Asthma (ARIA) (2) criteria. Within this group, 422 patients had a positive SPT, indicating that 81.6% (422/517) of the rhinitis patients had allergic rhinitis (AR), while 18.4% (95/517) had a negative SPT, thereby meeting the criteria for inclusion in the study.

Out of the eligible patients, forty-five (47%) were successfully recruited via telephone; 27 of them underwent NAC with Dp and Bt, followed by an evaluation of the results. Among these, 7.4% (2/27) were excluded from the final analysis due to being diagnosed with nonspecific nasal hyperreactivity following saline instillation, which triggered NAC positivity before the instillation of the allergens (**figure 2**).

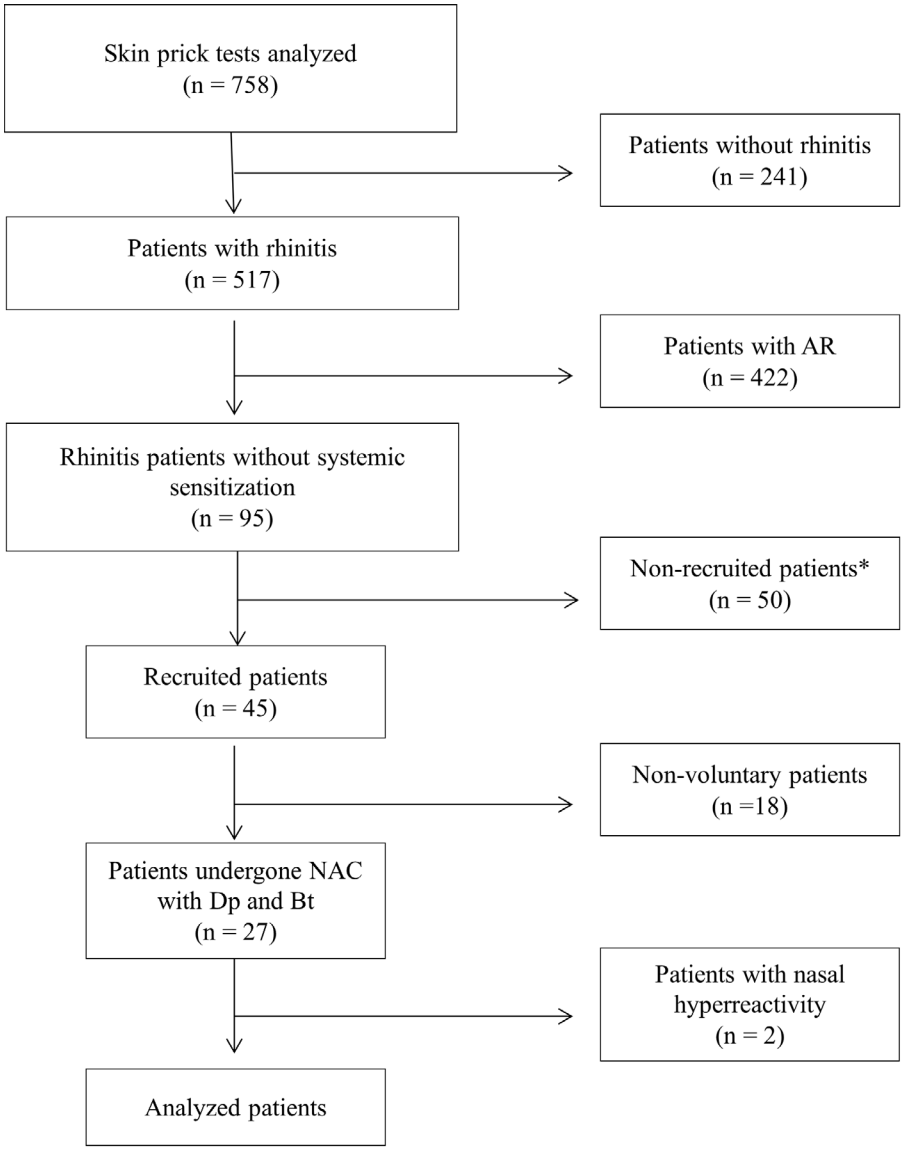
The median age of the remaining 25 patients was nine years (range: 8.5-12.5 years), with the median age of symptom onset being two years (range: 1.5-5 years). Of these patients, 44% (11/25) were female, and they had a median TNSS of 5 (range: 3-7). All patients included in the study were clinically evaluated on the day of the NAC and had mild symptoms or were asymptomatic. This assessment was considered as the baseline for starting NAC. Following the NAC with multiple allergens, 40% (10/25) of the patients tested positive and were subsequently reclassified as having LAR. At the conclusion of the NAC, the median variation in V5 for the LAR group was -22.66% (range: -26.10% to -21.39%), while the NAR group showed a median variation of -7.59% (range: -10.09% to -1.07%), as illustrated in **figure 3**. There was no significant difference in the variations of MCA1 and MCA2 between patients with positive and negative NAC outcomes (**table II**). Clinically, none of the patients undergoing NAC exhibited severe or pulmonary symptoms during or after the procedure.

Among the positive tests, nine were characterized by a greater than 20% reduction in V5, while only one was identified by a symptom score ≥ 3. Regarding the triggering allergens, one patient showed reactivity to both Dp and Bt, six exclusively to Dp, and three exclusively to Bt.

In the NAR group (n = 15), the median age was nine years (range: 8-12 years), the median age of symptom onset was three years (range: 1-5 years), with 46.7% (7/15) being female, and the median TNSS recorded as seven (range: 5-8). Four of these patients did not exhibit signs or symptoms of other allergic diseases such as asthma, atopic dermatitis, or conjunctivitis.

Conversely, in the LAR group (n = 10), the median age was 10.5 years (range: 8.5-13.5 years), the median age of symptom onset

Figure 2 *- Patient recruitment flowchart.*



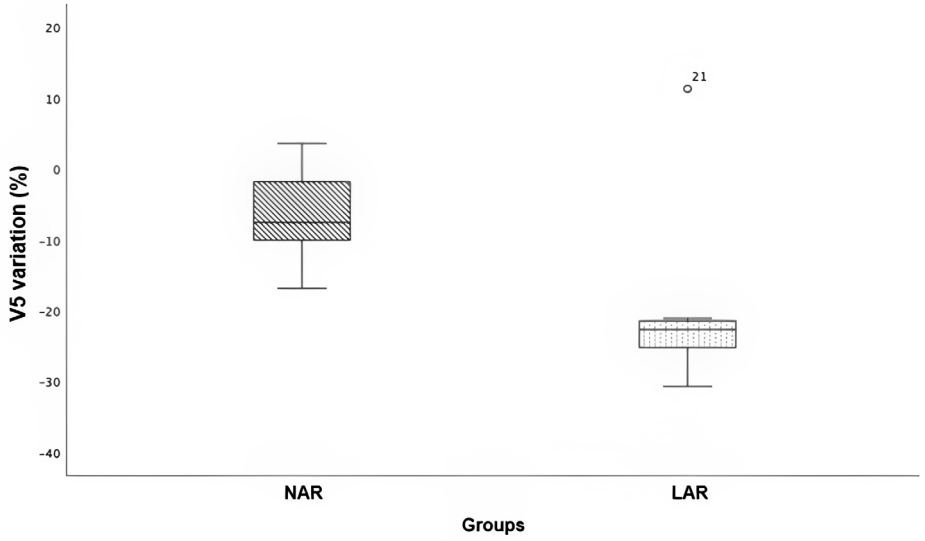
AR: Allergic Rhinitis; *reasons for non-recruitment: patient/family refusal to participate in the study, patients who were no longer regularly being monitored at the Allergy Clinic and/or who had outdated registration data, impossibility of carrying out NAC during the pandemic period by SARS-CoV-2.

was two years (range: 1.8-3.5 years), with 40% (4/10) being female, and the median TNSS noted as three (range: 2.5-6.3). Only one patient in this group showed no signs or symptoms of other allergic diseases.

The NAR and LAR groups had similar characteristics, with no statistically significant difference in the AcR parameters (baseline V5, baseline MCA1, and MCA2) or the clinical variables evaluated (age, TNSS, age at onset of symptoms). The specific characteristics of these groups are detailed in **table II**.

Patients in the NAR group demonstrated a trend ($p = 0.06$) towards having a higher TNSS compared to those in the LAR group (**figure 4**).

Figure 3 *- Variation in V5 (%) monitored by acoustic rhinometry, after NAC with Dp and Bt, in group NAR and group LAR.*



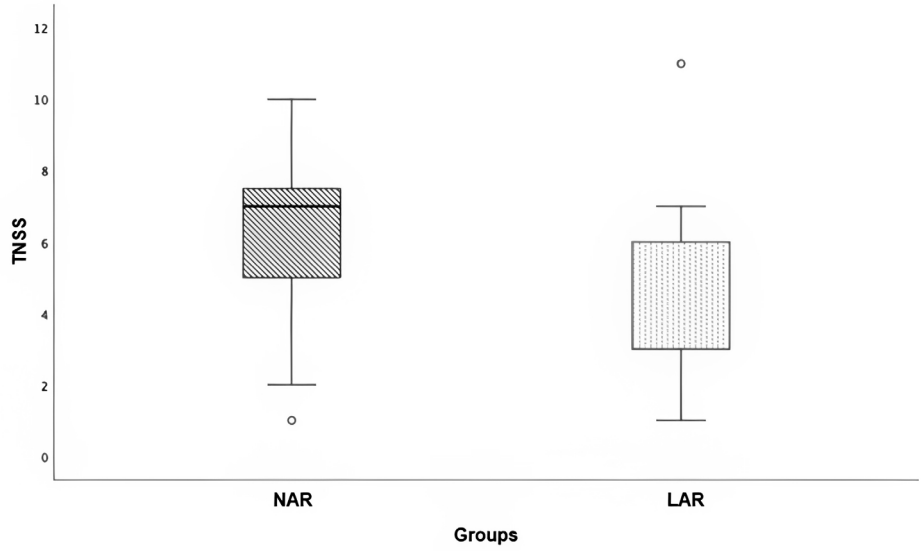
LAR: Local Allergic Rhinitis; NAR: Non-Allergic Rhinitis; p < 0.001.

Table II *- Demographic and clinical characteristics observed in non-allergic rhinitis (NAR) and local allergic rhinitis (LAR) patients.*

Characteristics	NAR group (n = 15)	LAR group (n = 10)	P-value
Age* (years)	9 (8–12)	10.5 (8.5–13.5)	0.53
Female gender – n (%)	7 (46)	4 (40)	0.74
Baseline MCA1* (cm^2)	1.01 (0.84–1.32)	1.06 (0.91–1.22)	0.56
Baseline MCA2* (cm^2)	1.87 (1.14–2.24)	2.21 (1.31–3.5)	0.28
Baseline V5* (cm^3)	8.74 (7.17–10.80)	9.09 (7.82–11.93)	0.46
Age at symptom onset* (years)	3 (1–5)	2 (1.8–3.5)	0.64
Association with other allergic diseases – n (%)			
Asthma	6 (40)	7 (70)	7 (70)
Conjunctivitis	7 (46)	2 (20)	2 (20)
Atopic Dermatitis	3 (20)	4 (40)	4 (40)
TNSS*	7 (5–8)	3 (2.5–6.3)	0.06
Mild – n (%)	2 (13)	7 (70)	0.06
Moderate – n (%)	11 (74)	2 (20)	0.07
Severe – n (%)	2 (13)	1 (10)	0.80

V5: volume of the first five centimeters of the nasal cavity; MCA1 and MCA2: the two smaller cross-sectional areas; TNSS: Total Sympton Score; Mean (IQR – Interquartile Range).

Figure 4 *- TNSS in LAR and NAR group.*



TNSS: Nasal Symptom Score; LAR: Local Allergic Rhinitis; NAR: Non-Allergic Rhinitis; p = 0.062.

Discussion and conclusions

To our knowledge, this study represents the first investigation of LAR in child and adolescent subjects in Latin America, contributing significantly to the understanding of its prevalence and characteristics in this demographic. This research facilitates comparisons with data from other parts of the world.

Dp and Bt were selected for the NAC based on the characteristics of AR in the Brazilian population. This choice underscores the dominant presence of perennial AR with sensitization to household allergens, particularly mites (11). As such, this protocol, if applied in populations with similar characteristics, enables reliable international comparisons.

In the present study, 18.4% of patients with rhinitis did not exhibit systemic sensitization. Prevalence studies of NAR are scarce in the pediatric population, due to the challenges in distinguishing NAR from viral infections, which are common in this age group. Despite these challenges, all of them indicate a decline in NAR prevalence throughout childhood (19, 20). Our study, being cross-sectional, did not allow for long-term evaluation of patient behavior. Nonetheless, the prevalence observed aligns with findings reported in other studies.

In the subset of patients who underwent NAC with Dp and Bt, 40% (10/25) tested positive, allowing for their reclassification as having LAR. The data is consistent with that obtained in Western countries (22.3% to 83.3%), as reported in a recent systematic review (9) that included ten studies and 1,024 patients. These rates are remarkably higher than those found in Eastern countries (3.7% to 16.6%), and the reasons for these regional differences remain unclear.

Upon examining the characteristics of rhinitis in Brazil, which is predominantly perennial and triggered by house dust mites, it appears unlikely that the type of rhinitis (seasonal *vs* perennial) or the different allergens (pollens *vs* house dust mites) used in NAC account for the variance in prevalence. The characteristics of rhinitis in Brazil more closely resemble those in some tropical countries, such as Indonesia, than in Western countries like Spain or Italy, where seasonal rhinitis and pollen involvement are more prevalent in the etiology of LAR.

In our study, a trend was observed towards higher TNSS among patients with NAR compared to those with LAR, particularly among patients with mild and moderate symptoms. However, we were unable to identify any clinical or laboratory features that could distinctly differentiate these two rhinitis phenotypes. This finding is consistent with conclusions drawn by other authors and a recent systematic review (9).

Currently, the NAC is predominantly used as a laboratory investigation and research tool. Yet, with the identification of LAR, the development of more comprehensive NAC protocols incorporating multiple allergens could streamline and enhance the screening process for patients with this specific rhinitis phenotype. The primary advantage of such screening would be the early initia-

tion of specific immunotherapy. This approach could significantly improve the quality of life for these patients during childhood, as the efficacy of this treatment has already been established in adult subjects (21).

It is important to highlight that the EAACI and AAAAI position papers on nasal allergen challenges (22, 23) were very important in standardizing NAC protocols, but unfortunately, to date, there are no Brazilian or Latin America NAC guidelines. However, these recent recommendations are not specific to children, since the parameters recommended as clearly positive were based on data obtained mainly in adults. Therefore, to define the test as positive, we chose to use criteria obtained in a study carried out specifically in Brazilian children. In this study, performed during histamine nasal challenges, a 19%-21% drop in V5 were the cutoffs with highest sensitivity and specificity when compared with 100% increase in total nasal resistance measured by anterior active rhinomanometry (15). Furthermore, the symptom score used in our study to monitor the clinical response to NAC also differs from international recommendations. We used a symptom score previously employed to standardize NAC with Dp and Bt in children and adolescents in Brazil (17) in a study carried out before the publication of the current recommendations (22, 23). The NAC protocol with Dp and Bt in child subjects was proven to be safe, as evidenced by the absence of significant pulmonary and extranasal symptoms during and after the procedure. This safety applied even to patients who had another allergic disease (asthma, atopic dermatitis, or conjunctivitis) alongside their rhinitis diagnosis. This result aligns with findings from other studies in adult subjects (10), indicating that NAC with multiple allergens does not increase the risk of cumulatively triggering positive results. In our study, both patients with LAR and NAR who exhibited clinical symptoms post-NAC predominantly presented nasal symptoms such as nasal secretion and sneezing, making it clinically challenging to differentiate between the two groups.

This study does have limitations, including its reliance on a convenience sample and a small number of patients from a tertiary service. The substantial number of patients who were not recruited (50/95) represents a notable constraint. However, the difficulty in recruiting these patients represents a challenge in specialized Allergy and Immunology Services, particularly following negative systemic sensitization tests (*in vivo* and/or *in vitro*), which can lead to frustration and perceived lack of clarity in diagnosis for patients and their families, thus discouraging continued follow-up in allergy outpatient clinics. Another limitation is that the NAC with multiple allergens was limited to house dust mites, excluding other common indoor allergens like pet dander, cockroaches, and fungi, which are prevalent in our population. A Brazilian survey on sensitization in atopic child subjects found the following rates: Dp (67.8%), Df (66.5%), Bt (57.1%), cockroach (34.4%), cat epithelium (12.2%), dog epithelium (8.1%), fungi (3.1%) (11). The absence of established protocols for these allergens in the pediatric age group justified their exclusion. However, not testing these allergens may have led to an underestimation of the frequency of LAR, potentially maintaining the NAR classification in patients who would have responded positively to other allergens.

To conclude, in this study we observed that 18% of child and adolescent subjects with rhinitis lacked systemic sensitization. Focusing on patients who underwent NAC, 40% (10/25) of them tested positive, enabling their reclassification as patients with LAR. Notably, we were unable to discern any clinical features that distinctly differentiate children with LAR from those with NAR. Additionally, our findings indicate that NAC with Dp and Bt is safe for use in child and adolescent subjects. However, further longitudinal studies are necessary to understand the reasons behind the decreasing prevalence rates of NAR throughout childhood and to clarify the disparities in LAR rates between Western and Eastern countries.

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Contributions

TRTG: data curation, investigation. DS: supervision, validation, visualization, writing – original draft, writing – review & editing. FYM, GFM: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing – original draft, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Diet quality, asthma and airway inflammation in school-aged children

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Key words

Diet quality; asthma; obesity; airway inflammation; children.

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Impact statement

Non-overweight/obese children with higher diet quality have lower levels of airway inflammation and reduced prevalence of asthma. Nonetheless, the same associations are not observed in overweight/obese children.

Summary

Background. *Asthma is a major public health problem, with increasing prevalence in most countries, particularly among children. Poor dietary quality is also increasing in children, and evidence of the overall quality of children's food patterns effects on asthma is scarce.* ***Methods.*** *This cross-sectional analysis (660 children: 49.1% females, aged 7-12 years) evaluated the association between diet quality and asthma (n = 56) and airway inflammation among school-aged children according to body mass index (BMI). Diet quality was assessed through the Healthy Eating Index (HEI)-2015, and categorized by tertiles. Higher scores represent a healthier diet. A questionnaire was used to enquire about self-reported medical diagnosis of asthma and asthma under medication. Lung function and airway reversibility were measured, and airway inflammation assessed measuring exhaled fractional nitric oxide (eNO). Two categories of BMI were considered: non-overweight/obese ($p < 85^{th}$) (n = 491) and overweight/obese ($p \geq 85^{th}$) (n = 169). The associations between diet quality and asthma and airway inflammation were estimated using logistic regression models.* ***Results.*** *Non-overweight/obese children in 2^{nd}tertile of HEI-2015 score had decreased odds of having eNO ≥ 35ppb (OR 0.43, 95%CI 0.19;0.98), medical diagnosis of asthma (OR 0.18; 95%CI 0.04;0.84), and asthma under treatment (OR 0.12; 95%CI 0.01;0.95), compared to children in the 1^{st}tertile.* ***Conclusions.*** *Our findings suggest that a higher diet quality associates with lower levels of airway inflammation and reduced prevalence of asthma among non-overweight/obese school-aged children.*

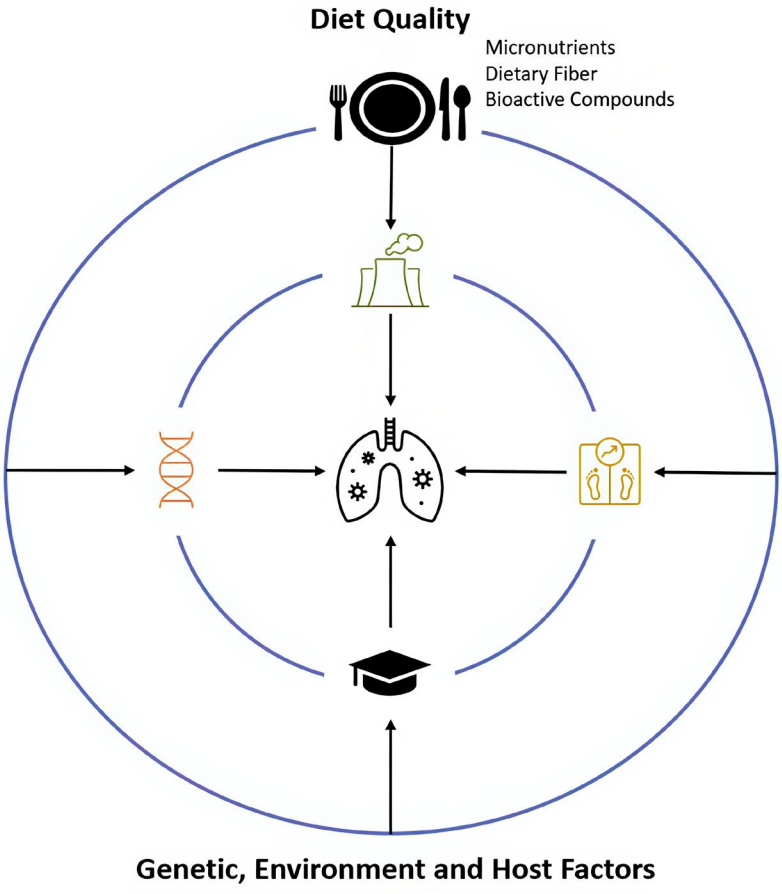
Introduction

Asthma is a major global health concern, and its prevalence and incidence are higher among children, especially in high-income countries (1). According to the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence of asthma in children has increased in many countries (2). Environmental factors, in conjunction with genetic susceptibility, can play a significant role in asthma pathophysiology (3) and it's possible that its prevalence has risen as a result of lifestyle and environmental

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changes (4). Dietary changes, such as increased consumption of highly processed and refined foods and decreased consumption of vegetables and fruits, may be an important contributor to this increase in asthma prevalence trend (**figure 1**) (4). Dietary patterns with the above-mentioned traits are likely to lead to obesity, which is a major public health concern, being simultaneously a disease modifier and a risk factor for asthma (4). Asthma has been increasingly associated with obesity (4, 5) and both the diseases appear to be driven by genetic and lifestyle factors (5, 6). Obese individuals have an increased risk of asthma, as well as more frequent and severe symptoms and exacerbations, a lower quality of life, and a reduced response to asthma medications (3, 7). In fact, children who were overweight had an increased adjusted risk for incident asthma (relative risk [RR] 1.17; 95% confidence interval [CI] 1.10-1.25) and for obese (RR 1.26; 95% CI 1.18-1.34) (8).
Although the role of diet has undoubtedly recognized mechanisms in some diseases (9), it has not been identified as a causal factor for asthma development (3). In this perspective, the majority of studies on diet and asthma association are performed upon specific foods or foods components (10). Nonetheless, foods are ingested as complex combinations, which include bioactive components, nutrients, and their specific effects in the food matrix, which interact with each other and lead to synergist effects modulating and influencing metabolic and health effects according to different dietary patterns (3, 4).
It has been demonstrated that higher dietary acid loads may modulate asthma-related miRNAs among school-aged children (11). Additionally, eating a higher dietary diversity of vegetables was linked to a lower risk of airway inflammation and to a lower prevalence of self-reported asthma (12). It has also been shown that diet's inflammatory characteristics may have a role in modulating the effects of indoor air pollution on asthma, indicating

Figure 1 *- Representation of the interaction between potential risk factors (as enviromental polution, education and socioeconomic status, weight and genetics) for asthma and airway inflammation and diet quality as a potential protector factor.*



that the exposure effect to PM2.5 and PM10 on children with asthma was significantly higher among those who have a pro-inflammatory diet compared to a more anti-inflammatory diet (13). The influence of food on asthma, asthma symptoms and lung function are topics of growing interest (3) and diet scores that evaluate diet quality, have been broadly used (4, 14). Dietary scores that can assess diet quality, based on established knowledge on the role of dietary intakes in prevention of major chronic diseases, may be of particular interest when investigating the role of diet in asthma (15).

In this context, the aim of this study was to investigate the effect of diet quality on asthma and airway inflammation in children. Additionally, we explored the association between diet quality, airway inflammation and three different definitions of asthma, considering a stratification according to children's BMI.

Materials and methods

Study design and participants

This is a secondary analysis of a cross-sectional study conducted between 2014 and March 2015. A total of 1602 children aged 7-12 years old in the 3rd and 4th grades, from 20 public school located in Porto, Portugal, were invited to participate (12). A total of 686 (42.8%) did not present the signed informed consent and 58 (3.8%) declined to perform clinical procedures. Among the remaining 858 children (53.6%), 660 (76.9%) had complete nutritional data (HEI-2015) and were considered for the analysis (**figure 2**). Written consent was obtained from every child's legal guardian. The study was done in accordance with Helsinki Declaration and The Ethics Committee of the University Hospital São João approved the study (ARIA 248-13).

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by The Ethics Committee of the University Hospital São João.(ARIA 248-13, date of approval: 20 of September of 2013). Informed consent was obtained from all subjects involved in the study.

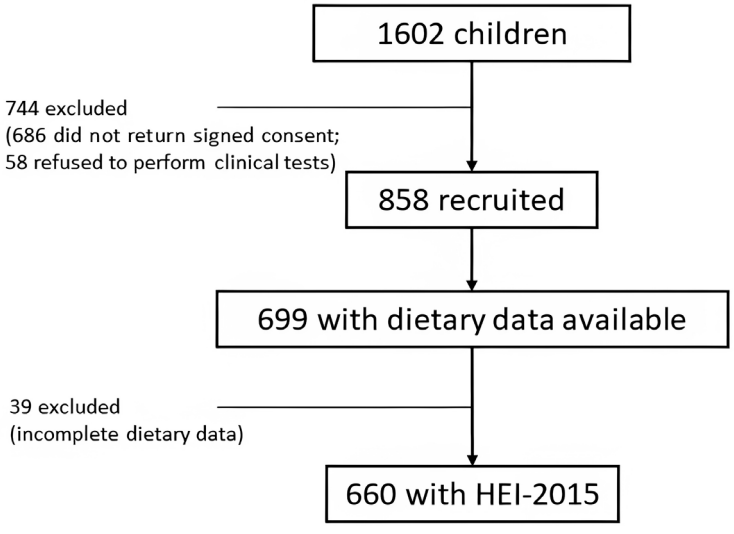
Participants assessment

Dietary and diet quality assessment

Dietary information was collected using a single interviewer-administered 24-hour food recall questionnaire answered by the children, following standard procedures, and using a photograph atlas to estimate portion sizes. Participants were asked in detail about their food and beverages intakes from the previous 24h, including brands and quantities (16). Nutritional data and total energy intake (kcal) were estimated through the software Food Processor® (ESHA Research, USA), that encompasses databases of Portuguese nutritional food composition.

Diet quality was evaluated by using the HEI-2015, which has 13 components that sum to a total maximum score of 100 points (17). This index has two sections: adequacy and moderation. Higher scores are provided on the nine adequacy components (total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins and fatty acid ratio) and reflect higher intakes. The other four components

Figure 2 *- Flow chart of the included participants.*



are moderation components, which are calculated so that higher scores indicate lower intakes (refined grains, sodium, added sugars, and saturated fats). For most of the components the ratio of the dietary constituents is 1,000 kcal of energy, except for fatty acids. Fatty acids use the ratio of the sum of monounsaturated and polyunsaturated fatty acids to saturated fatty acids. Also, two components, saturated fat and added sugars, are conveyed on a percent of energy basis (17, 18).

Since all components of the index are considered equally important, the HEI components are equally weighted. Some diet groups are represented by two components, each with a maximum of 5 points. All other components receive up to ten points. Total fruits, whole fruits, total vegetables, greens and beans, total protein foods, seafood and plant proteins are components that are scored to a maximum of 5 points when: total fruits ≥ 0.8 cup equivalent, whole fruits ≥ 0.4 cup equivalent, total vegetables ≥ 1.1 cup equivalent, greens and beans ≥ 0.2 cup equivalent, total protein foods ≥ 2.5 ounces equivalent, seafood and plant proteins ≥ 0.8 ounces equivalent. These components have 0 points when no food from the component's groups are consumed (17). Whole grains, dairy, fatty acid ratio, refined grains, sodium, added sugars, and saturated fats can have a maximum of 10 points, when: whole grains ≥ 1.5 ounces equivalent, dairy ≥ 1.3 cup equivalent, fatty acid ratio ≥ 2.5 cup, refined grains ≤ 1.8 ounces equivalent, sodium ≤ 1.1 grams, added sugars ≤ 6.5% of energy, and saturated fats ≤ 8% of energy. The standard for having a minimum score (zero) is as follows: on the whole grains and dairy components implies no consumption; for fatty acids having a ratio that is ≤ 1.2; for refined grains ≥ 4.3 ounces equivalent; for sodium ≥ 2.0 grams; for added sugars ≥ 26% of energy; and for saturated fats ≥ 16% of energy. Intakes between the minimum and maximum standards are scored proportionately (17). As for arranging the components of the HEI-2015 score: "Total Fruits" includes 100% fruit juice and whole fruits; "Total Protein Foods" includes meat, poultry, eggs, seafood, nuts, seeds, soy products, legumes (beans and peas); "Seafood and Plant Proteins" component comprises seafood, nuts, seeds, soy products, legumes (beans and peas); "Greens and Beans" consist of legumes (beans and peas) and dark-green vegetables; "Total Vegetables" enclose legumes (beans and peas), dark-green vegetables and all other vegetables. "Dairy" component contains all milk products, such as fluid milk, cheese, and yogurt, and fortified soy beverages (17). For dairy, meat, poultry and eggs, saturated fat is counted separately; when considering nuts, seeds and soy products it encloses nuts, seeds, and soy products (other than beverages) (17). As information was registered in grams, "Portions and Weights, 2017-2018 Food and Nutrient Database for Dietary Studies - At A Glance" was used to transform dietary components from grams to cups (19). The higher the overall HEI-2015 score, the better is the diet quality and adherence to a healthy eating pattern (17, 18). The HEI-2015 score was categorized into three groups according to the tertile score (1^{st}: ≤ 54.53; 2^{nd}: > 54.53 and ≤ 65.37; 3^{rd}: > 65.37). The use of nutritional supplementation (vitamins/minerals) by the children in the past year was also considered.

Anthropometry

Weigh was measured by a digital scale (Tanita™ BC-418 Segmental Body Analyzer) and recorded in kilograms, and height was measured by a portable stadiometer and recorded in centimeters (cm). BMI was obtained by the calculation of weight/height² and displayed in kilograms per square meters (kg/m²). Participants were then divided into two groups, non-overweight/obese ($p < 85^{th}$) and overweight/obese ($p \geq 85^{th}$) (20), according to specific age and sex percentiles provided by the US Centers for Disease Control and Prevention (21). The US CDC definition was grounded on an evaluation of the degree of agreement among several BMI classifications (US CDC, International Obesity Task Force, World Health Organization, and Percentage of Body Fat), with the US CDC showing the highest level of agreement with all the other classifications (data not presented) (22).

Airway inflammation

To quantify airway inflammation, FeNO was measured using a NObreath analyzer (Bedfont Scientific Ltd., Rochester, Kent, UK). The results were stratified in accordance with the official American Thoracic Society (ATS) criteria for children (23) and expressed as parts per billion (ppb). Exhaled NO was dichotomized using a cut-off point of equal or above 35 ppb representing increased levels of eNO.

Current asthma and respiratory symptoms assessment

The ISAAC in Childhood − based questionnaire was performed by the child's legal guardian. It enquired about social, demographic, and behavioral information and consisted of questions about the allergic/respiratory health and respiratory symptoms in the previous twelve months (24). Asthma symptoms (wheezing and cough symptoms) were defined by a positive answer to the question "*Had your child wheezing or whistling in the chest, in the past twelve months?*"; and "*Did your child suffer coughing at night in the last twelve months?*" or "*Did your child suffer coughing more than three months in the last year?*". Self-report of asthma diagnosed by a physician was defined based on an affirmative answer to the question "*Has your child ever been diagnosed with asthma by a physician?*"

Airway reversibility and lung function, were recorded before and after 15 minutes of the inhalation of 400 µg of salbutamol and evaluated through spirometry, following the official ATS/European Respiratory Society (ERS) guidelines (25).

Positive bronchodilation (+BD) was characterized by at least a 12% and over 200 mL increase in forced expiratory volume in one second (FEV1) as suggested by current GINA guidelines (52) and as a way to compare with the existing literature. Nevertheless, additionally, we also included in our analysis the new definition of +BD, suggested by the European Respiratory Society:

a change of > 10% relative to the predicted value in forced expiratory volume in 1 second (FEV1) (26).
Three different definitions of asthma were considered as previously described (27): 1) ever asthma: self-reported medical diagnosis; 2) +BD or medical diagnosis plus current asthma symptoms: self-reported medical diagnosis with reported symptoms (wheezing, dyspnea, or dry cough) occurring in the past 12 months or positive BD (12% and over 200 ml increase in forced expiratory volume in one second); and 3) medical diagnosis and under asthma treatment – self-reported medical diagnosis and currently under anti-asthma medication.

Atopy
Skin-prick tests (SPT) were performed on children's forearms using a QuickTest™ containing *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* , a mix of weeds, a mix of grasses, *Alternaria alternata*, cat dander, and dog dander, a negative control, and a positive control containing histamine at 10mg/mL (Hall Allergy®, Netherlands), and the results read after 15 minutes.(28) According to standard procedures(28), atopy was defined by a positive SPT to at least one of the tested allergens (wheal ≥ 3 mm diameter) coupled to a positive histamine response (wheal ≥ 3 mm diameter) and no positivity in the negative control (wheal < 3 mm diameter).

Indoor air quality
Air quality assessments were conducted by measuring concentrations of indoor pollutants, including PM2.5, PM10, ultrafine particles (UFP), carbon dioxide (CO_2), ozone (O_3), and nitrogen dioxide (NO_2) at each school. These measurements took place over a 5-day period, specifically from Monday morning to Friday afternoon, during the winter season. To analyze PM2.5 and PM10, a portable TSI DustTrak DRX photometer (model 8533; TSI Inc) was utilized. This photometer employed laser technology and light scattering principles to measure particles. With an accuracy reading of ± 0.1% at 1 µg/m³ and a measuring range of 1-150 × 103 µg/m³, the equipment provided reliable measurements. The photometer was equipped with an internal battery-powered diaphragm pump that allowed for a flow rate of 3.0 L/min. Continuous measurements were collected for a minimum of 8 hours (29, 30).

Socioeconomic data
Parental education level was described as the number of completed school years. It was then divided into 3 categories established by the parent with the highest education level: ≤ 9 years, between ≥ 10 and ≤ 12 years, and > 12 years, and was used to denote the socio-economic status (31, 32).

Statistical analysis
All statistical analyses were performed using the SPSS® statistical package software v27.0 and R studio software.

To check normality for continuous variables, skewness and kurtosis test was used. The characteristics of the participants are presented for the whole sample by sex as percentages for categorical variables, and as median (25^{th}-75^{th} percentile) for non-Gaussian distributed continuous variables, and as mean ± standard deviation (SD) for normal distributed continuous.
In order to determine differences between sexes, the independent-samples t-test for continuous variables and chi-squared test for categorical variables were used. The Mann-Whitney test was used for inferential analysis when non-Gaussian distributions were observed.
The associations between our independent variable, HEI-2015 score, (continuous and categorical) and airway inflammation and asthma, our dependent variables, were estimated using logistic regression models (OR, 95% CI).
When considering categories of the HEI-2015 score by tertiles: the reference and first tertile is ≤ 54.53, second tertile is > 54.53 and ≤ 65.37, third tertile is > 65.37.
The Hosmer-Lemeshow test was performed to assess the fit of the logistic regression model.
The selection of potential confounders was made through a combination of conceptual reasoning and empirical evidence (33). Factors such as age, sex, atopy, dietary factors, air quality, and parental education were chosen based on both our understanding of the subject matter and the evidence available in prior literature (34). Confounders were considered such as age, sex (33), parental education (31-33, 35-38), atopy (33, 39-41), school (13, 30), total energy intake (TEI), and nutritional supplementation use (33). Significant differences were defined with an α-value of less than 5%, 95% confidence interval, ($p < 0.05$).

Results

The characteristics of participants included in the analysis are presented in **table I**. The mean (SD) age of children was 8.7 (0.8) years and 49.1% (n = 324) were girls. A total of 6.8% (n = 45) had a self-reported medical diagnosis of asthma; 8.5% (n = 56) had a medical diagnosis with asthma symptoms or +BD; and 5.6% (n = 37) had a medical diagnosis of asthma and were under asthma treatment. The prevalence of overweight/obese was 25.6% (n = 169).
No significant differences were found among boys and girls except for TEI, and dietary sodium obtained from the 24-hour recall questionnaire. Boys presented higher values for TEI [2,228 kcal (1,966; 2,581) *vs* 2,065 kcal (1,760; 2,403)] and dietary sodium [2,206 mg (1,689; 3,030) *vs* 1,923 mg (1,441; 2,591)] compared to girls.
Additionally, there were also significant differences between boys and girl for both definitions of positive bronchodilation: +BD (a change of > 10% relative to the predicted value in FEV1) (26) and +BD (12% and over 200 mL increase in FEV1) (25).

Table I *- Summary of participants characteristics.*

	Girls n = 324 (49.1%)	**Boys n = 336 (50.9%)**	**Total n = 660**	**P-value**
Age (years), mean ± SD	8.68 ± 0.8	8.69 ± 0.8	8.68 ± 0.8	0.907
BMI category				0.864
Non-overweight/obese	242 (74.7%)	249 (74.1%)	491 (74.4%)	
Overweight/obese	82 (25.3%)	87 (25.9%)	169 (25.6%)	
HEI-2015 Score, mean ± SD	59.6 ± 11.7	58.8 ± 11.1	59.2 ± 11.4	0.387
Carbohydrates, %VET	50.1 ± 7.1	50.9 ± 7.4	50.6 ± 7.3	0.142
Protein, %VET	17.8 ± 4.2	17.3 ± 3.8	17.5 ± 4.0	0.095
Fat %VET	28.8 ± 6.2	28.6 ± 6.4	28.7 ± 6.3	0.679
MUFA %VET	10.2 ± 3.0	10.2 ± 3.3	10.2 ± 3.1	0.815
PUFA %VET	3.8 ± 1.8	3.7 ± 1.5	3.8 ± 1.7	0.500
SFA %VET	9.0 ± 3.4	8.9 ± 3.1	9.0 ± 3.2	0.597
Fiber (g), median (25^{th} – 75^{th})	17.9 (13.3; 24.3)	18.8 (14.4; 24.3)	18.4 (13.8; 24.3)	0.345
Sodium (mg), median (25^{th} – 75^{th})	1923 (1441; 2591)	2206 (1689; 3030)	2053 (1513; 2769)	< 0.001*
Total energy intake (kcal), median (25^{th} – 75^{th})	2065 (1760; 2403)	2228 (1966; 2581)	2865 (1868; 2476)	< 0.001*
Nutritional Supplementation, n (%)	44 (15.4%)	43 (14.4%)	87 (14.9%)	0.496
+BD (> 10%), n%	73 (22.5%)	91 (27.1%)	164 (24.8%)	0.027*
+BD (> 12% and > 200ml), n (%)	21 (6.5%)	15 (4.5%)	36 (5.5%)	0.041*
Asthma Symptoms, n (%)	45 (13.9%)	44 (13.1%)	89 (13.5%)	0.820
Asthma medication, n (%)	45 (13.9%)	44 (13.1%)	89 (13.5%)	0.820
Increased levels of FeNO (≥ 35ppb), n (%)	36 (11.1%)	50 (14.9%)	86 (13.0%)	0.150
Asthma definitions, n (%)				
Ever	23 (7.1%)	22 (6.5%)	45 (6.8%)	0.759
Medical diagnosis with asthma symptoms or +BD	33 (10.2%)	23 (6.8%)	56 (8.5%)	0.124
Medical diagnosis and under asthma treatment	21(6.5%)	16 (4.8%)	37 (5.6%)	0.337
Atopy, n (%)	106 (33.3%)	121 (36.3%)	227 (34.9%)	0.422
Parental education, n (%)				0.236
< 9 years	81 (32.3%)	107 (38.5%)	188 (35.5%)	
10-12 years	84 (33.5%)	77 (27.7%)	161 (30.4%)	
> 12 years	86 (34.3%)	94 (33.8%)	180 (34.0%)	

*Statically significant differences; HEI: Healthy Eating Index; FeNO: Fractional exhaled nitric oxide; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; SFA: Saturated fatty acids; +BD: Positive Bronchodilation; %VET: Percent of Total energy value.

The score of the HEI-2015 showed no differences between sexes, with a total score of 59.6 ± 11.7 for girls and 58.8 ± 11.1 for boys. Components of the HEI-2015 among boys and girls are presented in **table II**. No statistically significant differences were observed. After adjustment for age, sex, atopy, supplementation used in previous 12 months, parental education level, school, and total energy intake, non-overweight/obese children in the 2^{nd} tertile of HEI-2015 score had decreased odds of having eNO ≥ 35ppb (OR 0.43; 95%CI 0.19;0.98), ever asthma (OR 0.18; 95%CI 0.04;0.84) and asthma under treatment (OR 0.12; 95%CI 0.01;0.95), as presented on **table III**.

The Hosmer-Lemeshow test was performed to assess the fit of the logistic regression model and it indicated a calculated chi-square value of 5,279 with a p-value of 0.727. At a significance

Table II *- Scores of the HEI-2015 components by sex (mean ± SD) or median (25^{th} - 75^{th}).*

	Girls n = 324 (49.1%)	**Boys n = 336 (50.9%)**	**Total n = 660**	**P-value**
Total Fruits, mean ± SD	3.44 ± 1.95	3.23 ± 1.96	3.34 ± 1.96	0.171
Whole Fruits, mean ± SD	3.86 ± 1.99	3.71 ± 2.03	3.79 ± 2.01	0.350
Total Vegetables, mean ± SD	1.91 ± 1.46	1.77 ± 1.38	1.84 ± 1.42	0.194
Whole Grains, median (25^{th} – 75^{th})	0.00 (0.00; 2.43)	0.00 (0.00; 2.06)	0.00 (0.00; 2.21)	0.434
Dairy, mean ± SD	6.90 ± 2.93	6.83 ± 2.81	6.87 ± 2.87	0.729
Total Protein Foods, median (25^{th} – 75^{th})	5.00 (4.71;5.00)	5.00 (4.90;5.00)	5.00 (4.86;5.00)	0.512
Seafood & Plant Proteins, mean ± SD	2.69 ± 2.42	2.96 ± 2.40	2.83 ± 2.41	0.148
Greens & Beans, mean ± SD	3.27 ± 2.02	3.24 ± 2.05	3.26 ± 2.04	0.841
Fatty Acids, mean ± SD	3.86 ± 3.57	3.71 ± 3.40	3.78 ± 3.49	0.564
Refined Grains, mean ± SD	2.63 ± 3.31	2.44 ± 3.12	2.53 ± 3.21	0.454
Sodium, median (25^{th} – 75^{th})	10.00 (8.31;10.00)	10.00 (8.29;10.00)	10.00 (8.29;10.00)	0.870
Added Sugars, median (25^{th} – 75^{th})	10.00 (7.99; 10.00)	9.37 (7.64; 10.00)	9.59 (7.86;10.00)	0.098
Saturated fats, mean ± SD	7.79 ± 2.77	7.88 ± 2.59	7.84 ± 2.68	0.644

HEI: Healthy Eating Index.

level of 5%, we cannot reject the null hypothesis. Therefore, we can conclude that the model was adequately adjusted.

Discussion and conclusions

This study revealed that having a higher-quality diet appears to reduce the odds of having higher airway inflammation, asthma diagnosed by a physician, and asthma under medication treatment among school-aged children who are not overweight or obese.

Other studies have proposed a beneficial effect of a higher-quality diet on asthma and airway inflammation, which is consistent with our findings (42-46). In a longitudinal study, lower scores in the Revised Brazilian Healthy Eating Index score increased the odds of wheezing in the previous year among young adults (18 and 22 years old) (OR 1.97, 95%CI 1.33;2.91 and OR 1.98, 95%CI 1.36;2.87, respectively). Accordingly, remaining on a poor diet from age 18 to 22, raised by more than three-fold the odds of chest wheezing (OR 3.28; 95%CI 1.84;5.84) compared to continuing on a high-quality diet (42). Findings from the PARIS birth cohort revealed that children in the higher tertile group of adherence to the Mediterranean diet, considered to have a higher diet quality, had a lower risk of having current asthma compared to children in the lowest tertile group (aOR 0.28, 95%CI 0.12;0.64) (44). Also, adults with high adherence to the traditional Mediterranean diet were more likely to have asthma under control as measured by lung function, symptoms, and exhaled NO (OR 0.22; 95%CI 0.05-0.85) (47). A recent systematic review revealed a protective role of the Mediterranean diet on childhood asthma (45). Moreover, the Mediterranean diet has been shown to modulate the production of some inflammatory mediators known to play a pathogenetic role in asthmatic airways as IL-4 and IL-17 (46) and eNO (48).

Cardinale *et al.* (40) suggested that high levels of pro-inflammatory cytokines could increase the activity of iNOS enzyme (40). Considering the previous hypothesis by Cardinale *et al.*, a higher dietary quality presents various dietary component with antioxidant and anti-inflammatory properties that may reduce the production of pro-inflammatory cytokines (3), and thus decreasing NO production and airway inflammation. A low antioxidant dietary intake, as usually reflected by a low consumption of fruits and vegetables, as well as an intake of foods or following dietary patterns associated with increased oxidative stress, such as saturated fat consumption and adhering to a typical western diet, can increase oxidative damage to the airways via the generation of ROS (49). Because nutrients are not consumed in isolation, the additional and synergistic effects of combining the overall nutrient and phytochemical content acquired from various food matrix and overall diet with higher quality may explain the current study's negative associations (50).

In our study, the protective effect of diet was only observed among children who were not overweight or obese. These results may be due to the low number of overweight/obese individuals. However, a previous study including French adults also found that higher dietary scores assessed by three different indexes were asso-

Table III - *Association between diet quality and airway inflammation and asthma.*

	HEI Score: CrudeModel OR (95% CI)	HEIScore: aOR (95% CI)	HEI Score Tertiles: Crude Model OR (95% CI)		HEI Score Tertiles: aOR (95% CI)		
	Continuous (n = 660)	Continuous (n = 660)	> 54.53 and ≤ 65.37 (n = 220)	> 65.37 (n = 220)	Reference ≤ 54.53 (n = 220)	> 54.53 and ≤65.37 (n = 220)	> 65.37 (n = 220)
Increased levels of eNO (≥ 35ppb)							
All participants	0.98 (0.96;0.99)*	0.98 (0.96;0.99)	0.63 (0.36;1.09)	0.68 (0.4;1.18)	1.0	0.58 (0.29;1.17)	0.74 (0.38;1.45)
Non-overweight/obese	0.97 (0.96;0.99)*	0.97 (0.94;0.99)	0.52 (0.28;0.96)*	0.62 (0.34;1.13)	1.0	0.39 (0.17;0.91)*	0.65 (0.30;1.40)
Overweight/obese	0.99 (0.948;1.04)	0.999 (0.95;1.05)	1.23 (0.34;4.52)	0.93 (0.24;3.65)	1.0	1.48 (0.32;6.91)	0.86 (0.17;4.36)
+BD (> 10%)							
All participants	1.00 (0.99;1.02)	1.00 (0.98;1.02)	1.3 (0.78,2.17)	1.3 (0.78,2.17)	1.0	1.37 (0.81,2.32)	1.36 (0.79,2.33)
Non-overweight/obese	0.99 (0.98;1.02)	0.99 (0.97;1.02)	1.85 (0.66,5.14)	1.62 (0.6,4.33)	1.0	1.93 (0.68,5.48)	2.05 (0.7,5.95)
Overweight/obese	1.02 (0.99;1.06)	1.04 (0.99;1.08)	1.2 (0.66,2.17)	1.22 (0.67,2.22)	1.0	1.24 (0.67,2.32)	1.27 (0.67,2.43)
Asthma (ever)							
All participants	0.97 (0.95;0.99)*	0.98 (0.95;1.01)	0.61 (0.29;1.28)	0.63 (0.31;1.31)	1.0	0.45 (0.18;1.15)	0.71 (0.31;1.62)
Non-overweight/obese	0.96 (0.94;0.99)	0.96 (0.93;0.999)	0.43 (0.17;1.08)	0.55 (0.23;1.29)	1.0	0.14 (0.03;0.69)*	0.53 (0.19;1.49)
Overweight/obese	0.99 (0.95;1.04)	0.999 (0.95;1.05)	1.38 (0.38,5.08)	0.93 (0.24;3.65)	1.0	1.62 (0.41;6.44)	1.19 (0.27;5.23)
Medical diagnosis w/asthma symptoms or +BD							
All participants	0.99 (0.97;1.02)	0.99 (0.97;1.02)	0.74 (0.38;1.47)	0.9 (0.47;1.72)	1.0	0.61 (0.27;1.41)	0.94 (0.44;2.01)
Non-overweight/obese	0.99 (0.96;1.02)	0.99 (0.96;1.02)	0.56 (0.25;1.27)	0.81 (0.38;1.72)	1.0	0.41 (0.14;1.24)	0.94 (0.38;2.32)
Overweight/obese	1.01 (0.96;1.06)	1.01 (0.96;1.07)	1.51 (0.43;5.27)	1.18 (0.32;4.33)	1.0	2.09 (0.47;9.24)	1.6 (0.35;7.25)
Medical diagnosis and under asthma treatments							
All participants	0.98 (0.95;1.00)	0.98 (0.95;1.01)	0.45 (0.19,1.07)	0.69 (0.32;1.48)	1.0	0.30 (0.09;0.94)*	0.76 (0.32;1.84)
Non-overweight/obese	0.97 (0.94;1.00)	0.97 (0.93;1.01)	0.37 (0.13,1.08)	0.61 (0.24;1.54)	1.0	0.09 (0.01;0.78)*	0.62 (0.2;1.87)
Overweight/obese	0.99 (0.94;1.05)	0.92 (0.83;1.02)	0.71 (0.16,3.12)	0.93 (0.24;3.65)	1.0	0.82 (0.17;3.95)	1.08 (0.24;4.78)

*Statically significant differences; aOR: Adjusted odds ratio; HEI: Healthy Eating Index; FeNO: Fractional exhaled nitric oxide; +BD: Positive Bronchodilation; Logistic regression was adjusted to age, sex, parental education, atopy, school, total energy intake, and nutritional supplementation use. Significant differences were defined with a α-value of less than 5%, 95% confidence interval ($p < 0.05$).

ciated with a lower asthma symptom score (4). Nevertheless, in the referred study, when separating individuals based on their BMI and analyzing the association of a higher diet quality with asthma symptom score, some statistically significant associations were lost when BMI was ≥ 25 and < 30 kg/m² and nearly all were lost when BMI was ≥ 30 kg/m² (4). Individuals with obesity can present higher circulating concentrations of many inflammatory markers (51) and the GINA guidelines have in its recommendations weight loss as a component of the strategy of asthma management in obese individuals (52). Also, according to a systematic review, for obese asthmatic adults, the more effective dietary intervention appears to be energy restriction, regardless of the specific dietary components or dietary pattern (53). Given that obesity is a strong risk factor for asthma, having a high dietary quality may not be enough to compensate the negative consequences of being overweight or obese. Furthermore, asthma and obesity have an intricate mechanistic interaction, and comorbidities caused by excess body weight may aggravate or even mimic asthma symptoms, leading to misdiagnosis (54). Moreover, obesity is known to stimulate inflammatory pathways, but most studies among obese children with asthma either observed no correlation or found a negative correlation between exhaled NO and obesity, and similar results were seen in adults (55, 56). There seems to exist a mechanical effect of weight at the thoracic level that inhibits the production and diffusion of nitric oxide (57) or an increase in oxidative stress might cause a higher production of reactive oxygen species with consequential conversion of airway nitric oxide into reactive nitrogen species (55).

Besides, children who are overweight or obese may have a higher index quality score at the expense of elements and food groups that have not been found to be asthma protective such as fruit juice consumption which leads to a higher score in the "Total Fruits" category. In some studies, fruit juice consumption has been linked to an increased risk of asthma (58, 59). When analyzing 100% fruit juice intake, the mean ± SD value in cups, is higher for the overweight/obese group when compared with the non-overweight/obese group (0.19 ± 0.52 cups *vs* 0.13 ± 0.41 cups); although not statistically significant, it results in higher values in the component "Total Fruit" at the expense of fruit juice. Likewise, non-overweight/obese children have overall higher final scores in components that have revealed positive impacts on asthma, namely Whole Fruits, Total Vegetables, Whole Grains, Greens and Beans, and Saturated Fats (data not shown), compared to overweight/obese children. This may also explain the not significant results observed among children in the highest tertile of the HEI-2015 score (**table III**).

In concordance, the U.S.-based Nurses' Health Study revealed that high AHEI-2010 scores were not associated with decreased risk of adult-onset asthma (60). A research with the aim of studying the association between a pro-inflammatory diet (as measured by the energy-adjusted Dietary Inflammatory Index [E-DII]) or a high dietary quality (as measured by the AHEI-2010) with current asthma, current asthma symptoms, and lung function in Hispanic adults, observed that a higher E-DII score (representing a more pro-inflammatory diet) was associated with current asthma (OR for quartile 4 *vs* 1: 1.35, 95%CI 0.97;1.90) and asthma symptoms (OR for quartile 4 *vs* 1: 1.42, 95%CI 1.12;1.81). However, the AHEI-2010 score was not significantly associated with any of the referred outcomes (61), and Han *et al*. (61) suggests that E-DII may be a better indicator of dietary patterns leading to airway inflammation than the AHEI-2010 (61).

In the same line, the index used in the present study (HEI-2015), assigns a positive score not only to the consumption of fruit juices, but also to dairy products, and both components exhibit no positive effects on asthma (58, 59, 62). Even though, not statistically significant, when analyzing 100% fruit juice intake, the mean ± SD value in cups is higher for the third tertile (0.20 ± 0.53 cups) compared with the second (0.16 ± 0.42 cups) and first (0.08 ± 0.34 cups) tertiles, creating higher values in the component Total Fruit. As for dairy, we also observed the same pattern, the third tertile has higher dairy values mean ± SD in cups, than the second and first tertile (7.67 ± 2.58; 6.74 ± 2.85, and 6.19 ± 2.97 cups, respectively).

Furthermore, although HEI-2015 has vegetables intake into consideration, favoring the consumption of green vegetables, it does not have the whole diversity of eaten vegetables into consideration. Mendes *et al*. (12) showed that a higher diversity of vegetables, independently of the amount of the vegetables consumed, was associated with less self-reported asthma and airway inflammation (12). The HEI-2015, likewise, does not take into account the n-6:n-3 PUFA ratio that a number of studies have demonstrated to be relevant in asthma (63, 64), as well as trans saturated fats intake that has been associated with an increase in sputum % neutrophils in asthmatic patients (65). Moreover, this score does not take into consideration the protective influence of microbes and commensal organisms' exposure on the development of asthma and allergy (66). As food-borne microbes may hold a protective effect on asthma (67), cooked or raw vegetables and fruit consumption can impact outcomes (68, 69).

We acknowledge a various number of limitations in our research. Firstly, because this is a cross-sectional study, reverse causation may occur (70), and we can speculate that children who have previously been diagnosed with asthma may have already changed their consumption behavior to a healthier diet, affecting the results. Also, the cross-sectional design precludes the establishment of causal relationships between diet quality with airway inflammation and asthma. Secondly, the HEI-2015 is not validated or adapted for Portugal nor Portuguese children and the recommendations present on this index may not fit this population. Nevertheless, epidemiologic studies are crucial for establishing potential causes of allergic diseases such as asthma, particularly when experimental study designs are challenging to do (71). The same research team

gathered detailed health data, assuring a relative unbiased evaluation of outcome prevalence. Moreover, respiratory, allergic, and dietary outcomes were assessed at the same point in time, even so, symptoms were based on the prior twelve months, identifying individuals that have long-term asthma (27). Other limitation is that we used a 24-hour recall questionnaire, a method primarily centered on short-term intake, and it does not take seasonality into consideration. Nevertheless, detailed data about common size containers, ingredients used in mixed dishes, and commercial product brand names were gathered, permitting a good quality characterization of consumption and dietary intake. Moreover, because one single day does not represent usual intake, multiple recalls are preferred to report an individual's habitual intake (72). Nonetheless, a 24-hour recall questionnaire can estimate the current diet without inducing alterations in children's dietary behaviors as a result of the time-consuming task of recording or knowing that their diet is being assessed (73). Despite the fact that children were asked to recall all of the foods and beverages they had consumed the day before, a more difficult cognitive task, such as comparing their food intake in the last 24 hours to a typical day, was not considered. Dietary data collected may be influenced by recall bias and indirect reporting, particularly because, due to limited food knowledge and memory, children's self-reports of diet are more prone to have errors (74). However, knowing that portion size is hard to estimate correctly and to avoid misreporting in dietary consumption, nutritionists and specially trained interviewers obtained 24-hour food recall questionnaires from the children, using photographs and food models to quantify portion sizes, with the advantage that they have experience probing information from children without suggesting responses (75). The 24-hour dietary recall detailed good agreement and adequate reporting between energy intake and measured total energy expenditure at group level (16). It may be easier for children to remember the most recent foods consumed and the 24-hour recall may be preferable when determining the usual dietary intake of large groups of subjects (76). Other researches have also used 24h questionnaires-reports to assess dietary quality (77, 78), and Kirkpatrick *et al.* (78) found that HEI-2015 scores based on 24-hour dietary recall data are generally well estimated (78). Also, even though confounders were selected centered on preceding research and knowledge of their link with diet and the outcomes studied, residual confounding could still be present.

In terms of anthropometry, weight classifications were determined using BMI. BMI does not take into account body composition (79) and body adiposity appears to be more appropriate when studying asthma (80-82). BMI was calculated using measured height and weight, avoiding parental self-perceptions of weight categories, as most parents underestimated their children's overweight/obesity status (83).

Our study also has a variety of strengths. To the best of our knowledge, this study is the first one evaluating the association between diet quality with the Healthy Eating Index-2015 with asthma and airway inflammation in children. This research involved a large number of individuals and objectively measured spirometry with bronchodilation, combining it with ISAAC self-reported responses to characterize different asthma definitions, and three different definitions were used. (27). Although previous studies observed a good agreement in parental reporting of offspring asthma onset (84), according to Silva *et al.* (27), a standardized definition of asthma should comprise a questionnaire score as well as airway reversibility as these measures address different manifestations of asthma. Our research took into account important potential confounders such as atopy, parental education level, nutritional supplementation, total energy intake, and surrounding environment, all of which have been considered relevant when addressing asthma-related outcomes in schoolchildren (33, 34).

The Healthy Eating Indexes have the benefit of being constantly revised and updated to agree with the latest guidelines for Americans (17). Even if the HEI-2015 is not adapted for Portugal nor Portuguese children, this index has the benefit of being scored on a density basis (17, 18), utilizing a less restrictive approach to defining standards for maximum scores, and enabling it to be employed to different groups, including children. The HEI-2015 evaluates quality over quantity (17). This index targets food subgroups that are most frequently low in diets and that have an exceptional nutrient profile, as legumes, dark green vegetables and seafood (17). Additionally, it has the benefit of not requiring any single food to have higher scores, having into regard food intake as a whole to characterize diet quality (17) carrying a more rounded approach to evaluate dietary intake that takes into consideration the potential interactions between the diverse components of the diet.

This study suggests that in non-overweight/obese school-aged children, a higher dietary quality is associated with a lower prevalence of self-reported medical diagnosis of asthma, self-reported medical diagnosis of asthma under asthma treatment, and lower levels of airway inflammation. This work underlines the significance of promoting a diet that is high quality as for example diets that are rich in vegetables, fruits, whole grains, greens and beans, healthy fats, high quality and diverse protein sources and that is low in saturated fats, added sugars, sodium, and refined grains. Understanding the potential effect of food consumption on asthma and airway inflammation might support the introduction of clinical guidelines and public health recommendations. Nevertheless, there are still significant gaps in the interpretation of the types of foods or diets that the population should incorporate in order to improve their respiratory health.

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Contributions

AM, PM: conceptualization. IP, JCR, DS: data curation. MCR, FCM, LD, AM, PM: formal analysis. AM: funding acquisition. MCR, FCM, PP, RB, IP, JCR, DS: investigation. MCR, FCM, AM, PM: methodology. AM: project administration. MCR, FCM, PM: writing – original draft. IP, PP, RB, JCR, DS, LD, AM: writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

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Delayed postoperative reactions to metamizole: a diagnostic challenge

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Key words

Allergy; delayed hypersensitivity; metamizole; non-steroidal anti-inflammatory drugs; postoperative.

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Impact statement

Immediate reactions to metamizole are well characterized, however few studies focus on delayed reactions. In this study we thoroughly characterize and emphasize the difficulty in evaluating delayed reactions to metamizole.

Summary

Background. *Metamizole, a non-steroidal anti-inflammatory drug from the pyrazolone group, is a frequent cause of immediate hypersensitivity reactions and, more rarely, of delayed drug hypersensitivity reactions. Due to its favorable pharmacokinetic characteristics, metamizole is widely used in the postoperative period for pain control.*

We evaluated the usefulness of skin tests, including intradermal and patch tests, and drug provocation tests for the diagnosis of delayed drug hypersensitivity to metamizole, in the complex postoperative multidrug setting. ***Methods.*** *Retrospective study of patients referred for allergological study between January 2012 and June 2022 for postoperative hypersensitivity reactions. Clinical and diagnostic data were collected through review of patients' medical records. Twenty patients with postoperative hypersensitivity reactions were referred, of which 10 presented delayed reactions. We analyzed the results of skin prick, intradermal and patch tests performed with an intravenous metamizole solution as well as provocation tests performed with metamizole and acetylsalicylic acid. Cross-reactivity to non-steroidal anti-inflammatory drugs was excluded by confirmation of clinical tolerance to non-steroidal anti-inflammatory drugs or by acetylsalicylic acid provocation test.* ***Results.*** *In 7 of the 10 patients a delayed reaction to metamizole was diagnosed. These reactions were characterized as maculopapular exanthema, occurring in multiple postoperative settings. Skin tests were negative, except for one patient with late mild erythema in the ipsilateral upper limb and no reaction at the site of intradermal injection. Delayed hypersensitivity was demonstrated by late positive metamizole provocation tests.* ***Conclusions.*** *This study demonstrated that for a correct diagnosis a high degree of suspicion about possible delayed hypersensitivity drug reactions to metamizole in the postoperative setting is needed. In the investigation, provocation test with metamizole was decisive for diagnostic confirmation.*

Introduction

Adverse drug reactions (ADR) constitute a relevant cause of hospital admissions and are estimated to occur in 10 to 15% of hospitalized patients, mainly in poly-medicated patients (1). Some of these ADR are caused by hypersensitivity reactions. Non-steroidal anti-inflammatory drugs (NSAID) are the most common cause of hypersensitivity reactions in adults in several countries and also in Portugal (2-4). They include reactions caused by immunolog-

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ical and non-immunological mechanisms, the latter being based on the excessive inhibition of cyclooxygenase (COX) enzymes in NSAID-sensitive patients, making these patients react to different, non-chemically related NSAID (5). Immune or allergic reactions to NSAID are usually directed to a single drug or to drugs belonging to the same chemical class (**table I**) and these reactions can be classified as immediate or non-immediate reactions (2). Metamizole is a pyrazolone derivative, with significant analgesic and spasmolytic properties, frequently used in Portugal in acute and chronic pain treatment. Due to its favorable pharmacokinetic characteristics, it is widely used in the postoperative period, in multiple types of surgeries, also because metamizole is almost devoid of gastric or hemorrhagic complications seen with other NSAID. However important side-effects such as agranulocytosis or shock have been reported in several patients, some countries banning its use due to these possible side-effects (6). As a group, pyrazolone derivatives are frequently involved in hypersensitivity reactions, metamizole being one of the analgesics that most frequently causes hypersensitivity reactions (7). In a large Portuguese study based on anaphylaxis reports by allergists, metamizole was responsible for more than 10% of all drug-induced anaphylactic reactions (4).

Immediate reactions to metamizole are much more frequent and better known, in many cases involving IgE-mediated mechanisms. It has been shown that some metamizole metabolites can be specifically recognized by IgE antibodies bound to the surface of basophils, causing anaphylactic reactions in sensitized individuals (8). On the other hand, non-immediate reactions are much less frequently described, T-cell mediated inflammatory response being frequently pointed out as the responsible mechanism in these cases.

In hypersensitivity reactions appearing in the postoperative period, we have to consider not only the possible role of drugs given during anesthesia and surgery but especially the probable role of a significant number of different drugs, including analgesics/NSAID, antibiotics, as well as several others, that usually are being used concomitantly in the first days after surgery, making it difficult to identify, on clinical grounds alone, the culprit drug. This is true for immediate reactions but even more so to delayed drug hypersensitivity reactions (DDHR), where the beginning of the reaction can be more easily missed, being more difficult to establish a clear relationship between drugs and DDHR. In these cases, it is crucial to perform a thorough allergological work-up, with skin tests to try to demonstrate the presence of delayed reactions and with drug provocation tests (DPT) to try to replicate the DDHR.

The aim of our study was to describe, in a series of patients investigated for drug allergy in a postoperative multidrug setting, between 2012 and 2022, the usefulness of a thorough allergological investigation, with intradermal and patch tests, and drug provocation tests in the diagnosis of delayed drug hypersensitivity to metamizole.

Materials and methods

This was a retrospective study, that analyzed clinical and diagnostic data collected through review of the medical records of patients, referred to our allergy department with suspected postoperative allergic reaction, from January 2012 to June 2022, and in whom a delayed allergic reaction to metamizole was confirmed. Reactions were classified as delayed if symptoms started more than 24 hours of metamizole administration.

Table I *- Main chemical groups of the different non-steroidal anti-inflammatory drugs.*

Chemical group	Main drugs belonging to that group
Salicylic acids	Acetyl salicylic acid, Salsalates, Salycilic acid
Acetic acids	Indomethacin, Sulindac, ketorolac, Etodolac
Propionic acids	Ibuprofen, Naproxen, Flurbiprofen, Ketoprofen
Phenylacetic acids	Diclofenac, Aceclofenac
Enolic acids	Meloxicam, Piroxicam, Tenoxicam
Fenamic acids	Mefenamic acid, Flufenamic acid
Para-aminophenol derivative	Acetaminophen
Pyridinic sulfonamide	Nimesulide
Naphtyl alkanones	Nabumetone
Pyrazolone derivatives	Metamizole, Propifenazone, Phenylbutazone
Diaryl heterocyclic acids	Celecoxib, Etoricoxib, Rofecoxib, Parecoxib, Valdecoxib

Patients' data were collected from the ENDA Questionnaire regarding clinical manifestations, time between drug administration and the onset of reaction, number of postoperative reactions until diagnosis, age at first reaction, personal background of rhinitis and/or asthma, and reported hypersensitivity to other NSAID (9).
Allergological investigation was based on the results of skin tests to metamizole and DPT to metamizole as well as skin prick tests to common aeroallergens. To exclude NSAID cross-reactivity and confirm a selective allergic reaction to metamizole, patients underwent acetylsalicylic acid (ASA) provocation test if tolerance was not known (10).
Written informed consent was obtained before starting the allergological investigation.
Descriptive statistics of the data was performed.

Atopy assessment
Skin prick tests (SPT) were performed using a battery with 23 common allergens including house dust mites, pollens, molds, animal dander and latex (Diater, Madrid, Spain). Histamine hydrochloride (10 mg/mL) and phenolated glycerol saline were used as positive and negative controls, respectively. Tests were considered positive if a wheal diameter > 3 mm than the diameter of negative control was obtained. We considered atopy to be present if SPT was positive to at least one of these allergens.

Drug skin tests
Drug skin testing was performed according to international guidelines (11). Readings were taken at 20 minutes and additionally at 6, 48 and 96 hours. For prick tests we used the undiluted concentration of intravenous metamizole solution (400 mg/mL) and for patch tests a 10% solution of metamizole in water (12). For intradermal tests, a concentration of 4 mg/mL (1/100) was used (12). Prick tests with a wheal of at least 3 mm in diameter and intradermal tests with a papule of at least 6 mm in diameter were considered positive at 20 minutes. For delayed reactions, the presence of papular and erythematous induration in intradermal tests after 48 hours was considered positive. Verification of an eczematous-like reaction, erythema with edema, papules, vesicles, or bullae, at 48 or 96 hours in patch tests was considered a late positive reaction.

Drug provocation tests
Progressively higher doses of metamizole (Placebo, 25, 50, 100, 150, 250 mg) and ASA (Placebo, 50, 150, 300, 500 mg) were orally administered at 60-minute intervals in our day hospital, according to the DPT protocols of the department. The therapeutic dose is reached in the first day. If after a gap of 24 hours there are no symptoms, therapeutic dose is maintained for 2 additional days.
During the first day of provocation, which took place in a day hospital, patients were closely monitored. Subsequently, symptoms surveillance was maintained on an outpatient basis for 7 days.

Ethical issues
The clinical part of the study, as well as *in vivo* tests, was carried out as part of the clinical routine evaluation. All patients signed an informed consent form before the investigation (skin tests and/or drug challenge tests), which describes the possible use of anonymized data for study purposes. The study followed the recommendations of the Ethics Committee and of the World Medical Association (Declaration of Helsinki revised in 2013).

Results

During the time of this study, 88 patients with suspected perioperative allergic reactions were referred for allergological investigation, 20 patients referred for postoperative reactions. In all patients, investigation was carried out for all drugs administered during the postoperative setting, if they had not yet shown tolerance.
DDHR were reported by 10 patients, metamizole allergy being confirmed in 7 patients. In all patients, metamizole was administered intravenously. **Table II** shows the demographic and clinical data of the patients with metamizole delayed hypersensitivity.
Among the 7 patients with confirmed delayed allergic reaction to metamizole 4 were female. Median age at first reaction was 62.6 ± (IQR 60.64) years.
All patients described at least one previous postoperative reaction, and six patients had more than one. The number of drugs involved in the postoperative setting varied between 3 and 7. Suspected antibiotic allergy was the reason for referral in 3 patients and allergy to pantoprazole in another. Three patients were referred with no indication of a suspected drug.
All patients had maculopapular exanthema (MPE). In 5 patients the MPE was generalized. In 2 patients, the non-pruritic MPE was located on the trunk and upper limbs, evolving with intense desquamation of the hands in one patient.
MPE appeared more than 24 hours after administration of metamizole in 3 patients and more than 48 hours in 4 patients.
Only 1 patient had rhinitis and asthma with positive SPT for house dust mites.
Table III refers to metamizole skin tests and DPT. All patients performed prick and intradermal tests, and 4 patients made patch tests. Patch tests were all negative. All patients had negative intradermal tests with metamizole, except patient 1 who had mild non-pruritic erythema in the ipsilateral upper limb at 48 hours, without injection site reaction.
In all 7 patients, metamizole DPT were positive, replicating the previous postoperative reactions. **Figure 1** shows MPE after metamizole DPT in patients 4 and 1. All these DPT were positive after 24 hours, in 2 patients MPE appeared only after 5 days.

Table II *- Characterization of demographic and clinical data of the patients with metamizole delayed hypersensitivity.*

Pts	Sex F/M	Age 1st reaction	Previous postop reactions	Clinical manifestation	Reaction time (hours)	Postoperative drugs
1	M	62	3	Nonpruritic MPE with scaling on trunk and upper limbs	> 48	CEF, ENOX, PANT, TRAM, MORF, ASA, MET
2	F	65	3	Generalized non-pruritic MPE	> 48	CEF, TRAM, MTCL, MET
3	M	62	2	Generalized pruritic MPE	> 48	PIP-TAZ, AMOX-CLAV, TRAM, PIROX, MET
4	M	58	3	Generalized pruritic MPE with scaling	> 24	NORF, CIPROF, ENOX, KET, MET
5	F	63	3	Generalized pruritic MPE	> 24	TRAM, KET, MET
6	F	45	1	Generalized nonpruritic MPE	> 24	AMOX-CLAV, TRAM, MET
7	F	83	2	Nonpruritic MPE on trunk	> 48	TRAM, MTCL, THIOC, KET, MET

Pts: patients; F: female; M: male; MPE: maculopapular exanthema; Postop: postoperative; MET: metamizole; Cef: cefazolin; Enox: enoxaparin; Pant: pantoprazole; Tram: tramadol; Morf: morfin; ASA: acetylsaliciylic acid; MTCL: metoclopramide; PIP-TAZ: piperacillin-tazobactam; AMOX-CLAV: amoxicillin-clavulanic; PIROX: piroxicam; NORF: norfloxacin; CIPROF: ciprofloxacin; KET: Ketorolac; THIOC: thiocolchicoside.

The patient with an intradermal test initially evaluated as negative (mild non-pruritic erythema in the ipsilateral upper limb and no reaction at the injection site) was also evaluated with DPT, which induced MPE with scaling of the palms (**figure 2**), improving only after 15 days with antihistamines and oral corticosteroids. Time to resolution of the reactions varied between 2 and 15 days. In 5 patients, treatment with antihistamines and oral corticosteroids was necessary for complete resolution of symptoms.
Four of the seven patients underwent ASA provocation test which was negative. The other three patients had already tolerated other NSAIDs, including ASA, after the postoperative reaction.

Discussion and conclusions

Our paper describes a series of 7 patients with DDHR to metamizole: pruritic and non-pruritic MPE, generalized or limited to the trunk and upper limbs, that appeared postoperatively, more than 24-48 hours after several drugs were administered. In our patients the number of drugs varied between 3 and 7, which reflects accurately a real-world postoperative setting. All patients had previous postoperative reactions, which could have facilitated referral to a specialized allergy center, but in fact metamizole had not been previously pointed out as a possible culprit.

Table III *- Results of the metamizole skin test and drug provocation test.*

Pts	Intradermal tests	Patch tests	Metamizole DPT	Reaction time after DPT (hours)	Treatment	Time to symptoms resolution (days)
1	Positive*	Negative	MPE on trunk/upper limbs with peeling palms	48	Anti-H1; OCS	15
2	Negative	ND	MPE on trunk	72	Anti-H1; OCS	3
3	Negative	Negative	Generalized pruritic MPE	120	Anti-H1; OCS	3
4	Negative	Negative	Generalized pruritic MPE	72	Anti-H1; OCS	7
5	Negative	Negative	Generalized pruritic MPE	24	Anti-H1	2
6	Negative	ND	Generalized nonpruritic MPE	24	Anti-H1	2
7	Negative	ND	Generalized nonpruritic MPE	120	Anti-H1; OCS	5

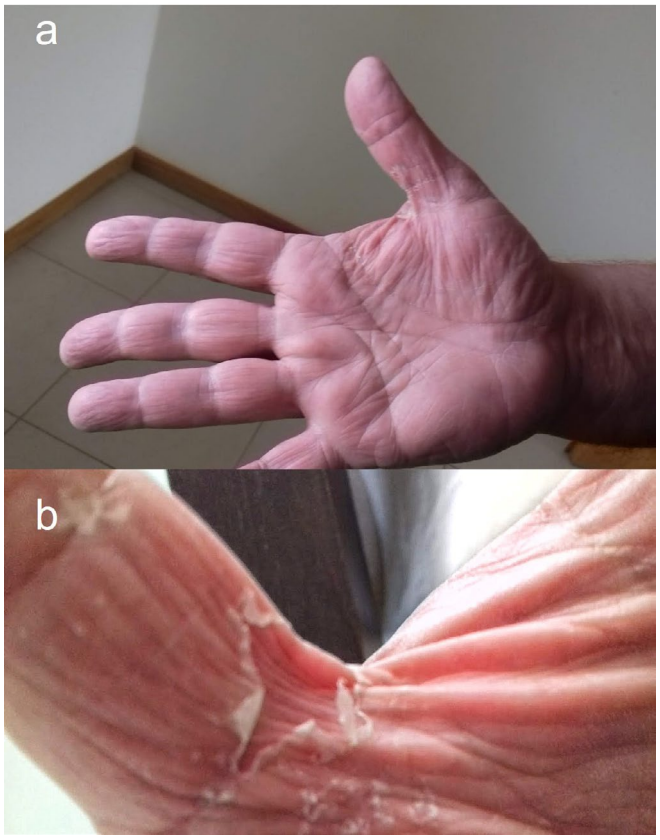
Pts: patients; DPT: Drug provocation test; MPE: maculopapular exanthema; ND: Not done; Anti-H1: 2nd generation antihistamines; OCS: oral corticosteroids; *no reaction at injection site; erythema on the ipsilateral upper limb at 48 hours.

Figure 1 *- Maculopapular exanthema after metamizole provocation test.*



(a) Maculopapular exanthema on the trunk of patient 4; **(b,c)** Maculopapular exanthema on the limb and trunk of patient 1.

Figure 2 *- Maculopapular exanthema with peeling palms after metamizole provocation test.*



(a,b) Aspect of intense scaling on the palms of patient 1.

Although metamizole hypersensitivity is already well-known, there are not so many studies addressing delayed reactions to metamizole. Borja et al. described in 2003, 3 patients with DDHR to metamizole confirmed by skin tests (13). Macias *et al.* described in 2007 a series of 12 patients with DDHR to metamizole but only 3 patients performed DPT (7). Blanca-Lopez *et al.* published in 2016 a series of 137 metamizole allergic patients but only 5 patients having had a delayed reaction: MPE in 60% of these patients (12). As far as we know, the largest series on DDHR to metamizole was published in 2020, by Trautmann *et al.*, although consisting of a retrospective analysis resulting in methodological heterogeneity and also including patients with non-selective NSAID hypersensitivity reactions (14). This German study that spanned a period of 19 years, described 239 patients with hypersensitivity reactions following metamizole administration, 69 with delayed reactions, mostly MPE; however, only 13 performed DPT to confirm the DDHR to metamizole (14). In 2016, Pinho *et al.* described a series of 14 patients diagnosed with DDHR to metamizole in a multidrug setting, in which 7 patients were diagnosed by patch test (15). It is worth mentioning that only in our study of postoperative setting and in the study by Pinho *et al.*, it is described that the reactions that motivated the allergy study occurred in the context of multidrug administrations. Postoperative drug hypersensitivity reactions (DHR) are reactions to drugs administered after a surgical procedure. Most often DHR are immediate reactions, DDHR being much more rarely identified and reported in the postoperative setting (16-18).

Due to the multitude of different drugs administered, allergological work-up poses particular challenges and, in fact, many cases have a presumptive diagnosis only based on retrospective clinical assessments. In the investigation of many postoperative DHR skin and laboratory tests are of limited value, making DPT an important step to establish a definitive and correct diagnosis. These diagnostic difficulties are highlighted in our study by the occurrence of previous postoperative reactions to metamizole in all patients that, until a thorough allergological investigation was done, remained unsuspected.

Antibiotics are frequently involved in postoperative DHR, but it is wise to assume that any drug administered postoperatively can be the culprit. In fact, 5 of our patients had received cefazolin and/or other antibiotics, which were demonstrated to be safe by the allergological work-up.

Analgesics and NSAID were also prescribed in all our patients, and these are drugs frequently involved in DHR in any setting. Non-selective reactions are more frequently observed in NSAID hypersensitivity, and if they are demonstrated they imply the avoidance of this important group of drugs to control postoperative pain. Therefore, it was important to exclude this possibility with provocation tests with ASA and other COX-1 inhibitors. This was done in our patients, all showing tolerance to ASA and other NSAID. On the other hand, DPT with metamizole triggered MPE in all patients, as shown in **figure 1**, replicating the previous delayed reactions.

Allergologic work-up of perioperative DHR always starts with thorough history taking with the patient, but it is crucial to access to the complete anesthetic/surgical record. It is very important to document if any drugs used in the perioperative period were subsequently used and if they were tolerated or not. Latex, dyes or disinfectants should also be incorporated as a cause of immediate or delayed reactions (16, 18, 19).

In DDHR it is indicated to use intradermal skin tests or patch tests with readings performed at 24, 48 hours and later. Regarding the results of the skin tests, we would like to point out some differences to other studies previously mentioned. Somewhat surprisingly all our patients had negative results in intradermal tests, performed according to guidelines, except one patient with erythema on the ipsilateral upper limb but without reaction at the intradermal test site, that was therefore considered as a positive test. This is in contrast with the positivity found in 60-70% of patients with DDHR to metamizole in other studies (7, 12-14). However, in these studies, if we restrict the analysis to patients with EMP, the percentage

of positive intradermal tests to metamizole decreases. Two recent Spanish studies showed that only 2 out of 14 patients (15%) and 2 out of 12 patients (17%) with the suspicion of selective metamizole delayed hypersensitivity reactions had positive intradermal tests (20, 21). We carried out patch tests with a 10% solution of metamizole in water on 4 patients, who had negative results. In Pinho *et al.* study, positive patch test reactions to metamizole were observed in 7 of 14 patients, including 4 of 8 patients with MPE (15). In this study, patch tests were performed with metamizole 10% petrolatum, which may explain the discrepancy in the results of patch tests. These results highlight the fact that it is not advisable to rely solely on skin tests in the diagnosis of DDHR to metamizole. In these very complex patients, DPT are an essential tool not only for the correct identification of the culprit drug but also for assessing tolerance to the multiple other drugs involved. In our series DPT with metamizole triggered MPE in all patients replicating the previous DDHR.

As expected, and similar to other published papers, atopy did not seem to play a role in these patients. Despite our investigation that also included latex, only one patient that also had respiratory allergy (15%) showed evidence of sensitization to aeroallergens (3). There is a scarcity of studies analyzing DDHR in the complex postoperative setting. In this way, our study is particularly relevant since it shows the importance of metamizole as a culprit drug in DDHR in the postoperative setting. The fact that all patients underwent drug challenges with metamizole showing a reproducible DDHR pattern, adds strength to our description. Clinical characteristics of the patients presented here point out the challenges that postoperative drug reactions in general, and delayed postoperative reactions in particular, pose to the allergologist in charge of the investigation of these very complex patients, that in our series had already had several other previous episodes that did not lead immediately to a correct diagnosis.

As far as we know this is the largest study addressing postoperative DDHR to metamizole, a drug widely used in this context across several southern European countries due to its favorable pharmacokinetic profile. Even when other more common suspects are present, such as antibiotics or non-selective NSAID hypersensitivity, our series shows that metamizole delayed hypersensitivity needs to be considered and investigated to avoid re-expositions to metamizole while making unnecessary avoidances of "innocent" drugs.

Fundings

None.

Contributions

AL, MBF: conceptualization. AL: project administration. AL, MP, ASS, EP, MBF: formal analysis, writing – original draft. All authors: writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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LETTER TO THE EDITOR

Eur Ann Allergy Clin Immunol Vol 57, N.4, 184-186, 2025

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Shiitake flagellate dermatitis: a case series from Italy

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Key words

Lentinula edodes; shiitake; flagellate dermatitis.

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To the Editor,

Shiitake flagellate dermatitis (SFD) is an acute eruption that appears some hours or days after ingestion of raw or undercooked mushrooms of the species *Lentinula edodes* (Berk.) Pegler, 1976, popularly known as "shiitake". SFD was first reported in 1977 in Japan (1). The first European cases were described in 1991(2). European cases of SFD increased in the last years because shiitake is cultivated in some European countries and it is easily available in supermarkets and restaurants. The diagnosis is based on the typical clinical presentation, as laboratory exams, histopathological picture and allergological tests are nonspecific or controversial. We present six Italian patients with SFD, with allergological and histopathological studies in four of them.

The case list consists of six Caucasian patients (4 males and 2 females, with an age ranging from 40 to 80 years). All patients were admitted to hospital because of the acute appearance of linear, erythematous, urticated streaks, similar to skin lesions caused by whiplashes, located on the trunk (all patients) and limbs (one patient) (**figure 1A-D**), accompanied by more or less severe pruritus. According to medical history, all patients had eaten shiitake mushrooms from 1 to 3 days before the appearance of the rash. Laboratory examinations were within normal ranges in all patients. Patch tests with dried and cooked (at 100 °C for 15 minutes) *Lentinula edodes* were carried out in three patients: they were negative at 48 hours and positive at 72 hours. Five healthy volunteers were negative. Prick-by-prick tests were not performed. In two patients, histopathological examination showed acanthosis, spongiosis, papillary edema, dilated capillaries and superficial, perivascular lymphocytic infiltrate with sparse eosinophils (**figure 2**).

Complete remission was observed in all patients within 3-5 days with oral antihistamines; in one patient a topical corticosteroid was added.

SFD is characterized clinically by linear, erythematous, urticated streaks, similar to skin lesions caused by whiplashes, usually located on the trunk, and accompanied by more or less severe pruritus. The rash usually lasts from 2 days to 2 weeks. Some rare cases of pustular (3,4) or purpuric (5) lesions and oral ulcers (4) have also been reported.

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Figure 1 *- **(A)** Patient 1: a 40-year-old man; **(B)** Patient 2: a 46-year-old man; **(C)** Patient 3: a 58-year-old woman; **(D)** Patient 4: a 40-year-old man.*

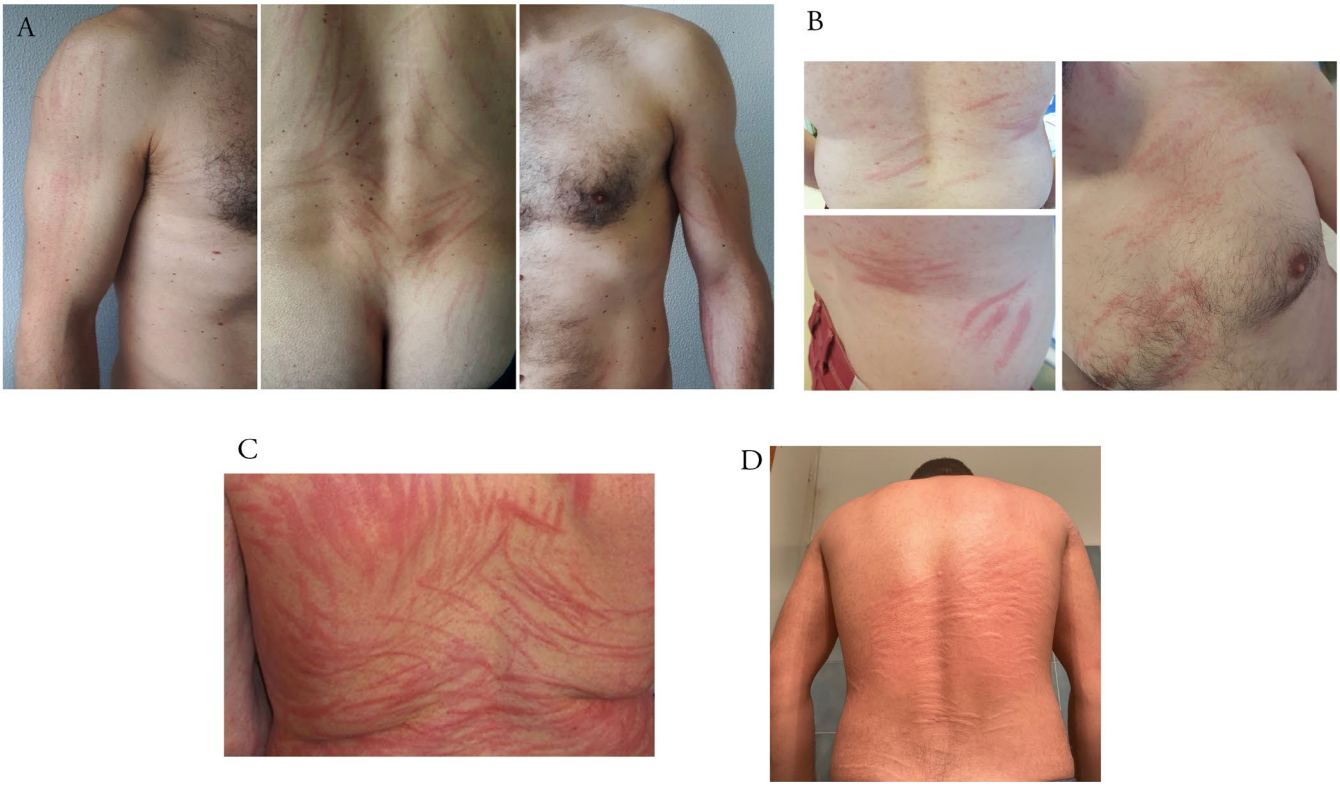
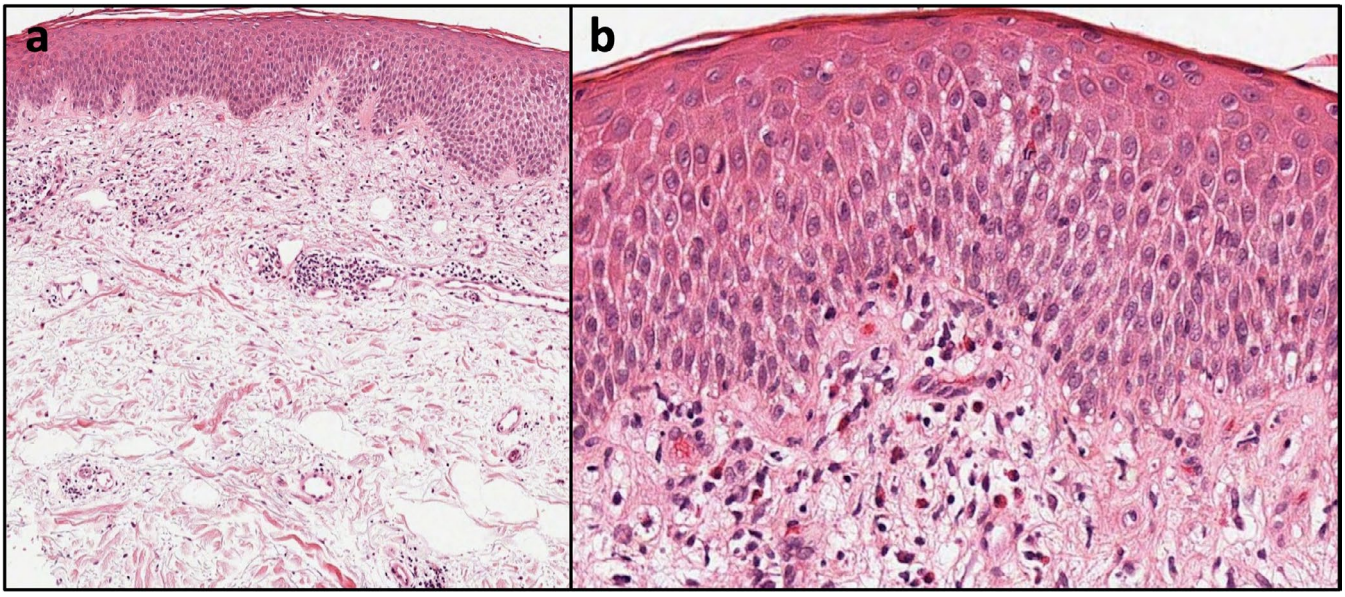


Figure 2 *- Histopathological picture.*



(a) Acanthosis, spongiosis, papillary edema, dilated capillaries and superficial, perivascular lymphocytic infiltrate with sparse eosinophils (H & E, x10); **(b)** High magnification of spongiotic dermatitis with eosinophils (H & E, x40).

The pathogenesis of the flagellate eruption is still unclear. Some authors consider SFD a toxic reaction to lentinan, a heat-sensitive β-1,3 b-glucan that is present in the cell wall of shiitake, leading to overexpression of interleukin-1 (5). This hypothesis is supported by frequent negative allergological exams and positive results in healthy controls (5). Patch and prick-by-prick tests have been rarely carried out and with conflicting results (5). Patch tests with raw *Lentinula edodes* were negative in some patients and positive in others (5): a type IV hypersensitive reaction to lentinan has been hypothesized (5). As previously mentioned, in three of our patients patch tests with *Lentinula edodes* were positive with dried and cooked (at 100 °C for 15 minutes) mushroom at 72 hours, and negative at 48 hours. In some patients, prick-by-prick tests showed delayed vesicular reaction (5). In spite of a careful review of the literature, the exact number of patients with positive and negative patch tests, as well as prick and prick-by-prick tests, is impossible because several different methods were used. For instance, shiitake was patch-tested as fresh, dried and cooked mushroom: the latter at a temperature ranging from 50 to 100 °C, for 5 to 15 minutes. Some cases of occupational allergic contact dermatitis in shiitake growers were published (6). Photosensitivity was also described (7).

As far as histopathology of SFD is concerned, approximately 10 patients have been published. Although some degrees of variability in microscopical features are present, most of the cases shows a spongiotic pattern with a perivascular lymphocytic infiltrate with eosinophils, as it has been observed in our patient (8). Therefore, histopathology alone is not specific to make a correct diagnosis: the latter should be based upon a good clinico-pathological correlation. Differential diagnosis includes flagellate dermatitis of dermatomyositis, exposure to bleomycin and Still's disease of adult. SFD is self-healing, resolving within days to weeks without treatment. Oral antihistamines and topical and/or oral corticosteroids can be of help in reducing pruritus. Prevention is based on cooking shiitake mushrooms at a temperature of at least 130 °C (5).

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Contributions

PB, SV: conceptualization. FD: data curation. FR: project administration. SV: writing – original draft. AC: writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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LETTER TO THE EDITOR

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Outcomes with one-bag desensitization protocol for biologic and chemotherapy agents in 451 procedures

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Key words

Desensitization; drug allergy; biological agents; chemotherapy; one-bag.

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To the Editor,

rapid drug desensitization is an essential procedure to allow the maintenance of first-line treatments in patients suffering from hypersensitivity reactions (HSR) to biological and chemotherapeutic agents (1-6).
Since our first description of the one-bag drug desensitization protocol in 2016 (2), several groups have implemented it in their clinical practice (1-8), demonstrating its good tolerance and efficacy.
In addition to the already proven effectiveness and security of the one- bag protocol, throughout these years of clinical practice we have been able to reduce the time of the standard procedure with no further appearance of adverse events, by shortening its initial steps, making it a more convenient option for both physicians and patients.
In this setting, we present the results of the application of the one-bag desensitization in two different hospitals of our region (Complejo Hospitalario Universitario de Santiago de Compostela and Ferrol), along six years of experience.
From April 2016 to December 2022, a total of 451 rapid desensitization procedures were performed in 86 patients (77% women, mean age 68 years-old [range 19-85]). More than one third of the patients (36%) were diagnosed with ovarian cancer. The remaining patients suffered from breasts (18%), colon (9%), prostate (7%), endometrium (7%), lung (4,5%), lymphoma (4,5%), uterus (3%), gastric (3%), liver (2%), gallbladder (1%), rectum (1%), kidney (1%) and central nervous system (1%) cancers. Platinum salts were the most common drugs involved in HSR (45%), shortly followed by taxanes (34%), biological therapies (18%), and alkylating agents (1%).
Most of the reactions had occurred during the first minutes after the administration of the drug involved in the reaction and had been well documented by the oncologist in charge who shortly after asked for allergic evaluation. Regarding the severity, 56%

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of the reactions were moderate while 20% were mild and 24% were severe, according to Brown's classification (10).

Between 15 and 21 days after the reaction, and prior to desensitization, patients underwent allergological assessment and according to the suspected immunological mechanism involved, skin testing was performed, if needed. For this purpose, standardized concentrations and doses approved for each agent were used (3). Only 42% of the patients did react against skin tests (92% of them with immediate positivity), being platinum salts the most frequently drugs responsible for these results. Thus, 87% of patients with platinum salt hypersensitivity showed a positive result. However, 97% of taxanes and 100% of biologics were tested negative, which is consistent with other previously published series (8). Two patients with a suspected non-IgE-mediated reaction to rituximab and temozolamide were not skin tested.

Desensitizations were performed in a short-stay hospital bed under the supervision of a chemotherapy nurse and an allergist. Informed consent was obtained prior to the desensitization procedure. Patients received standard oncologic premedication for their drug and premedication according to the symptoms and type of their initial HSR as previously suggested (8). Dexchlorpheniramine 5 mg IV was administered to every patient 5 minutes before starting the procedure (3).

According to our previously published protocol, once the dose required for each patient had been calculated, it was diluted in 0.9% saline solution for taxanes and biological agents and in 5% dextrose solution for platinum salts to reach a final concentration of 1 mg/mL, 0.5 mg/mL or 0.1 mg/mL, depending on the total amount of the drug so that the volume to be administered differed from patient to patient (an example of the protocol, with a total amount of 650 mg of drug to be administered and a required concentration of 1mg/ml can be found in **table I**). The line (15 Micron Filter in Sight Chamber, polyethylene-lined light-resistant tubing, distal microbore tubing 272 cm/12 mL) was primed with the antineoplastic agent and clamped. The distal line was connected to a 3-way stopcock (BD Connecta, Becton Dickinson Infusion Therapy, Stockholm, Sweden). An infusion pump with automated multistep infusion options (Icumedical Plum360, ICU Medical BV, The Netherlands) was used, but infusion rates were changed manually every 15 minutes until the last two steps when infusion rates were changed after 30 minutes. Using this standard protocol, the duration of the procedure was 4:30 hours for every patient. However, most recently, we have implemented in our daily clinical practice a shortened schedule in those patients who had well tolerated the first desensitization cycle. Thus, in a total of 17 patients and 93 desensitizations, the procedure was shortened, removing a mean of the 4 initial steps from the protocol, and consequently, reducing the time of the procedure to a mean of 3:30 hours.

Using the one-bag procedure, all the patients were able to receive the complete dose of their drug. However, despite desensitization, 7 patients (57.4% of them with a severe initial HSR), experimented a HSR during the drug administration. In 43% of them, the HSR appeared in the first desensitization cycle and 43% continued experiencing HSR in two or more cycles. The percentage of patients suffering from HSR using our procedure (8.1%) was fewer than in other multiple-bag and one-bag desensitization protocols (1, 11). Most of the reactions were moderate (57.4%) and were successfully treated. None of the patients who underwent the shortened protocol experienced any adverse events. The clinical characteristics of these patients, including the number of previous tolerated cycles, description of the reaction and results of skin tests with the drug involved in the reaction, are shown in **table II**.

In conclusion, we present an extension of our previously published protocol (2), increasing the number of patients in our series, proving its safety and well- tolerability. We also propose a quicker version of the protocol, shortening its initial steps with no further appearance of hypersensitivity reactions. Thus, we consider the one-bag procedure to be the best and more convenient option for both clinicians and patients for the management of HSR in either low, moderate or high-risk patients in daily clinical practice.

Table I *- Example for the administration of 650 mg of chemotherapy using one bag at a concentration of 1 mg/ml.*

Desensitization schedule for 1 mg/ml concentration			
Step	**Time (min)**	**Rate (mL/h)**	**Dose (mg)**
1	15	0.2	0.05
2	15	0.3	0.075
3	15	0.7	0.175
4	15	1.3	0.325
5	15	1.6	0.4
6	15	3.25	0.8125
7	15	6.5	1.625
8	15	13	3.25
9	15	16	4
10	15	33	8.25
11	15	65	16.25
12	15	130	32.5
13	15	144	36
14	15	289	72.25
15	15	361	180.5
16	30	578	Remaining: 293.5375

Table II *- Clinical characteristics of patients with HSR during desensitization.*

Age (Gender)	Cancer	Drug	HSR's cycle (Severity) [Latency]	Skin test result	Number of procedures	Number of HSR during desensitization (description)
36 (F)	Cervix	Paclitaxel	1st (moderate) [immediate]	Negative	3	1 1st cycle, step 1: five minutes after starting the infusion, two self-limited hives which resolved with no treatment.
44 (F)	Ovary	Paclitaxel	1st (moderate) [immediate]	Negative	3	3 1st cycle, step 14: warmth sensation in the scalp, face, chest erythema, and palmar itching. Cycle was completed without requiring further medication. 2nd cycle, last step: retroauricular itching with mild erythema. Treated with dexchlorpheniramine with recovery in 15 minutes. 3rd cycle, step 15: face, ear and chest warmth with erythema. Treated with hydrocortisone, being able to continue the procedure after 10 minutes with no further complications.
78 (F)	Linfoma	Rituximab	1st (moderate) [immediate]	Negative	4	1 1st cycle step 15: chills and hypotension. Paracetamol and methylprednisolone were administered after stopping the procedure. Desensitization completed afterwards.
70 (M)	Lung	Oxaliplatin	10th (severe) [immediate]	Negative	4	2 3rd cycle, step 15: shivering followed by dizziness and sweating, dyspnea, desaturation and chest oppression at step 16. 4th cycle, step 13: face erythema treated with dexchlorpheniramine. At step 15, chills, tachycardia and desaturation treated with salbutamol, IV corticosteroids and ipratropium bromide, being able to continue with the procedure.
68 (F)	Breast	Trastuzumab	1st (severe) [immediate]	Negative	12	1 5th cycle, step 15: facial erythema, dyspnea and headache treated with antihistamines and corticosteroids, completing the cycle.
52 (F)	Ovary	Carboplatin	2nd (moderate) [immediate]	Positive	10	1 10th cycle, step 16: eyelid, mandibular, neck, chest and palms of hands erythema and itching.
69 (F)	Ovary	Carboplatin	2nd (severe) [immediate]	Positive	7	3 1st cycle, step 9: erythema in forearms treated with antihistamines and corticosteroids. 2nd cycle, step 12 generalized erythema, requiring adrenaline. Cycle was completed afterwards. 3rd cycle, step 14: generalized erythema treated with antihistamines and corticosteroids.

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Conflict of interests

SLF: Expert Witness for ALK, ALLERGY THERAPEUTICS. Other authors declare that they have no conflict of interests.

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LETTER TO THE EDITOR

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Hypersensitivity to lipoic acid

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Key words

Lipoic acid; allergy; hypersensitivity; mast cells; tryptase.

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To the Editor,

though we daily deal with adverse reactions to almost any kind of allergen, sometimes our job can still be surprising. We examined a 44-year-old woman with autoimmune hypothyroidism and essential hypertension, who was regularly taking Eutirox® and Triatec HCT® tablets (**table I**). A recent immediate (< 60'), diffuse, self-limiting (about 2-3 hours) urticarial rash after the intake of Destior R+® (Sintactica, Italy) stood out in her allergological history. Destior R+® is an antioxidant-multivitamin product containing lipoic acid (LA, 600 mg), thiamine, pyridoxine, DL-alpha-tochopheryl acetate, lysine, lactose, carboxymethylcellulose (50 mg) (1) microcrystalline cellulose, stearate, and talc. Planning the diagnostic path, we decided to bypass the skin tests phase because of the moderate features of the adverse event and the low/uncertain sensitivity and predictive values expected. During a first challenge test (DPT) with Destior R+®, about 25 minutes after completing the whole dose, the patient developed another widespread urticarial reaction, without other complaints; complete resolution was obtained with prompt administration of antihistamines and steroids. Serum tryptase was elevated at 5.3 mcg/L, compared to a baseline of 1.8 mcg/L. Since we couldn't acquire pure components of Destior R+® except carboxymethylcellulose, we decided to surrogate them with commercially available products. DPTs with pure carboxymethylcellulose (80 mg; Roquette, France), thiamine (100 mg; Benerva®, Teofarma, Italy), pyridoxine (100 mg; Benadon®, Bayer, Germany), DL-alpha-tochopheryl acetate (100 mg; Evion®, Dompé, Italy) were performed uneventfully; conversely, our patient reacted to LA (670 mg; Tiobec®, Laborest, Italy) developing another urticarial rash, easily controlled again without the need for epinephrine administration; serum tryptase was 4.2 mcg/L.

Lipoic acid, also known as thioctic acid, is a medium-chain fatty acid derived from caprylic (octanoic) acid by addition of two sulphur atoms to form a five-membered ring (**figure 1**) (2). Small amounts of LA are found in various foods. It acts principally as an antioxidant, and its R (alpha) enantiomer has been proposed for the treatment of several conditions (3).

We couldn't find cases of generalized immediate reactions to LA or orally administered vitamin B1/B6/E in the scientific literature (PubMed, Google Scholar, Web of Knowledge). Allergic reactions to lipoic acid have previously been rarely described, mainly of the delayed type, both as local contact dermatitis (4, 5), and in one case as a delayed skin rash due to the consumption of another LA oral supplement (6); recently, a case of contact urticaria to LA has also been reported (7). Until now, systemic immediate reactions to LA were only generically supposed (8) or just self-reported without any evidence (9). Here, challenge tests led to the diagnosis of systemic immediate hypersensitivity to LA, showing

***Figure 1** - Lipoic acid*



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Table I *- Components of the aforementioned products.*

Product	Producer	Components
Eutirox®	Merck	Thyroxine; corn starch, citric acid, carboxymethylcellulose, gelatine, stearate, mannitol
Triatec HCT®	Sanofi	Ramipril, hydrochlorothiazide; hydroxypropyl methylcellulose, corn starch, microcrystalline cellulose, stearyl fumarate
Destior R+®	Sintactica	Lipoic acid 600 mg, vitamin B1 as thiamine 1.1 mg, vitamin B6 as pyridoxine 1.4 mg, vitamin E as DL-alpha-tochopheryl acetate 24 mg; lysine, lactose, carboxymethylcellulose, microcrystalline cellulose, stearate, talc
Benerva®	Teofarma	Thiamine 100 mg, talc, povidone K90, stearate, methacrylate/ethyl acrylate copolymer, macrogol 6000, carboxymethylcellulose
Benadon®	Bayer	Pyridoxine 100 mg, povidone K90, talc, stearate, methacrylate/ethyl acrylate copolymer, macrogol 6000, carboxymethylcellulose
Evion®	Dompé	DL-α-tochopheryl acetate 100 mg, sucrose, isomalt, corn starch, skimmed milk, talc, arabic gum, orange flavour, titanium dioxide, red iron oxide, stearate
Tiobec®	Laborest	Alpha-lipoic acid 800 mg, microcrystalline cellulose, dicalcium phosphate, silicon dioxide, talc, stearate, carboxymethylcellulose, glyceryl behenate, hydroxy-propyl methylcellulose, polyvinylpyrrolidone, shellac, microcrystalline cellulose, stearic acid, fatty acids mono- and acetate diglycerides, titanium dioxide

once again their essential role in our clinical practice. A further DPT with pure LA was not performed because of ethical concerns: indeed, the clinical picture was clearly indicative of hypersensitivity to LA, being LA the only relevant antigen contained in any product which caused our patient an immediate urticarial reaction and not contained in the tolerated products. The rise of serum tryptase levels after LA intake suggests that the reactions occurred through mast cell activation (10).

In the end, we learnt that in case of strong suspicion of an allergic reaction to a LA-containing product, hypersensitivity to LA must also be considered among the possible causes.

We report that ethical approval not necessary; written informed consent for anonymous disclosure was obtained.

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Contributions

FM: conceptualization, investigation, methodology, project administration, visualization, writing - original draft, writing - review & editing. AC: resources, supervision, writing - review & editing.

Conflict of interests

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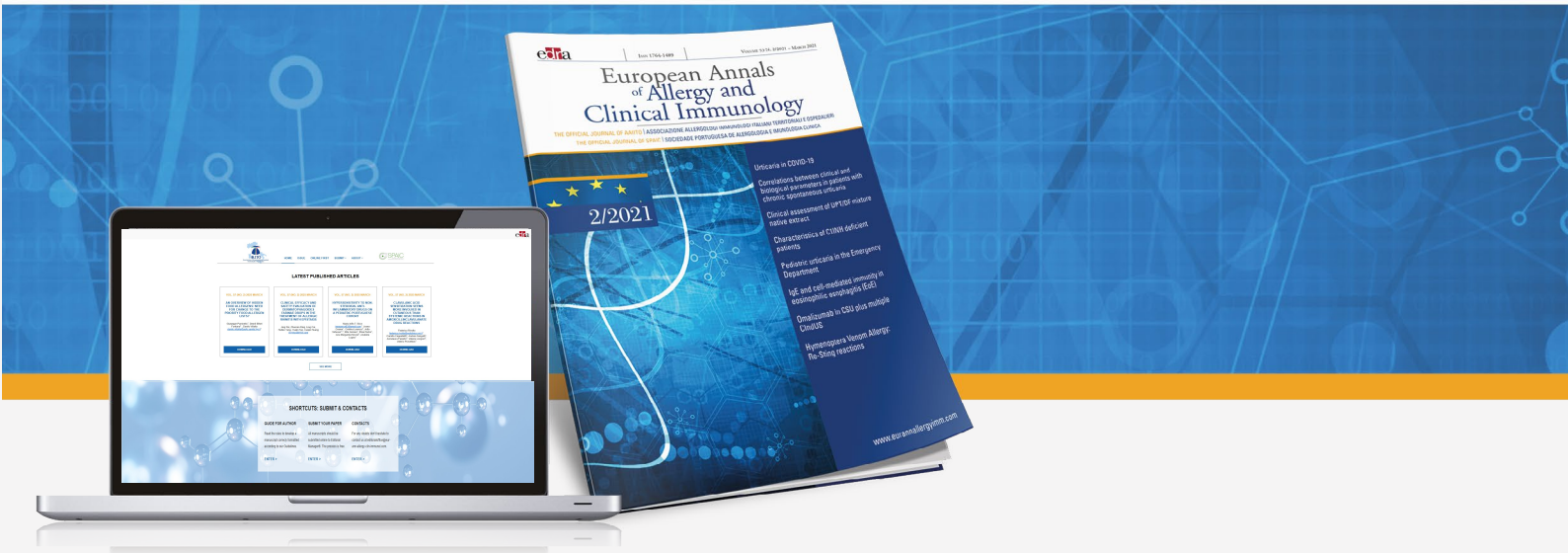
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