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E-Issn 2845-7285

Volume 58 N. 1/2026 – January 2026

European Annals of Allergy and Clinical Immunology

THE OFFICIAL JOURNAL OF AAIITO | ASSOCIAZIONE ALLERGOLOGI IMMUNOLOGI ITALIANI TERRITORIALI E OSPEDALIERI

THE OFFICIAL JOURNAL OF SPAIC | SOCIEDADE PORTUGUESA DE ALERGOLOGIA E IMUNOLOGIA CLINICA



1/2026

2023 Journal Impact Factor: 2.6



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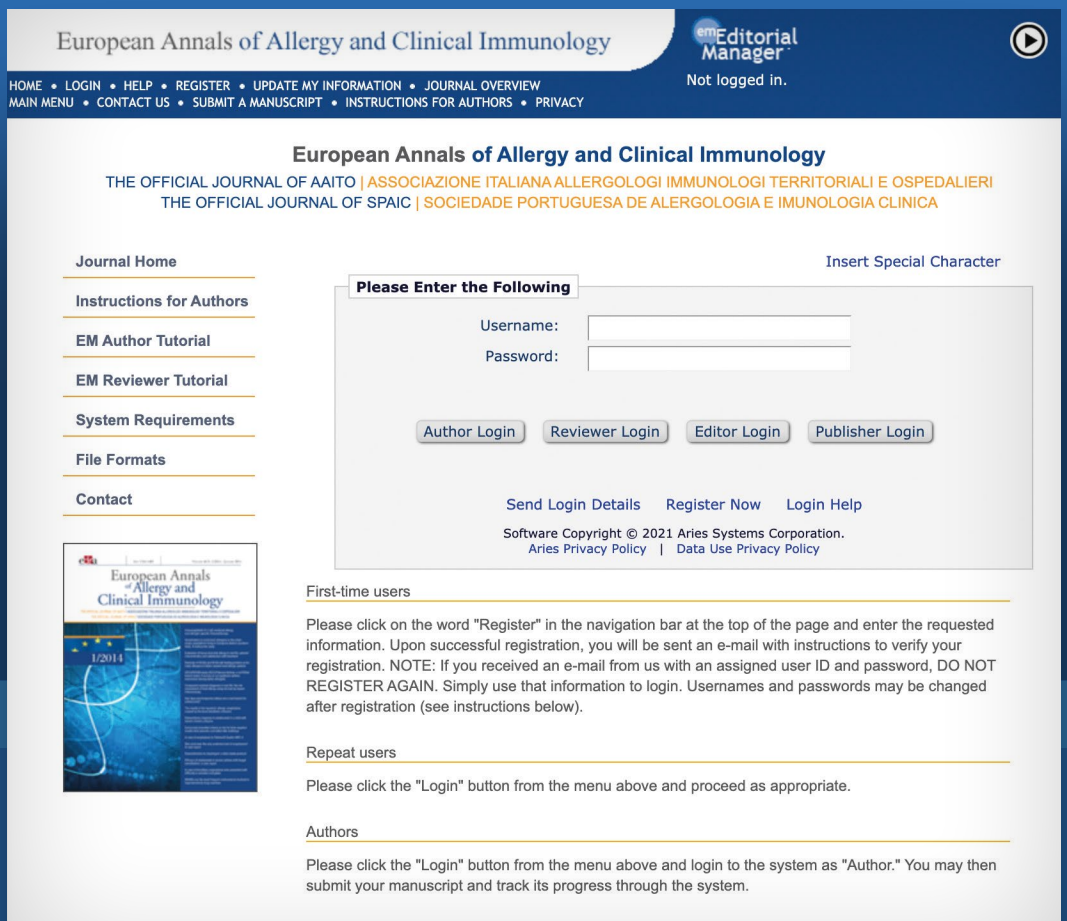
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Viale Forlanini, 21
20134 Milano - Italy
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Fax 0039 (0)2-88184.301
www.edizioniedra.it

"European Annals of Allergy and Clinical Immunology" registered at Tribunale di Milano - n. 336 on 22.10.2014

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Acknowledgments

The Editors thank the following colleagues and experts for their invaluable help in reviewing the manuscripts submitted to *European Annals of Allergy and Clinical Immunology* for the year 2025 (January-December).

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Frederico S. Regateiro[1-4], Ezequiel Barros[5,6], José Luís Plácido[7], José Pedro Moreira da Silva[8]; on behalf of GI IG

A clinical update on chronic rhinosinusitis and nasal polyposis

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Key words

Chronic rhinosinusitis; nasal polyps; phenotype; endotype; biologics.

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Doi
10.23822/EurAnnACI.1764-1489.385

Impact statement

Chronic rhinosinusitis causes significant morbidity. This narrative review focuses on the disease's pathophysiology and discusses key aspects of diagnosis and treatment based on the authors' clinical experience.

Summary

Chronic rhinosinusitis (CRS) is a complex heterogeneous disease of the nose and paranasal sinuses that presents different phenotypes and endotypes. CRS is a common health problem associated with significant morbidity, as well as with high health care expenditure. As our knowledge on inflammation, tissue remodeling and pathophysiological mechanisms develops, both diagnosis and therapeutic approaches to CRS improve. This review outlines key drivers in the pathogenesis of CRS with and without nasal polyps, current diagnostic tools clinicians can rely on in clinical practice, and current and future treatment options, while providing a general overview of up-to-date guidelines for CRS diagnosis and management. A better understanding of CRS can pave the way for the optimization and development of novel therapies, benefiting patients who suffer with more severe phenotypes and allowing a personalized approach to the disease.

Introduction

The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) international consensus defines rhinosinusitis in adults as an inflammation of the nose and paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), with or without facial pain/pressure or reduction or loss of smell, or both. Besides these

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symptoms, endoscopic signs of nasal polyps and/or mucopurulent discharge primarily from the middle meatus and/or edema/mucosal obstruction primarily in middle meatus must be present, and/or mucosal changes within the ostiomeatal complex and/or sinuses must be seen by computerized tomography (CT) (1). In children, the definition of rhinosinusitis differs in one criterion: the interference on smell in adults is replaced by the presence of cough in children (1) (**figure 1**) Chronic rhinosinusitis (CRS) is defined as the maintenance of two or more symptoms, one of which should be either nasal blockage or obstruction or congestion or nasal discharge, for at least 12 weeks without complete resolution (1). CRS is associated with a significant impact on quality of life (QoL) and on healthcare costs, particularly indirect costs (1).

In 2011, a large-scale study calculated a CRS prevalence of 10.9% in the adult population of Europe based on EPOS criteria (2). The prevalence of CRS based on symptoms varies between 5.5% and 28%, being more common among smokers than non-smokers (2-5). This variation from 5.5% to 28% corresponds to higher prevalences found in Europe, followed by United States, China, and Brazil, where lower prevalence rates were found (2-5). Several factors may account for this wide variation in prevalence between countries, including differences in healthcare systems and access to medical services, which can influence diagnosis rates. Additionally, environmental factors, such as air pollution and occupational exposures, can vary by region and may contribute to the differences in CRS prevalence (6). Furthermore, different studies may use varying definitions or diagnostic criteria for CRS, which could lead to inconsistencies in reported prevalence (2-5). The prevalence of physician-diagnosed CRS ranges from approximately 1% to 9% of the general population (7).

Traditionally, CRS has been divided into two main phenotypes: with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP) (8). According to other clinical features, these may be subdivided into several phenotypes, or divided into endotypes, according to the pathophysiological mechanisms involved (7, 9, 10). EPOS2020 proposed a new classification of CRS into primary and secondary CRS and a division based on anatomic distribution: localized and diffuse disease (8).

This paper aims to review the existing literature on CRS in both adults and children and provide a practical approach and expert considerations on the diagnosis, management, and available therapies for CRS. Several systemic inflammatory disorders can affect the nasosinusal mucosa and present with CRS symptoms, such as Eosinophilic Granulomatosis with Polyangiitis (or Churg-Strauss syndrome) and Granulomatosis with Polyangiitis (or Wegener's granulomatosis) (7). These diseases have distinct pathophysiology and management, and are outside the scope of this review.

Pathophysiology

CRSsNP and CRSwNP are not unique nosological entities, as several phenotypes/endotypes have been proposed, and their classification remains non-consensual (7, 9, 11, 12). A review proposed four distinct (but overlapping) endotype classifications of CRSwNP based on the presence of 1) type 2 cytokines; 2) eosin-

Figure 1 - *The definition of rhinosinusitis in adults and children, as outlined by the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020)) (1).*

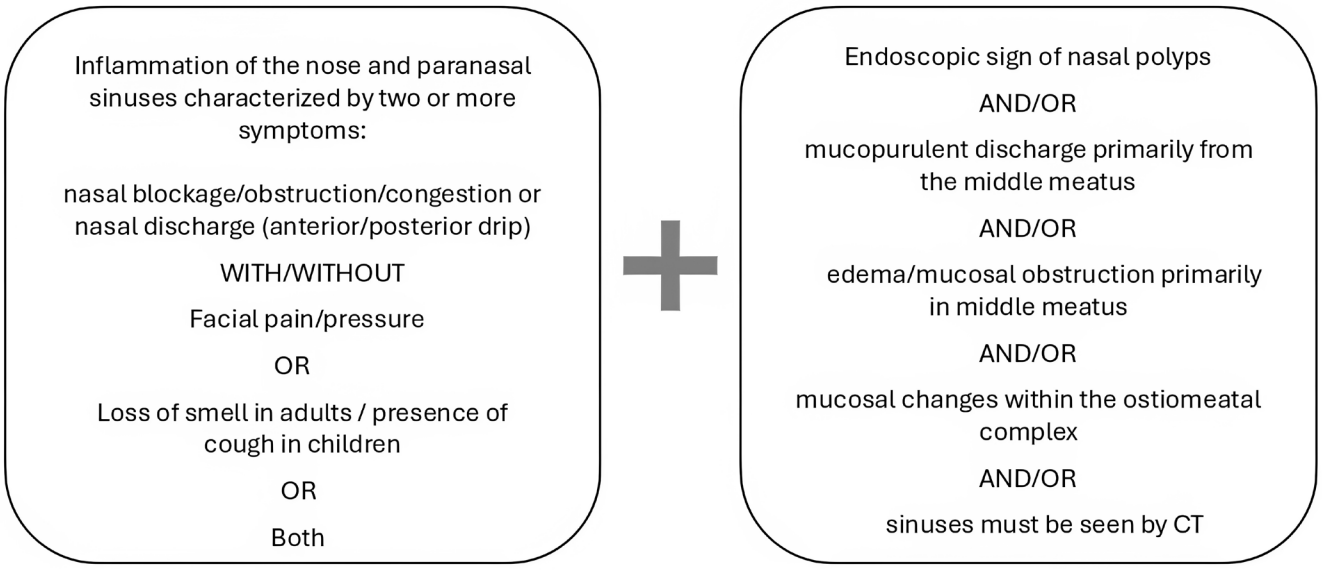
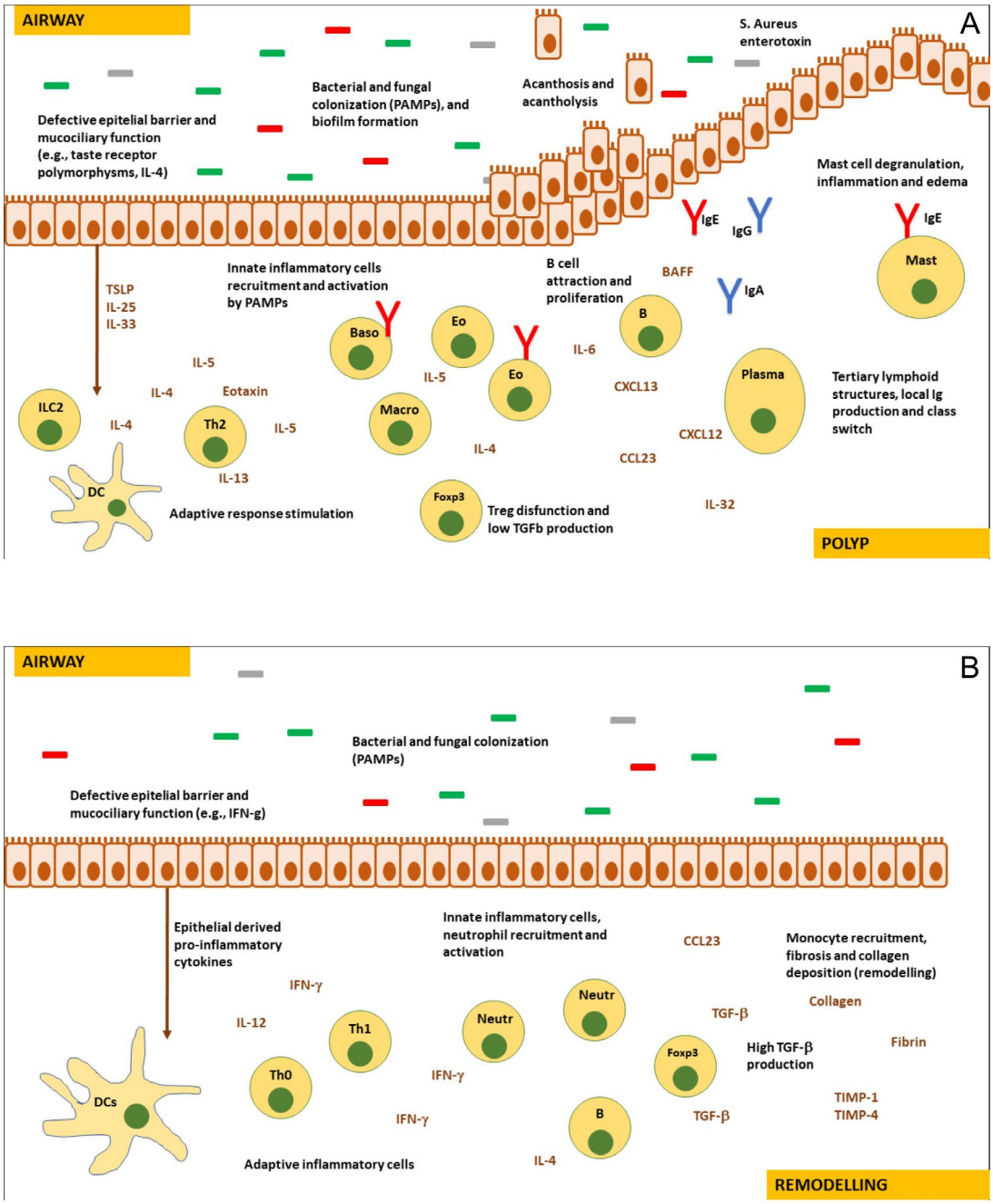


Figure 2 *- Summary of pathophysiological mechanisms of chronic rhinosinusitis (CSR).*



Pathogenesis of CSR with nasal polyps (CSRwNP) and without nasal polyps (CSRsNP) is influenced by microbial, systemic and genetic factors. **(A)** CSR tissues present a variety of innate (eosinophils, neutrophils, basophils, mast cells, type 2 macrophages, and type 2 innate lymphocytes (ILC2s)) and adaptive immune cells. In patients with CRSwNP, both Th2 and eosinophilic inflammation are most often observed together with high levels of cytokines IL-5 and IL-13, eotaxin-2, and monocyte chemoattractant protein (MCP)-4. ILC2 cells are sources of IL-13 in response to IL-33 and contribute to Th2 polarization. IgE promotes eosinophil and mast cell degranulation, maintaining inflammation and edema, while local IgE production may be stimulated by *Staphylococcus aureus* enterotoxin**.** Other mechanisms include bacterial and fungal colonization of the sinonasal tract. *Staphylococcus aureus* biofilms have been associated to recalcitrant CRS. **(B)** Remodelling is driven by induced fibroblast proliferation via TGF-β leading to up-regulation of collagen synthesis. In CRSwNP there is an up-regulation of metalloproteinases (namely MMP7 and MMP9), and down-regulation of natural tissue inhibitors (TIMP1 and TIMP4). Therefore, in CRSwNP, there is a deficit in collagen with degradation of the extra-cellular matrix (ECM) and formation of vacuoles. Deposition of albumin also occurs in CSRwNP, while CRSsNP is characterized by fibrosis.

ophils; 3) immunoglobulin E (IgE); or 4) cysteinyl leukotriene (CysLT) (13). Both phenotyping and endotyping may provide relevant information about the diagnostic, response to treatment, and prognosis. **Figure 2** summarizes the main pathophysiological mechanisms involved in CRS.

Chronic rhinosinusitis pathogenesis

Paranasal sinuses have complex and variable anatomy. The ostiomeatal complex is critical for the correct ventilation and drainage of the maxillary, anterior ethmoidal, and frontal sinuses, and anatomical or inflammatory alterations may predispose to acute and/or chronic sinusitis (14). Viral infections followed by bacterial superinfection are well-established causes of acute rhinosinusitis (most often by *Streptococcus pneumoniae*, *Haemophilus influenza*, *Moraxella catarrhalis*, and *Staphylococcus aureus*) (15, 16). However, the role of bacterial infection in the pathogenesis of CRS is less clear. Both aerobic and anaerobic bacteria have been found in CRS, but it is unclear whether infection is a primary cause or a consequence of compromised sinus function (17).

Several other local, systemic, microbial, environmental, genetic, and iatrogenic factors may be important for the pathogenesis of CSRwNP and CRSsNP (7, 18) and may contribute in variable degrees to the development of particular endotypes/phenotypes. Despite some efforts (19), there is no established animal model of CRS to help distinguish mechanistic contributions from consequences of CRS uncontrolled inflammation. A review examined six broad theories on the etiology and pathogenesis of CRS. These include the microbiological-based hypothesis which encompass: 1) the "superantigen hypothesis," 2) the "biofilm hypothesis," 3) the "microbiome hypothesis" (all "bacterial-based hypotheses,"); and 4) the "fungal hypothesis". Additionally, the review covered 5) the "eicosanoid hypothesis" and 6) the "immune barrier hypothesis," both of which focus on host-specific factors (20).

CRSsNP vs CRSwNP immunopathology

Polyps are edematous formations of inflammatory tissue grown into the nasal cavity. Etiological differences may determine their occurrence. Remarkably, CRSwNP patients have a higher prevalence of acute rhinosinusitis, allergic rhinitis, and asthma before CRS development, whereas CRSsNP patients have a higher prevalence of upper and lower respiratory tract infections (21).

CRS tissues are rich in innate (eosinophils, neutrophils, basophils, mast cells, type 2 macrophages, and group 2 innate lymphoid cells, ILC2s) and adaptive immune cells (22). Nasal polyposis can be divided into two main types: a neutrophilic polyposis and polyposis associated with conditions such as chronic eosinophilic rhinosinusitis, (23), allergic fungal rhinosinusitis, Nonsteroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (N-ERD) (11, 13, 24), and asthma (11, 13, 25). Traditionally, CRSsNP has been classified as neutrophilic and CRSwNP as eosinophilic. However, neutrophils may be present in normal tissues and also in CRSwNP, and this classification based in the presence of neutrophils has been questioned (26).

On the other hand, Type 2 (T2) inflammation and eosinophilic inflammation are observed in most patients with CRSwNP. Compared to CRSsNP and control subjects, the nasal mucosa of CRSwNP patients shows increased levels of IL-5 (a pivotal cytokine for eosinophils production, maturation, and activation), IL-13, eotaxin-2, and monocyte chemoattractant protein (MCP)-4 (27). CRSwNP also presents higher percentages of innate lymphoid cells (ILC), particularly ILC2, in the diseased mucosa compared to CRSsNP. These cells are important sources of IL-13 in response to IL-33 and contribute to the Th2 polarization of the disease in CRSwNP (27). Blockade of IL-5, IL-4, and IL-13 using monoclonal antibodies showed the importance of these cytokines in CRS immunopathology (28-30). TSLP, an epithelial alarmin, drives Type 2 inflammation, promoting tissue remodeling and nasal polyp formation. The TSLP-blocking antibody Tezepelumab is under investigation for treating CRSwNP (31).

Antibodies of all isotypes have been found in polyps, in strike contrast to CRSsNP (32), and a clear role for IgE in the pathophysiology of CRSwNP was demonstrated in a study using anti-IgE treatment with omalizumab (33). IgE may also lead to eosinophil and mast cell degranulation perpetuating the inflammation and edema observed in CRSwNP (34). Local production of antibodies, in particular specific IgE, may be stimulated by *Staphylococcus aureus* enterotoxin B (35).

Different remodeling processes also differentiate CRSwNP and CRSsNP. CRSwNP is characterized by a deficit in collagen, by degradation of the extra-cellular matrix (ECM), development of vacuoles, deposit of albumin in nasal polyps, and edema. Contrarily, CRSsNP is characterized by fibrosis. Recent data also shows that remodeling in CRSsNP occurs independently from the inflammatory process and precedes it (36).

Diagnosis

According to several guidelines (1, 37-40), the clinical diagnosis of CRS must include symptom assessment and objective documentation of sinonasal inflammation. A position paper from EUFOREA, ARIA, EPOS, and AIRWAYS ICP recommends that CRS clinical diagnosis should be based on the presence of two or more sinonasal symptoms plus a CT scan for non-otorhinolaryngologists, supplemented by allergy tests in case of suspicion of concomitant allergy, and/or nasal endoscopy by otorhinolaryngologists for phenotyping into CRSwNP and CRSsNP (41). The presence of nasal polyps must be confirmed, and it remains a challenge to distinguish between CRSwNP and CRSsNP based on clinical impression alone, since there is considerable overlap of symptoms in patients with and without nasal polyps (42). In children, clinical symptoms are often the primary means of diagnosis due to the difficulty of tolerating nasal endoscopy and the limita-

tions of sinus radiologic imaging in uncooperative patients (43). In the differential diagnosis of nasal masses, age is an important clue: in children aged < 2 years, congenital malformations with a herniated endocranial mass are the most frequent; from 2 to 20 years of age, mucoviscidosis or eosinophilic polyposis must be considered; and in adults > 20 years, inflammatory polyposis is the likeliest cause (44).

The development and validation of questionnaires, along with the resulting diagnostic algorithm may contribute to accurate diagnoses, with high level of sensitivity and specificity (45, 46). However, the correlation between questionnaire-based and clinical-based diagnoses of CRS has shown only moderate agreement, indicating that adjustments to the questionnaires are necessary (47).

Nasal endoscopy or CT scan, remain the gold standard imaging in CRS for documenting sinonasal inflammation (8). **Figure 3** presents an example of nasal endoscopy and CT imaging that is common in clinical practice.

Magnetic resonance imaging (MRI) can complement CT scan for the imaging of paranasal sinuses and diagnosis (48) (**figure 4**). Several challenges limit the broader use of MRI in clinical practice when compared to standard nasal endoscopy and CT scan, including the lower definition obtained for bone structures, longer scanning times and higher costs associated (48). However, MRI has no radiation risks and provides improved soft tissue definition over CT scan, increasing the ability to differentiate between soft tissue masses and retained/obstructed secretions (48, 49). Others recommend MRI only to differentiate benign obstructed secretions from tumors and to assess the spreading to outside the nasal cavity and sinuses (38, 39). We consider that MRI should be performed if eosinophilic CRS is suspected since eosinophilic mucin is only detected by MRI (50).

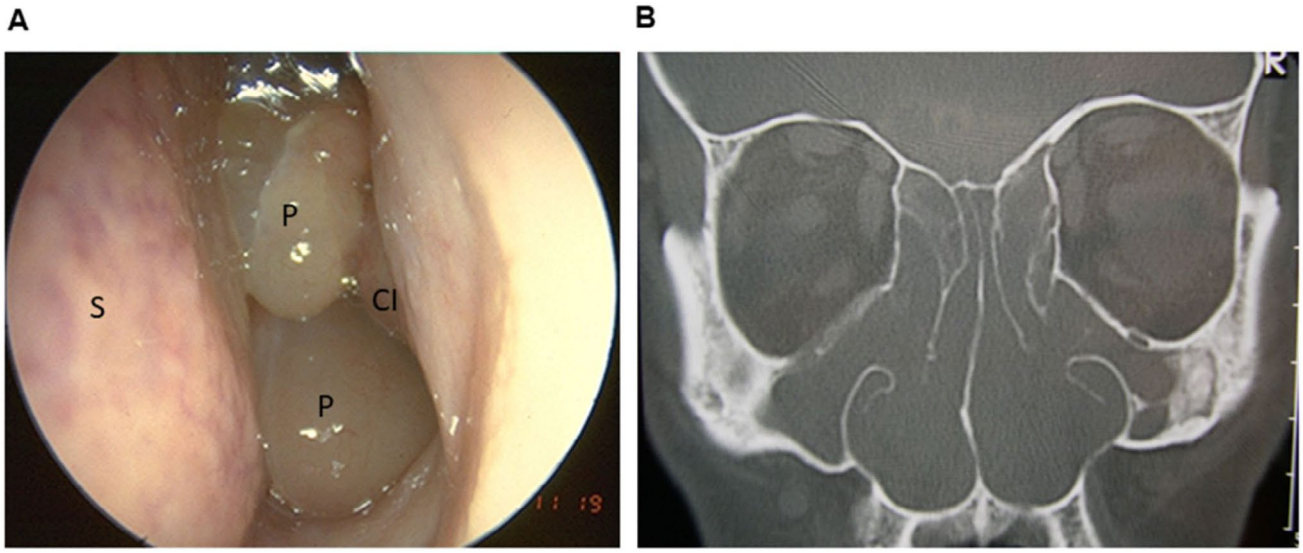
Bacteriology tests are relevant for the etiological diagnosis as specific inflammatory endotypes are associated with the intramucosal presence of specific bacteria (51). Additionally, a relationship between intramucosal microorganisms and inflammatory patterns in subgroups of CSR patients has been reported (51). There is much debate regarding the role of fungi in CRSwNP (1, 38, 39, 49) and whether the diagnostic group of allergic fungal rhinosinusitis (AFRS) truly represents a unique disease.

Nasal NO is a sensitive indicator of inflammation (high values) and ciliary dyskinesia (low levels) (52). However, very low levels in the nose may be related to significant sinus obstruction/severe polyposis, while elevated levels suggest nasal inflammation despite osteomeatal patency. Also, wide variability in the baseline levels of NO limit its value for diagnosis and management (53). NO may, however, be used as an outcome measure to monitor response to therapy (53).

Skin prick tests and/or measurement of specific IgE to aeroallergens in the serum are routinely performed in clinical practice to evaluate respiratory allergy and its contribution to the overall nasal symptoms (1).

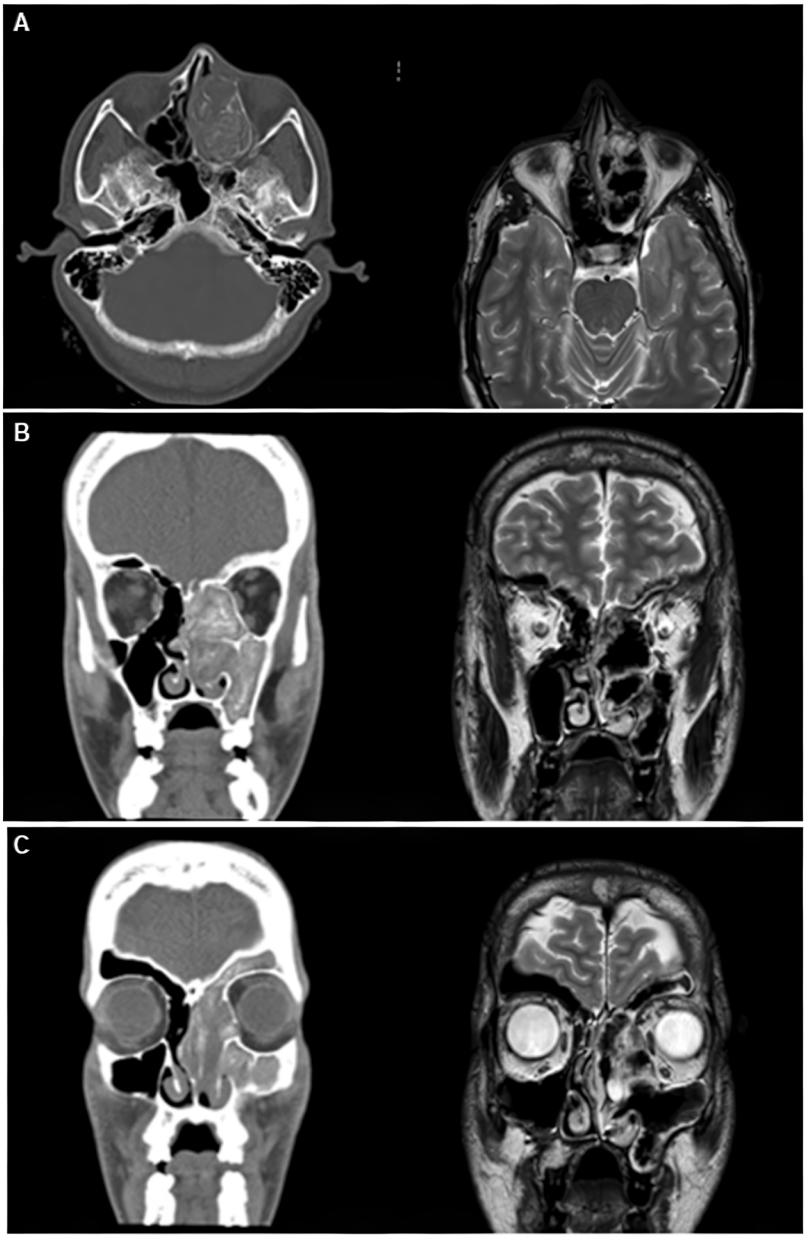
In some patients, a nasal allergen provocation test (NAPT) may be performed (1). This is a safe procedure to demonstrate local mucosal allergy (54), to confirm hyperreactivity to specific allergens before immunotherapy (54), and to identify clinically rel-

Figure 3 *- Nasal endoscopy and compute tomography (CT) are gold standard imaging in chronic rhinosinusitis (CRS).*



(A) Nasal endoscopy of the left nasal fossa. Several inflammatory polyps are visualized. **(B)** CT of the paranasal sinuses in coronal section of a patient with CRS with nasal polyps (CRSwNP). CI: inferior turbinate; P: polyp; S: nasal septum.

Figure 4 - *Magnetic resonance imaging (MRI) often complements computed tomography (CT) in chronic rhinosinusitis (CRS) imaging.*



(A) CT (left) and T2-weighted MRI (right) in axial section of the paranasal sinuses. Filling of the ethmoidal cells and compression of the right eyeball are visible with CT while mucosal hypertrophy is observed with MRI. **(B)** CT (left) and T2-weighted MRI (right) in coronal section of the same patient, encompassing the maxillary sinus and ethmoidal cells. The heterogeneity of the paranasal sinuses is observed in CT. **(C)** CT (left) and T2-weighted MRI (right) in coronal section of the same patient, encompassing the maxillary sinus, ethmoidal and frontal cells.

evant allergens in case of sensitization to multiple allergens (54, 55). Several guidelines aim to standardize this procedure (1, 55). Histopathology is important for differential diagnosis and for CRS endotyping (1, 56). We consider that routine histopathological analysis of nasal polyps, whenever possible, is important to evaluate differential diagnoses such as hamartoma, inverted papilloma or even adenocarcinoma, severe pathologies with an essential impact on therapeutic approach and prognosis. Histopathology may also provide cues regarding endotype, treatment choice and response to treatment. The quantification of eosinophils,

specifically the number of eosinophils per high-powered fields, can be performed, significantly correlates with prognosis and disease severity, and eosinophil-dominance might help direct medical and surgical treatment options, as discussed below (56, 57).

CRS impact and comorbidities

Comorbidities

CRS patients are likely to present with asthma, COPD, primary immunodeficiencies, acquired immunodeficiencies including human immunodeficiency virus (HIV) infection, immunosuppression due to transplant, diabetes mellitus, medications, malignancies, and ciliary dyskinesia (49). In adults, the comorbidities with the highest relative proportions were asthma (38%) and allergy (34%). In CRSwNP, the relative proportions of asthma and allergy were 49% and 36%, respectively, while in CRSsNP, these proportions were 32% for both conditions (43).

It is important to note that comorbidities may differ between pediatric and adult CRS patients, as allergy, chronic otitis media, and tonsils disease were more prevalent among pediatric patients (43).

N-ERD is a type of CRS that requires specific management and should be considered in asthma-associated CRS (49, 58). The relative proportion of N-ERD among patients with CRSsNP and CRSwNP was 1.7% and 6.6%, respectively (59). The oral aspirin challenge remains the gold standard for N-ERD diagnosis (49, 58).

Quality of life

Patients with CRS could experience a complex range of symptoms and therefore CRS related QoL (60) should also be assessed. Several instruments are available to measure CRS related QoL, such as chronic sinusitis survey (CSS), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), Rhinosinusitis Disability Index (RSDI) and SNOT-22, which is the most widely used questionnaire (1). A recent review showed that the key symptoms reducing quality of life (QoL) include loss or reduction of smell and sleep disturbances, which in turn may lead to additional physical and mental health consequences (59).

Treatment

Treatment should be directed by phenotypes and, whenever possible, by endotypes. However, the EPOS 2020 based treatment in the new classification: localized (often unilateral) or diffuse (always bilateral) (1); the primary classification for the approved therapies is CRSsNP and CRSwNP.

Pharmacological

Intranasal corticosteroids (INCS)

INCS are highly effective and recommended in CRSsNP (1, 7, 18, 61). In CRSwNP, INCS are also recommended (7, 49), but efficacy depends on effectively delivering INCS to the paranasal sinuses. The surgical state of the sinuses treated, *i.e.*, whether the sinuses are open and topical INCS can penetrate the sinus cavity, seems particularly relevant and appears to influence response to treatment significantly (49, 62). In children, INCS is the first-line treatment in CRSwNP and CRSsNP, but caution is needed when long-term treatments and high-doses are prescribed (1).

Systemic corticosteroids

Short term treatment with oral steroids (OCS) may be used in CRSwNP (1, 7, 18, 63, 64). However, it was found that three to six months after the end of the treatment, there is little or no improvement in health-related QoL or symptom severity (64). The risks of short courses of OCS are cumulative over the years, and significant adverse events must be considered (1, 7, 63). OCS should be used cautiously in patients with diabetes, uncontrolled hypertension, and peptic ulcer disease (18). OCS use in CRSsNP is optional due to insufficient evidence (1, 7, 63).

Until recently, it was common to use steroid depot injections. However, in light of the evidence regarding the increased risk of diabetes (65), osteoporosis (65, 66), and secondary adrenal insufficiency (66) associated with these steroid depot injections, we consider that steroid depot injections must be avoided.

Antihistamines

There is no compelling evidence for antihistamine treatment of CRSsNP in adults, and therefore this is not recommended (1). Also, current data yield insufficient evidence to recommend antihistamines in non-allergic patients for the treatment of CRSwNP, although in patients with CSR and concomitant allergic rhinitis, antihistamines may be indicated (1, 25).

The EPOS 2020 guideline recommends using these agents for children with documented allergic rhinitis (1).

Leukotriene modifiers

One meta-analysis concluded that leukotriene receptor antagonist (LTRAs), administered as monotherapy, effectively treated CRSwNP, however have limited benefit when used as an adjunctive therapy to INCS, proposing that additional studies are required to determine the most beneficial strategy for their use (67). EPOS 2020, based on the very low quality of evidence, only recommends its use when patients do not tolerate INCS (1).

No data exists about the potential efficacy and thus usefulness of leukotriene modifiers in the context of CRS in children. The EPOS 2020 guideline recommends the use of these agents for children with documented allergic rhinitis (1).

Antibiotics

Antibiotics should be used if there is enough evidence of infection. However, the evidence regarding the use of short-term antibiotics for CRS, acute exacerbation of CRS, or long-term antibiotic for CRS is very low and conflicting, and further studies

are needed, taking into account the possible secondary effects and the emergence of antibiotic-multiresistant bacteria (68, 69).

Nasal douching

Nasal douching is recommended for both phenotypes (1, 7, 18, 38, 39) and irrespective of age group (1). It is often recommended as an additional non-pharmacological treatment; however, it could also be considered a first-line treatment. Although there is no consensus on the solution to be used, the most suitable device, or the optimal treatment schedule, there is a trend suggesting that once- or twice-daily administration of hypertonic solutions, enriched with the natural minerals and trace elements found in seawater and certain thermal waters, may provide greater clinical benefits, better endoscopic scores, and improved nasal resistance compared to isotonic solutions (70, 71).

Aspirin desensitization

Aspirin therapy after desensitization (ATAD) should be considered in patients with N-ERD (7). ATAD involves the administration of gradually increasing doses of aspirin under medical supervision to induce tolerance, enabling patients to continue daily aspirin therapy. This approach has been shown to alleviate both upper and lower respiratory symptoms and delay the recurrence of nasal polyps (72). More recently, intranasal administration of lysine-aspirin has demonstrated clinical efficacy in improving nasal airflow and sense of smell, with fewer side effects compared to oral aspirin desensitization (73). However, ATAD is associated with potential side effects from daily aspirin intake, and discontinuing the treatment at any stage results in the loss of its clinical benefits (73). Overall, ATAD remains a valid option for carefully selected candidates, taking into account the indications, contraindications, side effects, and patient preferences (74).

Immunotherapy with bacterial lysates

Bacterial lysates are immunostimulants clinically prescribed for the prevention of respiratory tract infections (75). For CRSsNP, bacterial lysates such as oral OM-85 BV treatment may be considered adjunct to standard medical treatment in adults and children (1). Despite these indications and recommendations, the heterogeneity of published studies highlights the need for double-blind, placebo-controlled, multicenter, randomized clinical trials for each specific population (75).

Allergen-specific immunotherapy

For adults with CRSsNP, no data is available regarding the use of this immunotherapy (1). Concerning CRSwNP, few studies investigated the association between sensitization to aeroallergens and NPs, and even fewer tested the efficacy of specific immunotherapy (SIT) in the prevention of relapse after endoscopic sinus surgery (ESS). However, allergen-specific immunotherapy, combined with anti-IgE therapy, might have a promising future for preventing polyps relapse (76, 77). Furthermore, in patients with CRSwNP and concomitant allergic rhinitis symptoms, it is likely that allergen-specific immunotherapy might reduce the global overlapping symptoms.

Surgery

The ideal moment for CRS surgery is debatable (8, 78). A RAND/UCLA appropriateness study concluded that ESS could be appropriately offered to adults with uncomplicated CRSwNP when CT Lund-Mackay score is ≥ 1 and there has been a minimum trial of INCS plus a short-course of a systemic corticosteroid with a post-treatment total 22-item Sinonasal Outcome Test (SNOT-22) score ≥ 20 (78-80). CRSsNP is often treated adequately with surgery (66, 81, 82). ESS is the preferred technique (83) and has been associated with improvements in symptoms scores (especially nasal obstruction and discharge), disease-specific and generic QoL, as well as objective measures. If the adult has CRSsNP, the surgical criteria should include CR Lund-Mackay score ≥ 1, and, at least, one course of INCS plus, either a short-course of a broad spectrum/culture directed systemic antibiotic or the use of a prolonged course of systemic low-dose anti-inflammatory antibiotic with a post-treatment total SNOT-22 score ≥ 20 (78).

Since CRS is a chronic disease, usually related to endonasal anatomical abnormalities, ESS should be considered a step in disease management, correcting these anatomical abnormalities and creating better conditions for local treatment (1).

The most common surgical approach in children with CRS in whom "maximal" medical therapy has failed probably consists of an initial attempt at an adenoidectomy with a maxillary sinus wash plus/minus balloon dilation followed by ESS in case of symptoms recurrence. "Maximal" medical therapy usually includes a course of antibiotics and intranasal and/or systemic steroids and differs widely between practitioners and practice locations (84). Unfortunately, most data supporting this recommendation are not based on randomized prospective studies, and prospective, randomized, controlled clinical trials are required (1).

The long-term efficacy of surgery is influenced by choice of postoperative medical treatment regimen and compliance. Prolonged postoperative medical treatment with INCS improves the outcome post-ESS (1), delays the recurrence after surgery, and postpones the need for a new surgery (18, 85). OCS are strongly recommended in the perioperative period for CRSwNP and AFRS but not for CRSsNP (63).

CRSwNP tends to recur in a high percentage of subjects (18, 66, 81, 82) over 10 years or more and it is often associated with comorbid asthma (86). An investigation into both surgical and medical management strategies is warranted to reduce recurrence (81). Improved CSR phenotyping may allow better tailoring of surgical treatments in the future (83).

Recently, the concept of reboot surgery was introduced for type 2 inflammatory CRSwNP. This approach involves the removal of all inflamed sinus mucosa and allowing the regrowth of func-

tional nasal mucosa (87). This technique has shown a significantly reduced recurrence rate of nasal polyps for 30 months (17% *versus* 45% with the classical approach) (87, 88). Furthermore, this approach significantly improved olfactory function (88, 89). Therefore, reboot surgery should be considered for patients with uncontrolled severe CRSwNP, particularly when ESS has failed, to achieve long-term smell and maintain a polyp-free status (88).

Biologics

The criteria for the use of biologics in CRSwNP, first developed by EPOS 2020 (1), established that biologics are only indicated for CRSwNP patients with a history of previous surgery or, if surgery not appropriate, have three of the following criteria: evidence of type 2 disease; need of at least two courses of systemic corticosteroids per year or long-term (>3 months) continuous use of low-dose systemic corticosteroids; significantly impaired QoL; significantly loss of smell; diagnosis of comorbid asthma. However, the currently updated EPOS/EUFOREA 2023, recommends that evidence of type 2 inflammation should not be mandatory (90). The current EPOS/EUFOREA 2023 also defined five criteria to evaluate the response to biologicals in CRSwNP after 6 months and 1 year of treatment: reduced nasal polyp size; reduced need for systemic oral corticosteroids; improved QoL; improved sense of smell; reduced impact of comorbidities (90). Treatment should be discontinued if no response is observed in any of the criteria (90). Currently, dupilumab, omalizumab and mepolizumab are approved biologics for the treatment of adults with CRSwNP not appropriately controlled with standard therapies, and can be prescribed both in the presence or absence of concomitant asthma (91). Clinical trials with other biologics for the treatment of CRSwNP are ongoing (92).

Dupilumab

Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signalling by specifically binding to the IL-4Rα subunit that is shared by the IL-4 receptor and the IL-13 receptor complexes. Two-phase III randomized clinical trials, Liberty NP SINUS-24 and Liberty NP SINUS-52 evaluated dupilumab added to standard of care in patients with severe CRSwNP (1, 93). An improvement in SNOT-22, rhinosinusitis total symptoms score (VAS), nasal congestion score, sense of smell, nasal polyp score, Lund-Mackay CT score and, asthma control test were observed (1, 93). Dupilumab is well tolerated being the most common adverse event nasopharyngitis, injection-site reactions, and headache (94). A post-hoc analysis of the patients with N-ERD of the phase II study (28) demonstrated that dupilumab reduces sinus opacification across all sinuses and related symptoms (95).

Omalizumab

In adult patients with refractory CRSwNP with inadequate response to nasal corticosteroids, omalizumab is an option as an add-on treatment (96). Omalizumab is an anti-IgE that specifically binds to the high-affinity FcεR1 domain of free circulating IgE. Omalizumab prevents binding of free serum IgE to effector cells, reducing IgE levels and downregulating FcεR1 expression on mast cells and basophils. Consequently, blood eosinophils and nasal tissue eosinophils are decreased. Omalizumab also decreases albumin in the nasal fluid after the allergen challenge, preventing increased vascular permeability. The efficacy of this drug confirms the involvement of IgE as an inflammatory mediator in nasal polyposis (97).

Omalizumab is well tolerated, and adverse events are generally mild-moderate, not significantly different from placebo, and anaphylactic reactions are rare (98).

Omalizumab demonstrated clinical efficacy in treating nasal polyps with comorbid asthma (33, 99-103), irrespective of the presence of allergy (33, 61). A review from 2014 concluded that the use of omalizumab might be an effective therapeutic alternative in CRSwNP, especially in patients with more aggressive forms of the disease, such as those with a history of nasosinusal surgery and those with allergic asthma (104). Some studies also support omalizumab in refractory AFRS with (105) or without concomitant asthma (106).

The recently published results of two replicate phase III clinical trials POLYP 1, and POLYP 2, showed that omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes compared to placebo at week 24 and was well tolerated (107). Patients included in these studies were patients with severe CRSwNP, inadequately controlled despite daily INCS therapy (107). An open-label extension study, OLE, including patients from POLYP 1 and POLYP 2 trials, showed gradual worsening of Nasal Polyps Score (NPS), Nasal Congestion Score (NCS), and SNOT-22 after omalizumab withdrawal, even though these remained below pretreatment levels at week 76 (108).

Mepolizumab

Mepolizumab is a humanized monoclonal IgG1k antibody that inhibits the bioactivity of IL-5 by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signaling and reducing the production and survival of eosinophils (109). It has been approved as an add-on therapy with INCS for the treatment of adult patients with severe uncontrolled CRSwNP (109). The SYNAPSE phase 3 trial showed that, after 52 weeks, adult patients with severe CRSwNP treated with mepolizumab decreased nasal polyp size and obstruction, improved median endoscopic NPS, and decreased median nasal obstruction VAS scores compared to placebo. Fewer patients on mepolizumab required rescue systemic corticosteroid treatment, showed a significant longer time to first nasal surgery, and demonstrated improvement in sinonasal symptoms via VAS scores and Health-related Quality of Life (HRQoL) via SNOT-22. Adverse events were similar

between mepolizumab and placebo groups (110). Other clinical studies have shown similar results (92).

Due to the lack of head-to-head studies comparing the approved biologics for CRSwNP treatment, indirect comparisons through systematic literature reviews and network meta-analyses (NMA) have been conducted (111-113). These analyses have highlighted the positive effects of various biologics in outcomes such as reducing the need for rescue nasal polyp surgery, lowering the use of oral corticosteroids (OCS), and improving quality of life and the sense of smell, while maintaining a favorable safety profile. While dupilumab has shown favorable results, these findings must be interpreted with caution due to the high heterogeneity of the original studies in terms of patient inclusion criteria, disease severity, and outcomes (111-113). Head-to-head comparisons and real-world evidence are needed to confirm these findings, especially for specific patient subgroups. The personalized choice of biologic may also be influenced by the presence of allergic multimorbidity and other individual factors. Additionally, the availability of biologics can differ across countries and healthcare systems, highlighting the importance of having a diverse range of treatment options to ensure optimal patient care.

We consider that dupilumab, omalizumab, and mepolizumab are effective therapies for CRS. Biologics interfere with significant pathophysiologic pathways and may be disease modifying agents that help prevent remodeling and reduce the need for further surgeries. More data are expected regarding these long-term outcomes.

While taking into consideration that, in the majority of CRSwNP patients, surgery is likely not curative, we still believe that surgery, when possible, is an important clinical intervention for most of the CRSwNP patients and that surgery might be important to guarantee the efficacy of the chronic medical therapy that should be continued after surgery when indicated.

In conclusion, many questions are pending concerning the etiology and inflammatory mechanisms underlying CRS. However, as our knowledge and understanding on the pathophysiological mechanisms of CRS expands, new therapeutic approaches can be envisioned. Although the medical treatment for CRS is currently oriented to different phenotypes, the definition of endotypes with specific biomarkers will be paramount for a tailored clinical application of directed and personalized therapies.

The panel emphasizes the critical role of a multidisciplinary team, including otolaryngologists, pulmonologists, and allergists/clinical immunologists, in collaboratively determining the most effective therapeutic approach tailored to each patient's needs.

Fundings

This work was supported by Novartis via funding for third-party medical writing of this manuscript.

Contributions

EB, JLP, FSR, JPMS: conceptualization. EB, JLP: data curation. EB, JLP, FSR, JPMS: formal analysis. FSR, JPMS: funding acquisition. EB, JLP: investigation. EB, JLP: methodology. FSR, JPMS: project administration. EB, JLP: resources. EB, JLP: software. FSR, JPMS: supervision. FSR, JPMS: validation. EB, JLP, FSR, JPMS: visualization. EB, JLP, FSR, JPMS: writing – original draft. EB, JLP, FSR, JPMS: writing – review & editing.

Conflict of interests

FSR reports speaker and advisory fees from Novartis outside the submitted work. The other authors declare that they have no conflict of interests.

Acknowledgements

This manuscript was prepared with the medical writing support of Irina Duarte, Diana Gaspar and Constança Coelho from X2 Science Solutions, financially supported by Novartis Portugal.

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ORIGINAL ARTICLE

Eur Ann Allergy Clin Immunol Vol 58, N.1, 18-23, 2026

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Could egg yolk be the first approach in oral challenges for egg allergy tolerance?

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Key words

Egg allergy; food allergy; oral food challenges; egg yolk; pediatric patients.

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Doi
10.23822/EurAnnACI.1764-1489.388

Impact statement

This study demonstrates that boiled egg yolk can be safely consumed by most children with egg allergies, potentially improving dietary options and quality of life.

Summary

Background. *Hen's egg allergy is one of the most common pediatric food allergies, requiring accurate diagnosis and management strategies. Oral food challenges (OFCs) are critical in evaluating food allergies; however, limited research has focused on the outcomes of challenges involving egg yolks. This retrospective study aims to assess the outcomes and characteristics of pediatric patients who underwent oral challenges with boiled egg yolk.* ***Methods.*** *We evaluated patients diagnosed with egg allergy who underwent an OFC with egg yolk between 2019 and 2022.* ***Results.*** *The study included 123 patients with a median age of 12 months. The first presentation of symptoms occurred at a mean age of 6 months. Initial symptoms included eczema flare-ups (70%), urticaria (13.8%), and anaphylaxis (8.9%). The median age of the first egg yolk OFC was 12 months. For the first egg white OFC to assess the tolerance, the median age was 16 months. Of the 123 egg yolk OFCs, 115 (93.4%) patients were tolerant and consumed egg yolk at home. In the egg yolk-tolerant group, the mean duration of egg white tolerance was 4 months post-OFC; for non-tolerant patients, this extended to 11 months. The egg yolk non-tolerant group had higher egg white-specific IgE levels than the tolerant group (28 kU/L [IQR: 2.4–85.9] vs 4.2 kU/L [IQR: 0.9–8.8], $p < 0.01$).* ***Conclusions.*** *Though mild symptoms may occur, most children with egg allergies can safely consume boiled egg yolk. Consuming hen's egg yolk after a negative OFC could expand dietary options and improve quality of life.*

Introduction

Egg allergy is a common food allergy affecting 0.5% to 2.5% of young children (1). Notably, it has the highest prevalence in children with atopic dermatitis and is second only to milk allergy in overall prevalence (2-4). The diagnosis of egg allergy is typically based on clinical history, skin prick testing (SPT), specific IgE (sIgE) measurements, and especially oral food challenge (OFC), which is considered the gold standard for determining tolerance levels and guiding dietary recommendations (5). These diagnostic criteria have been critical in identifying allergic reactions to hen's egg proteins, particularly the egg white fraction.

Boiled egg yolk is commonly used in dining, salads, and meals and is often better tolerated than egg white (6-7). Previous studies on egg allergies have mainly focused on the whole egg or egg white, with limited research investigating the outcomes of challenges involving boiled egg yolk. Considering that consuming egg yolk may lead to earlier tolerance and that incorporating various egg products can improve the nutritional variety and quality of life for children, it is important to pay more attention to this subject (8, 9).

Accurate diagnosis and management of egg allergy are essential to minimize the risk of adverse reactions and improve the qual-

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ity of life for affected individuals. This retrospective study aims to evaluate the outcomes and safety of oral food challenges with boiled egg yolk in patients who have experienced a recent allergic reaction to a hen's egg and have highly elevated skin tests and specific IgE values.

Materials and methods

Study participants

This retrospective study analyzed data from the charts of patients with hen's egg allergy who underwent OFC for boiled egg yolk at Dr. Sami Ulus Children's Hospital between 2019 and 2022. The study included children who had their first egg OFC between the ages of 6 and 72 months and had a history of allergic reaction to whole hen's egg and tested positive for sIgE or SPT with egg, as specified in food allergy guidelines (10). Patients whose first provocation involved egg white were excluded from further analysis. Additionally, participants who were lost to follow-up after the initial diagnostic OFC and those with missing data regarding prognosis were also excluded.

Diagnostic procedures

Patients diagnosed with an egg allergy underwent a boiled egg yolk OFC after a 6-month follow-up period. Before the yolk OFC, all foods containing egg protein were removed from the children's diet. Participants who did not pass the first yolk OFC underwent a second challenge with egg yolk after a repeated 6-month elimination period, following our clinic's procedure. Participants who successfully completed the egg yolk OFC were instructed to consume boiled egg yolk once daily at home. Subsequently, an OFC with boiled egg white was planned, with the timing varying depending on factors such as the patient's test results, accidental exposure at home, the severity of the initial reaction, and the family's readiness, and was performed after they consumed egg yolk at home without any issues. Participants who did not pass the initial egg white OFC underwent a subsequent egg white OFC at least 6 months later.

The levels of sIgE were assessed using the fluorescent enzyme immunoassay (FEIA) system (IMMULITE Siemens, Germany). The results obtained from the fluorometer were evaluated in kU/L by the IgE standard calibrator. A measurement was considered positive if it was ≥ 0.35 kU/L.

Allergen extracts (Lofarma, Italy) were used for SPTs, which were performed on either the volar surface of the forearm or the back. SPTs were performed on the back in younger children for practical reasons, as it provided a larger surface area for testing and reduced movement during the procedure. Each test included both negative and positive controls to ensure accuracy and reliability. The negative control used was a saline solution, while the positive control was histamine. The mean wheal diameter was calculated 15 minutes after the test by determining the mean value of the longest diameter and the diameter perpendicular to it. To prevent any potential interference with the test results, any drugs that could impact the test, such as antihistamines, were discontinued seven days before the test.

Oral Food Challenge Protocol

This study utilized a 10-minute-boiled egg yolk for the egg yolk OFC and a 10-minute-boiled whole egg for the egg white OFC. The procedures were performed openly under the supervision of the same physicians and nurses at Dr. Sami Ulus Children's Hospital. The challenge food was administered at 15-minute intervals, starting with 1/16 of the total amount and increasing to 1/8, 1/4, 1/2, and the rest of the whole egg yolk or white. The OFC was terminated when the child developed severe symptoms, such as generalized urticaria, continuous coughing, severe abdominal pain, or vomiting. If mild objective symptoms, such as localized urticaria or pruritus, appeared during the OFC, the participant was carefully monitored for any worsening of symptoms. If the mild objective symptoms subsided, the OFC continued. In the event of an adverse reaction, the necessary medication was administered according to anaphylaxis guidelines (11). Additionally, patients were monitored for delayed reactions at home. In cases where delayed symptoms, such as eczema flare-ups, occurred after a negative OFC, patients were re-evaluated in the clinic to ensure proper management and adjustments to their diet.

Data collection

The main objective of this study was to evaluate the incidence of reactions during egg yolk OFC and determine whether participants could safely include egg yolk in their diet until they developed tolerance to egg white. The study included secondary data on allergy-related symptoms observed during the OFC and follow-up details, such as the duration of egg white tolerance.

Statistical analysis and ethical considerations

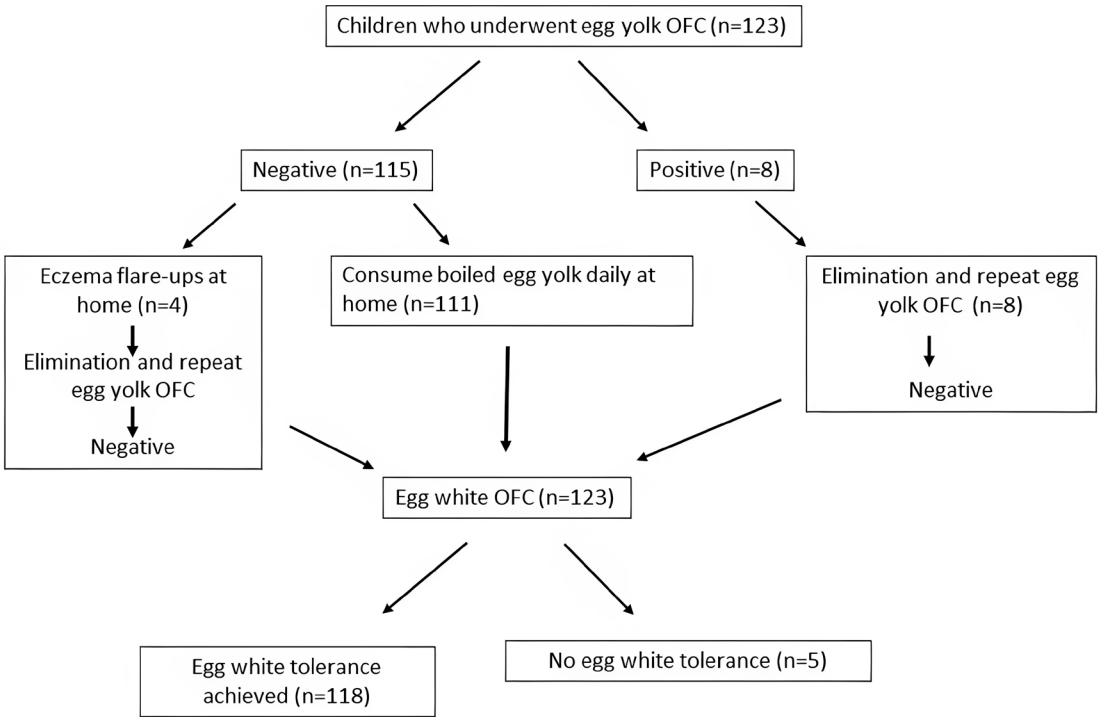
For statistical comparisons between the two groups, we used the Mann-Whitney U-test or Fisher's exact test. Differences in mean values were considered significant at $p < 0.05$. SPSS 26.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. Categorical changes were compared with chi-square. The study was approved by the Clinical Research Ethics Committee of Ankara Training and Research Hospital (decision no: E-23-1233), and all procedures were conducted in accordance with ethical standards, ensuring privacy and confidentiality.

Results

Study participants

We analyzed the medical records of 210 patients who had undergone OFC for hen's egg allergy in our clinic. However, 30 patients

Figure 1 *- Flowchart of the enrolled patients.*



OFC: oral food challenge.

Table I *- Clinical characteristics of the study group who underwent an egg yolk OFC.*

Characteristics	All (n = 123)	EY-tolerant (n = 115)	EY-non-tolerant (n = 8)	P-value
Male gender, n (%)	80 (65)	76 (66)	4 (50)	0.22
Age, months	12 (9-16)	12 (9-16)	11 (8-15)	0.31
History of anaphylaxis, n (%)	11 (8.9)	9 (7.8)	2 (25)	0.063
Atopic dermatitis, n (%)	87 (70.7)	81 (70.4)	6 (75)	0.96
Asthma, n (%)	20 (16.2)	19 (16.5)	1 (12.5)	0.92
Allergic rhinitis, n (%)	9 (7.3)	7 (6)	2 (25)	**0.027**
Total IgE, IU/ml	25 (17-89)	25 (17-79)	53 (15-223)	0.47
Eosinophils, /µL	350 (220-550)	350 (220-550)	405 (270-508)	0.83
Basophils, /µL	50 (30-70)	45 (30-70)	50 (40-60)	0.99
Egg white sIgE, kUA/l	4.3 (1.1-13.1)	4.2 (0.9-8.8)	28 (2.4-85.9)	**<0.01**
Egg yolk sIgE, kUA/l	1.8 (0.2-6.8)	1.7 (0.2-4.2)	6.4 (1.4-12.6)	**<0.01**
Egg white SPT, mm wheal	5 (1-6.5)	5 (0-6.5)	5 (4.4-7.5)	0.20
Egg yolk SPT, mm wheal	0 (0-4)	0 (0-4)	3.5 (0-4.5)	0.10
Multiple FA, n (%)	71 (57.7)	66 (57.3)	5 (62.5)	0.69

EY: egg yolk; FA: food allergy; IgE: immunoglobulin E; sIgE: specific immunoglobulin E; SPT: skin prick test. Data are expressed as median (interquartile range) unless otherwise noted.

who were already tolerating egg yolk when they presented to our clinic were excluded from the study as they underwent OFC with egg white only. Furthermore, 57 patients (egg yolk tolerant: n = 55; egg yolk reactive: n = 2) were excluded from the study as they lacked follow-up information after undergoing OFC with egg yolk, making it unclear whether they developed tolerance to egg white. Therefore, the final study cohort consisted of 123 patients (**figure 1**).

Clinical characteristics

The study population had a median age of 12 months, as shown in **table I**. Eleven patients (8.9%) had a history of anaphylaxis to hen's egg. Atopic dermatitis was the most common allergic condition (70.7%), followed by asthma (16.2%). All patients with atopic dermatitis in our study experienced eczema flare-ups specifically after consuming egg, and these flare-ups improved when eggs were removed from their diet, indicating an allergic reaction. Among children with egg allergies, 57.7% had multiple food allergies. There were no significant differences in age, gender ratio, history of egg anaphylaxis, or comorbidities between the OFC-positive and OFC-negative groups. The group that tested positive during the OFC had higher serum total IgE and sIgE levels related to egg white and egg yolk.

OFC outcomes and tolerance

Out of 123 egg yolk OFCs, 115 (93.4%) patients were found to be tolerant and consumed egg yolk at home. For patients who could tolerate egg yolk, the average duration of egg white tolerance was 4 months after the initial OFC. However, the period was extended to 11 months for those unable to tolerate egg yolk.

Symptoms and treatment during OFC

We analyzed induced symptoms and symptom severity during the OFC. Skin symptoms were the most frequently reported, while two patients required intramuscular adrenaline injections due to anaphylactic symptoms during the egg yolk OFC. Both patients had a history of anaphylaxis after consuming eggs. One patient experienced a diffuse urticarial rash and recurrent vomiting, while the other had a persistent cough, dyspnea, and vomiting. After repeat elimination, participants who failed the initial yolk OFC underwent a second yolk OFC. Participants who passed the OFC for egg yolk were advised to consume boiled egg yolk daily at home. They then underwent a boiled egg white OFC after consuming the egg yolk at home without any problems. None of the patients who were OFC-negative with egg yolk developed a type 1 allergic reaction at home. However, in four patients, even though the oral challenge test was negative, it was necessary to discontinue egg consumption at home due to eczema flare-ups. In these cases, a repeat OFC was performed in a hospital setting before reintroducing eggs into the diet.

Discussion and conclusions

Most patients tolerate egg yolk OFCs well, unlike whole egg OFCs. Compared to 6.5% positive OFCs in our study, Yanagida *et al*. (12) reported a higher rate of 17%, while Okada *et al*. (8) reported a positive rate of 9.1% for egg yolk. In our study group, SIgE-egg white was measured at 4.3 kUA/L, similar to the value reported by Okada *et al*. (6.6 kUA/L), which is lower than the results of Yanagida *et al*. (13 kUA/L). The positive rates of OFC were found to be directly proportional to the sIgE levels of the group undergoing OFC, as expected. Studies have shown differences in pre-challenge-specific IgE levels. However, cut-off values predicting pre-challenge positivity rates cannot be applied uniformly across all studies. This is because the decision for the challenge depends not only on laboratory tests but also on factors such as the severity of the patient's previous reactions, accidental exposure at home, and the willingness of the family to accept the challenge. These positivity rates were notably lower than those reported in studies investigating whole egg OFCs, which ranged between 23% and 42% (13-14). Our study highlights the favorable safety profile of egg OFCs, consistent with other studies. This is supported by lower positive rates compared to whole egg challenges reported in the literature.

However, it is important to address the potential impact of the 57 patients (31.6%) lost to follow-up. While the number of patients lost to follow-up may raise concerns, it is crucial to note that the majority of these patients were lost during the pandemic period, when families were often hesitant to visit hospitals due to safety concerns. Clinical observations suggest that patients who develop tolerance to foods at home rarely return for follow-up evaluations, whereas those with persistent symptoms are more likely to seek follow-up care. This pattern suggests that most of the patients lost to follow-up likely tolerated egg yolk at home without significant symptoms, which supports the validity and robustness of our findings. Additionally, a worst-case scenario analysis was conducted to assess the impact of the 57 patients lost to follow-up. In this analysis, we assumed that the 55 patients who tolerated egg yolk did not achieve egg white tolerance, while the 2 patients who were reactive to egg yolk did achieve egg white tolerance. Despite these conservative assumptions, the results remained statistically significant, confirming the robustness of our findings.

Only two patients (1.6%) had severe reactions during OFC requiring intramuscular epinephrine injection. This is consistent with the results of other studies of egg yolk OFC (12, 15). None of the patients who tolerated egg yolk during OFC in our study had severe reactions at home. Exceptionally, four patients had to discontinue egg consumption at home because of eczema flares, even though the oral challenge test was negative. These delayed reactions underscore the importance of monitoring patients not only during the OFC but also afterward,

as some allergic responses may manifest later. This is consistent with previous studies evaluating the safety of home consumption of egg yolk after a negative OFC (12, 15). These findings support the safe introduction of egg yolks at home, with careful follow-up to manage any delayed reactions, ultimately improving patients' quality of life.

For patients who were able to tolerate egg yolk, the average duration of egg white tolerance was 4 months after the first OFC. However, for those who could not tolerate egg yolk, this period was extended to 11 months. This is similar to the report by Okada *et al.* that the median time between the first egg yolk OFC and the first egg white OFC was 3.7 months for egg yolk-tolerant participants and 18.0 months for egg yolk-reactive participants (8). These findings suggest that tolerance to egg yolk could potentially predict the course of egg allergy.

Our findings suggest that incorporating boiled egg yolk into the dietary regimen of children with egg allergies offers a unique and complementary approach to established methods like egg white laddering. While these methods are highly effective with minimal adverse events, the introduction of egg yolk provides additional dietary flexibility and may serve as an intermediary step towards egg white tolerance, potentially enhancing overall quality of life for affected children.

This study had several limitations. One limitation of our study is the absence of an egg white OFC before the first egg yolk OFC. It is possible that some children had already outgrown their egg allergies by the time of the first egg yolk OFC. Additionally, the OFCs were not double-blind or placebo-controlled. Another limitation of the study was the small number of participants in the egg yolk reactive group. Therefore, further studies with larger sample sizes may be necessary. Given that our study was conducted during the pandemic, concerns about patients seeking medical attention and physicians' reservations about unnecessary hospital visits may have led to deviations from strict adherence to testing protocols. It is important to note that these deviations were not intentional and may have impacted the accuracy of our results. Furthermore, specific IgE measurements for Gal d 1 and Gal d 2, the main molecular components of egg, were not performed due to resource limitations. We recognize that these tests could have provided deeper insight into tolerance prediction and suggest their inclusion in future studies.

Most pediatric patients with an allergy to heated hen's egg can safely consume heated egg yolk. Although some children with egg allergies may experience mild symptoms, most can eventually tolerate egg yolk. This can improve their quality of life by making egg yolk products available after a negative OFC. The findings of the study emphasize the significance of sequential OFCs, beginning with heated egg yolk, for the diagnosis and evaluation of tolerance. These insights can inform clinical practice and provide a safer approach for reintroducing eggs into the diets of children with egg allergies.

Fundings

None.

Contributions

ST: conceptualization, methodology, data curation, visualization, writing – original draft. SD: conceptualization, data curation, formal analysis. MO: data curation, methodology. SS, SO: supervision, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

Eur Ann Allergy Clin Immunol Vol 58, N.1, 24-31, 2026

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Obstructive sleep apnea: a risk for uncontrolled and more severe asthma in adults that we should keep an eye on

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Key words

Asthma; comorbidity; obesity; respiratory function tests; sleep apnea syndromes.

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Doi
10.23822/EurAnnACI.1764-1489.324

Impact statement

Obstructive sleep apnea is an underrecognized comorbidity that can have a detrimental influence on asthma outcomes. The association between obstructive sleep apnea and uncontrolled and more severe asthma makes necessary to assess this comorbidity.

Summary

Background. *Asthma control can be influenced by several factors, including obstructive sleep apnea (OSA). The literature reports variable prevalence and magnitude of OSA impact on asthma outcomes. The aim of our study is to analyze the frequency of high-risk for OSA in asthma patients and its impact on disease severity and control.* ***Methods.*** *We conducted a cross-sectional study at an Allergy Department with adult asthma patients recruited while undergoing routine lung function tests. Data on sex, age, body mass index, allergen sensitization, smoking habits, risk of OSA (using the Berlin questionnaire), rhinitis control (through CARAT), asthma severity (based on GINA 2023), asthma control (using the ACT), adherence to asthma treatment (through Treatment Adherence Measure) and pulmonary function test results were collected.* ***Results.*** *We included 216 patients, predominantly women (70.4%), with a median (P25-P75) age of 29.0 (21.0-45.0) years, of whom 28.2% were on GINA treatment levels 4-5. In 75.5% of cases asthma was controlled. High-risk for OSA was identified in 21.8% of patients. Asthma patients with high-risk for OSA were more likely to have uncontrolled [(47.8%; n = 22) vs (15.8%; n = 26); p < 0.001] and more severe disease [(44.7%; n = 21) vs (23.7%; n = 40), p = 0.006]. In multivariable analysis, high-risk for OSA (OR 2.81 [95%CI: 1.1.28-6.17], p = 0.010), sex (women) (OR 5.21 [95%CI 1.70-15.96], p = 0.004), uncontrolled rhinitis (OR 3.65 [95%CI: 1.38-9.64], p = 0.009) and GINA asthma treatment steps 4-5 (OR 2.46 [95%CI 1.15-5.26], p = 0.020) were associated with uncontrolled asthma.* ***Conclusions.*** *It is crucial to actively investigate OSA, especially in patients with uncontrolled and more severe forms of asthma.*

Introduction

Asthma is a heterogeneous disease usually characterized by chronic inflammation of the airways. It is defined by respiratory symptoms that vary in time and intensity, associated with variable expiratory airflow limitation (1).

Many factors can contribute to poor control of the disease, including comorbidities. All comorbidities must be assessed when treating patients with asthma, including obstructive sleep apnea (OSA) (1).

OSA is a breathing disorder characterized by narrowing of the upper airway that interferes with normal ventilation during sleep (2). The prevalence of OSA varies considerably depending on the population studied (2). It is higher in disease-specific populations, including patients with coronary artery disease, congestive heart failure, cardiac arrhythmias, refractory hypertension, type 2 diabetes, polycystic ovary disease or asthma (2-4). In general, the prevalence of OSA in asthma patients appears to be about two to three times higher than in patients without asthma (3). A

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recent systematic review found an estimated prevalence of OSA in asthma patients of 8%-52.6%, which is even higher (50-95%) in patients with severe asthma (5). Despite the higher prevalence in patients with asthma, especially those with severe asthma, different prevalence estimates are reported in the literature (3, 4).
OSA is an underestimated comorbidity that can have a negative impact on asthma outcomes. In most published studies, the presence of OSA is associated with poorer asthma control, more exacerbations and more emergency department visits, hospital admissions and ICU admissions (6-8). On the other hand, some studies showed no significant association between asthma severity or control and the presence of OSA (4, 9).
In this study, we aimed to analyze the frequency of high-risk for OSA in patients with asthma and assess its impact on disease severity and control.

Materials and methods

Study design, setting and participants

This cross-sectional study was conducted in the Allergy and Clinical Immunology Department of a tertiary hospital in Lisbon, Portugal.
All adult patients scheduled for an examination in our center's lung function test laboratory due to their asthma between January 2022 and December 2022 were invited to participate. Participation eligibility conditions were to be ≥ 18 years-old, to have a medical diagnosis of asthma, to present an asthma A2 score ≥ 2, and be able to perform a spirometry. Exclusion criteria were the inability to understand the consent form or the questionnaires.
This study was approved by the Ethics Committee of the Centro Hospitalar Universitário de Lisboa Central. All participants provided written informed consent to participate in this study.

Data collection

Data were collected using a self-administered standardized questionnaire that included questions on sociodemographic data, medical history, OSA risk (Berlin Questionnaire), rhinitis control (Control of Allergic Rhinitis and Asthma Test, upper airway subscore - CARAT-UA), asthma control (Asthma Control Test - ACT) and treatment adherence (MAT - Treatment Adherence Measure). The lung function test results conducted on the questionnaire's day were recorded. Daily prescribed asthma medications and information about sensitization to airborne allergens were obtained from electronic medical records. Asthma severity was defined according to the Global Initiative for Asthma (GINA) 2023 classification (steps 1-5).
The A2 score comprises eight questions, being the score the sum of positive answers. It can be used to rule in/rule out asthma in epidemiological studies and clinical screenings. Asthma can be excluded for results of 0 to 1 (10).
The Berlin Questionnaire is an OSA screening questionnaire with ten questions organized in three categories: the first comprises five questions on snoring and cessation of breathing, the second includes four questions about daytime sleepiness and fatigue/tiredness, and the last comprises information about arterial hypertension and obesity. A score of at least two is warranted for categories one and two to be considered positive. The third category is positive if there is a history of high blood pressure or a body mass index > 30 kg/m². Patients with a positive score in two or three categories are considered to have high-risk for OSA (11-13). The Berlin Questionnaire has a sensitivity, specificity, positive predictive value and negative predicted value of 72.1%, 50%, 87.7% and 26.7%, respectively, for an apnea-hypopnea index>5; of 82.6%, 44.8%, 58.4% and 73.3% for an apnea-hypopnea index>15; of 88.4%, 39.1%, 35.4% and 90% for an apnea-hypopnea index > 30 (13).
The CARAT-UA encompasses the first four questions of CARAT answered on a 4-point Likert that address upper airway symptoms over a four-week period, with a total possible score ranging from 0 (minimum control) to 12 (maximum control) (14).
The ACT Questionnaire contains five questions about the frequency of asthma symptoms and required rescue medication use during the previous four weeks. The scores range from 5 (worse control) to 25 (total control), with a cut-off value for asthma control of 20 (15).
The MAT comprises seven questions that assess patient behavior patterns associated with the use of medicines. The answers are rated on a six-point scale, and the result is expressed as the sum of the score of all questions divided by seven, ranging from 1 (minimum adherence) to 6 (maximum adherence). The patient is considered to have good medication adherence if MAT≥5 (16).

Lung function tests

Global Lung Function Initiative (GLI) reference equations for spirometry were used. The lower limit of normal (LLN) was defined as the 5th percentile (corresponding to a z-score of -1.645).

Sample size

Considering n = 1,000 as the number of adult patients with asthma assessed in our lung function test laboratory each year, and assuming a 25% prevalence of OSA, for a confidence level of 95% and a 5% margin of error, we would need to include 224 participants.

Variables

The primary outcome variable of the regression analysis was the presence of non-controlled asthma (ACT < 20). High-risk for OSA, obesity (body mass index ≥ 30 kg/m²), non-controlled rhinitis, to be on GINA treatment steps 4-5, current allergy sensitization to house dust mites, pollens, pets or mold evaluated by skin prick tests, low treatment adherence (according to MAT),

former or current smoker, pre/post-bronchodilator FEV_1 and FEV_1/FVC < LLN were considered as potential risk factors for non-controlled asthma and sex and age were considered potential confounders.

An additional regression analysis was also conducted, considering asthma severity (GINA treatment steps 4-5) as the main outcome.

Statistical analysis

An exploratory analysis was carried out for all variables. Categorical data were presented as prevalence rates (with 95 % confidence intervals - 95%CI) and continuous variables as median (with 25^{th} - P25 and 75^{th} - P75 percentiles).

Logistic regression models were used to explore the association between non-controlled asthma (outcome) and the above-mentioned risk and confounding factors. Covariates with a P-value < 0.25 were selected as candidates for the multivariable analysis, and a purposeful selection was used to choose the variables in the final model.

Crude regression coefficients and corresponding odds ratio (OR) with 95%CI were calculated first. Adjusted ORs were obtained as a result of fitting the multivariable logistic regression models to the data. The level of significance was $\alpha = 0.05$. Data analysis was performed using IBM SPSS Statistics version 26 (New York, USA).

Results

Characterization of the population

We included 225 patients, but due to missing data, only 216 were included in the analysis. The majority were women (70.4%; n = 152), with a median age of 29.0 (P25-P75: 21.0-45.0) years and a median BMI of 24.6 (P25-P75: 21.6-29.1) kg/m². Regarding asthma severity, 28.2% (n = 61) of patients were taking medication corresponding to GINA steps 4-5. Rhinitis was controlled in 34.7% of patients (n = 74) and asthma was controlled in 75.5% of patients (n = 163). High-risk for OSA was considered in 21.8% of patients (n = 47).

The baseline characteristics of our sample are described in **table I**.

High-risk for OSA patients' characteristics

High-risk for OSA patients were mostly women [(83.0%; n = 39) *vs* (66.9%; n = 113), p = 0.046], older [41.0 (26.0-49.0) *vs* 28.0 (21.0-42.5) years, p = 0.001] and had a higher body mass index

Table I *- Baseline characteristics of the participants (n = 216).*

Characteristics	
Sex (women), % (95%CI)	70.4 (63.8-76.4)
Age - median (P25-P75), years	29.0 (21.0-45.0)
BMI - median (P25-P75), kg/m²	24.6 (21.6-29.1)
Obesity, % (95%CI)	21.3 (16.0-27.4)
Past or current smoking habit, % (95%CI)	27.8 (21.9-34.3)
Rhinitis, % (95%CI)	97.2 (94.1-99.0)
Sensitization to airborne allergen, % (95%CI)	89.4 (84.5-93.1)
House dust mites, % (95%CI)	84.7 (79.2-89.2)
Pollens, % (95%CI)	58.8 (51.9-65.4)
Pets, % (95%CI)	51.4 (44.5-58.2)
Molds, % (95%CI)	6.9 (3.9-11.2)
Controlled rhinitis (CARAT-UA >8), % (95%CI)	34.7 (27.5-40.5)
Asthma on GINA treatment steps 4-5, % (95%CI)	28.2 (22.3-34.8)
Controlled asthma (ACT ≥20), % (95%CI)	75.5 (69.2-81.1)
High-risk for OSA, % (95%CI)	21.8 (16.5-27.9)
Good asthma medication adherence (MAT ≥5), % (95%CI)	76.9 (70.7-82.3)
Pre-bronchodilator FEV_1 (z-score) <LLN, % (95%CI)	18.5 (13.6-24.4)
Pre-bronchodilator FEV_1/FVC (z-score) <LLN, % (95%CI)	18.1 (13.2-23.9)
Post-bronchodilator FEV_1/FVC (z-score) <LLN, % (95%CI)	6 (3.2-10.1)

ACT: asthma control test; BMI: body mass index; CARAT-UA: Control of Allergic Rhinitis and Asthma Test, upper airway subscore; CI: confidence interval; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; LLN: lower limit of normal; OSA: obstructive sleep apnea.

Table II *- Associations with uncontrolled asthma (ACT<20).*

Variable	Crude OR (95%CI)	P-value	Adjusted OR (95%CI)*	P-value#
Sex				
Men	1			
Women	6.24 (2.14-18.23)	0.001	5.21 (1.70-15.96)	**0.004**
Age				
One-year increment	0.99 (0.96-1.01)	0.207	-	-
Obesity				
BMI <30 kg/m²	1			
BMI ≥30 kg/m²	2.76 (1.34-5.68)	0.006	-	-
GINA treatment steps				
Step ≤3	1			
Step 4-5	2.88 (1.47-5.66)	0.002	2.46 (1.15-5.26)	**0.020**
High-risk for OSA				
No	1			
Yes	4.90 (2.40-10.01)	<0.001	2.81 (1.28-6.17)	**0.010**
Former or current smoker				
No	1			
Yes	1.38 (0.69-2.77)	0.359	-	-
Rhinitis				
No	1			
Yes	0.188 (0.03-1.16)	0.071	-	-
Sensitization to airborne allergens				
No	1			
Yes	0.38 (0.15-0.94)	0.037	-	-
Rhinitis control				
CARAT-UA ≤8	4.70 (1.89-11.70)	0.001	3.65 (1.38-9.64)	**0.009**
CARAT-UA >8	1			
Non-adherence to asthma medication				
MAT ≥5	1			
MAT <5	1.45 (0.64-3.32)	0.375	-	-
Pre-bronchodilator FEV_1 (z-score)				
≥LLN	1			
<LLN	1.50 (0.68-3.30)	0.316	-	-
Pre-bronchodilator FEV_1/FVC (z-score)				
≥LLN	1			
<LLN	1.33 (0.59-2.98)	0.495	-	-
Post-bronchodilator FEV_1/FVC (z-score)				
≥LLN	1			
<LLN	1.14 (0.30-4.39)	0.848	-	-

*Adjusted for sex, age, obesity, GINA treatment step, OSA and sensitization to airborne allergens; #Only variables with a P-value < 0.05 are reported; CARAT-UA - Control of Allergic Rhinitis and Asthma Test, upper airway subscore; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; LLN: lower limit of normal; MAT: Treatment Adherence Measure; OSA: obstructive sleep apnea.

[31.8 (29.0-34.0) *vs* 24.0 (21.2-27.1), p < 0.001] than patients without a high-risk for OSA, as expected, since obesity is part of the Berlin questionnaire. Obesity was present in 70.2% (n = 33) of high-risk for OSA patients.

High-risk for OSA patients also presented more frequently uncontrolled rhinitis [(89.1%; n = 41) *vs* (58.7%; n = 98), p < 0.001], uncontrolled asthma [(47.8%; n = 22) *vs* (15.8%; n = 26), p < 0.001] and with asthma on GINA asthma treatment steps 4-5 [(44.7%; n = 21) *vs* (23.7%; n = 40), p = 0.006]. Regarding lung function, high-risk for OSA was not associated with significant variations in pre-bronchodilator or post-bronchodilator FEV_1 and FEV_1/FVC.

High-risk for OSA: association with uncontrolled asthma

Patients with uncontrolled asthma were more frequently classified as having high-risk for OSA compared to patients with controlled disease [(45.8%; n = 22) *vs* (14.7%; n = 24), p < 0.001].

In the univariable analysis, women sex, obesity, sensitization to airborne allergens, uncontrolled rhinitis, GINA asthma treatment steps 4-5 and high-risk for OSA were associated with uncontrolled asthma (**table II**).

In the multivariable analysis, after adjusting for other variables, high-risk for OSA persisted as a risk factor for uncontrolled asthma in the final model together with female sex, uncontrolled rhinitis, and GINA treatment steps 4-5 (**table II**).

High-risk for OSA: association with higher asthma severity

Patients on GINA asthma treatment steps 4-5 had a greater frequency of high-risk for OSA compared to patients with lower asthma severity [(34.4%; n = 21) *vs* (16.8%; n = 26), p = 0.006].

In the univariable analysis, age, obesity, ACT < 20, high-risk for OSA, pre-bronchodilator FEV_1 < LLN, pre-bronchodilator FEV_1/FVC < LLN and post-bronchodilator FEV_1/FVC < LLN were associated with more severe asthma (**table III**).

In the multivariable analysis, after adjusting for other variables, only high-risk for OSA, uncontrolled asthma and post-bronchodilator FEV_1/FVC < LLN remained significantly associated with more severe asthma in the final model (**table III**).

Discussion and conclusions

Our study showed that asthma patients with high-risk for OSA were likelier to have uncontrolled asthma and more severe disease.

In a cross-sectional study conducted in Portugal in 2014, the prevalence of OSA in the general population aged 25 years or older was estimated to be 0.89% (17). Different prevalence estimates have been reported for the higher incidence of OSA in patients with asthma. A systematic review found a prevalence of OSA (from thirteen questionnaire-based studies) in asthma patients ranging from 8% to 52.6% (5). In a meta-analysis by Kong *et al.* the prevalence of OSA in asthma patients was reported to be 49.5% (3). In our study we observed an estimated frequency of OSA of almost 20%, which is higher than the prevalence observed in the general population and consistent with previous studies conducted in asthma patients (8).

In our analysis, patients with high-risk for OSA were mostly women, older and had a higher BMI. Our results are consistent with the published literature on the general population, as higher BMI and age are major risk factors for OSA (18, 19). Although we should emphasize that 30% of high-risk for OSA patients were not obese, suggesting that this single characteristic should not be considered synonymous with OSA.

In the general population, OSA is generally more common in men (18, 19). In asthma patients, however, the dominance of sex varies (9, 20, 21). High-risk for OSA has not been associated with significant variations in lung function, which is consistent with other studies, such as that of Oyama *et al.* in which no significant correlation was found between lung function and the presence or severity of OSA, although OSA patients had more severe asthma (22).

In recent years, there is increasing evidence of a relationship between OSA, and asthma based on shared pathophysiological factors and bidirectional interactions (23, 24). Although asthma and OSA share some similar risk factors, such as rhinitis, obesity and gastroesophageal reflux, there are specific characteristics that may contribute to this relationship (24). OSA is associated with increased bronchial hyperreactivity and inflammation (23). Chronic intermittent hypoxia associated with OSA has been shown to shift the inflammatory profile in the airways from type 2 to type 1 T helper cells, contributing to lung remodeling and airway dysfunction (24, 25). This altered profile may lead to a reduced response to inhaled corticosteroid therapy (24, 25). On the other hand, airway, and systemic inflammation together with the use of systemic and inhaled corticosteroids in asthma patients may contribute to the remodeling of pharyngeal structures and redistribution of adipose tissue, favoring its collapse (23, 26).

According to our findings, it is crucial to screen asthma patients for OSA, especially those with uncontrolled asthma and uncontrolled rhinitis who are women and comply with GINA treatment levels 4-5. These findings are consistent with those of a study by Al-Lawati *et al*. in which the incidence of high-risk for OSA, also assessed by the Berlin questionnaire, was 46% in patients with uncontrolled asthma (20). Rhinitis is a common comorbidity in asthma patients, affecting most of them (1). Furthermore, rhinitis symptoms, particularly nasal congestion, have been linked to an increased risk of sleep breathing disorders in asthma patients, with longer and more frequent apneas in some studies (27), while in others this association is not as clear (4). We did not find an association between the presence of rhinitis and the risk of OSA, although patients with uncontrolled rhinitis were at higher risk of OSA. Studies addressing the relationship between rhinitis control and OSA are currently lacking.

Table III - *Associations with higher asthma severity (asthma on GINA treatment steps 4-5).*

Variable	Crude OR (95%CI)	P- value	Adjusted OR (95%CI)*	P-value#
Sex				
Men	1		-	
Women	1.60 (0.81-3.17)	0.180	-	-
Age				
One-year increment	0.97 (0.95-0.99)	0.002	-	-
Obesity				
BMI <30 kg/m²	1			
BMI ≥30 kg/m²	2.15 (1.08-4.24)	0.028	-	-
Asthma control				
ACT ≥20	1			
ACT <20	2.88 (1.47-5.66)	0.002	2.26 (1.09-4.72)	**0.029**
High-risk for OSA				
No	1			
Yes	2.61 (1.33-5.12)	0.005	2.51 (1.19-5.28)	**0.015**
Former or current smoker				
No	1			
Yes	1.15 (0.60-2.22)	0.670	-	-
Rhinitis				
No	1			
Yes	0.248 (0.04-1.53)	0.133	-	-
Sensitization to airborne allergens				
No	1			
Yes	0.57 (0.23-1.41)	0.224	-	-
Rhinitis control				
CARAT: UA ≤8	1.21 (0.64-2.29)	0.555	-	-
CARAT: UA >8	1			
Non-adherence to asthma medication				
MAT ≥5	1			
MAT <5	0.67 (0.28-1.57)	0.355	-	-
Pre-bronchodilator FEV_1 (z-score)				
≥LLN	1			
<LLN	3.76 (1.84-7.67)	<0.001	-	-
Pre-bronchodilator FEV_1/FVC (z-score)				
≥LLN	1			
<LLN	2.67 (1.30-5.47)	0.007	-	-
Post-bronchodilator FEV_1/FVC (z-score)				
≥LLN	1			
<LLN	6.53 (1.93-2.11)	0.003	7.20 (2.01-25.79)	**0.002**

*Adjusted for sex, age, obesity, asthma control, GINA treatment step, OSA, sensitization to airborne allergens and pre-bronchodilator FEV_1 < LLN; #Only variables with a P-value < 0.05 are reported; ACT: asthma control test; CARAT: UA: Control of Allergic Rhinitis and Asthma Test, upper airway subscore; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; GINA: Global Initiative for Asthma; LLN: lower limit of normal; MAT: Treatment Adherence Measure; OSA: obstructive sleep apnea.

In our work, high-risk for OSA was associated with higher odds of uncontrolled asthma. Previous studies on asthma and OSA showed similar results, although the magnitudes of the effects varied. Teodorescu *et al*. examined the relationship between OSA risk (assessed by questionnaire) and asthma control (measured by the Asthma Control Questionnaire) in adults and concluded that high OSA risk was associated with 2.87-fold higher odds of uncontrolled asthma, even after adjustment for factors known to worsen asthma control (28).

In our study, high-risk for OSA was also associated with more severe asthma, especially in patients with bronchial obstruction and uncontrolled asthma. This result is consistent with other published studies that show crescent prevalence estimates based on asthma severity (3, 5). Julien *et al*. compared the prevalence of OSA (assessed by polysomnography) in patients with severe and moderate asthma and in non-asthmatic patients (4). They showed that OSA was related to asthma severity, occurring in 88% of patients with severe asthma and 58% of patients with moderate asthma, compared with 31% in patients without asthma (4). Guven *et al*. found a prevalence of 74.5% of OSA (assessed by polysomnography) in patients with difficult-to-treat/severe asthma (21). In our work, the estimated frequency of OSA (34.4%) in patients with severe asthma was lower than in these studies (4). This could be explained by the definition of OSA (Berlin questionnaire) we used, and by different population characteristics. In the study by Al-Lawati *et al*. the prevalence of OSA (assessed by polysomnography) in patients with severe asthma was 32.4%, which is more in line with our results (20).

The presence of OSA may be associated with worse outcomes in asthma patients, as a higher rate of severe asthma exacerbations, a higher risk of non-invasive positive pressure ventilation and longer length of hospital stay, a higher risk of readmission after hospitalization for an asthma exacerbation (8, 29, 30). Therefore, it is important to identify asthma patients with OSA, as its treatment has positive effects on asthma symptoms, asthma control and severity, as well as quality of life (31-36).

Our study has some limitations. First, it is a unicentric study and conducted in an Allergy and Clinical Immunology Department, so our results may not be generalizable to the general asthma patients. Second, it is a questionnaire-based study, so the identification of OSA patients may not have been entirely accurate, despite the Berlin Questionnaire being a validated OSA screening tool. Nevertheless, our findings highlight the need to actively look for the presence of OSA, a comorbidity that has a negative impact on asthma control, especially in those patients with uncontrolled and more severe asthma.

Fundings

None.

Contributions

GMDS: conceptualization, formal analysis, investigation, methodology, writing - original draft. PSC: conceptualization, investigation, methodology, writing - original draft. JGM: conceptualization, methodology, writing - original draft, writing - review & editing. SaSe, SaSa, AB: investigation, writing - original draft. PCM: conceptualization, formal analysis, methodology, writing - original draft, writing - review & editing. PLP: methodology, writing - review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE
Eur Ann Allergy Clin Immunol Vol 58, N.1, 32-40, 2026

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Food-dependent exercise-induced allergic reactions in lipid transfer protein (LTP) hypersensitive subjects: new data and a critical reappraisal

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Key words

Food allergy; allergens; lipid transfer protein; anaphylaxis; food-dependent exercise-induced anaphylaxis.

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Doi
10.23822/EurAnnACI.1764-1489.334

Impact statement

Food-dependent exercise-induced allergic reactions are associated with specific allergens (LTP proteins and omega-5-gliadin), and are characterized by sIgE levels that are intermediate between simple sensitization and classic food allergy.

Summary

Background. *Lipid transfer protein (LTP) is the main cause of both primary food allergy and food-dependent exercise-induced allergic reactions (FDEIAR) in Italy. What characterizes LTP-hypersensitive patients with FDEIAR is still unclear. We investigated the key characteristics of LTP-hypersensitive patients with or without FDEIAR in a large cohort of individuals sensitized to this allergen.* ***Methods.*** *1,203 food-allergic patients, diagnosed on the basis of unequivocal clinical history and presence of circulating food allergen-specific IgE were studied. Serum IgE reactivity was assessed using the Allergen ExplorerALEX® system (Macroarray Diagnostics, Vienna, Austria). Association of specific IgE reactivities with FDEIAR was investigated, and patients with and without FDEIAR sensitized to LTP were compared.* ***Results.*** *116 subjects (9.6%) had FDEIAR. Among these, 77 (66.3%) were LTP-reactors and 16 (13.8%) were sensitized to Tri a 19 (omega-5-gliadin). Different LTPs and omega-5-gliadin emerged as the sole allergens clearly associated with FDEIAR. Severity of allergic reactions paralleled the level of specific IgE to LTPs. Patients with FDEIAR showed significantly lower IgE levels than their counterparts with food allergy at rest, and displayed nearly identical IgE levels regardless of the severity of allergic reactions induced by exercise.* ***Conclusions.*** *FDEIAR are associated with specific allergens. Specific IgE levels in LTP-hypersensitive patients with FDEIAR show an intermediate titer between those simply sensitized and those showing classic food allergy.*

Introduction

Food-dependent exercise-induced allergic reactions (FDEIAR) represent a distinctive expression of IgE-mediated food allergy, characterized by the onset of wheals, angioedema, or anaphylaxis subsequent to exercise. FDEIAR appear within 6 hours, typically within 2-4 hours, of consumption of the offending food (1, 2). While the role of exercise and other cofactors in food allergic reactions has already been explored (reviewed in 3), a comprehensive understanding of these phenomena remains elusive. It has been hypothesized that exercise may enhance allergen bioavailability by increasing intestinal permeability and allergen absorption (4, 5), but recent studies suggest that this effect is specific to individuals with food allergy and does not occur in normal control subjects (6). Some authors posit that exercise induces heightened blood circulation in various body regions, resulting in relative hypo-perfusion of the gastrointestinal tract and increased permeability (7). Additionally, recent findings suggest a potential influence of exercise-induced prostaglandin inhibition on gut permeability (8).

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A distinctive characteristic of patients with FDEIAR is the frequent presence of food-specific IgE at low titers (9), and skin testing reactions that often fall below the established 95% Positive Predictive Value (PPV) for diagnosing food allergy (10). While FDEIAR can be associated with various foods, certain sources are more commonly linked to these allergic reactions. Notably, wheat (11, 12), crustaceans and mollusks (12, 13), and fruits (14, 15) are frequently implicated. The prevalence of wheat-related reactions is very high and has led to the recognition of a distinct clinical entity termed Wheat-Dependent Exercise-Induced Anaphylaxis (WDEIA) (16). Globally, Omega-5-gliadin is identified as the primary allergen responsible for WDEIA (8, 17). In Italy, however, the situation differs, with Lipid Transfer Protein (LTP) being the main allergen responsible for both FDEIAR (18) and WDEIA (19), although the reasons for this discrepancy remain unclear. Previous studies have underscored LTP as the most common cause of primary food allergy in Italy (20) as well as in other Mediterranean countries (21). In this study, we examined the key characteristics of LTP-hypersensitive patients, both with and without FDEIAR, in a large cohort of individuals sensitized to this allergen.

Materials and methods

Study design

We conducted a single-center cross-sectional observational clinical survey on patients with FDEIAR who were visited at the Outpatient Allergy Unit of IDI-IRCCS, a National Reference Center for Dermatological Diseases located in Rome, Italy. All patients underwent a comprehensive clinical instrumental assessment, which included the evaluation of IgE sensitization through a commercial multiplex system encompassing key environmental and food allergens.

Setting

A total of 2,695 unselected participants born in Central or Southern Italy, presenting for a visit due to a history of adverse reactions to foods, allergic rhinitis, bronchial asthma, and/or atopic eczema, were consecutively enrolled. Data collection occurred between January 2021 and December 2023. Demographic information and clinical data were thoroughly documented using a tailored electronic database.

Participants

The primary eligibility criterion for inclusion in the study was a history of adverse reaction to food, ranging from oral allergy syndrome to generalized urticaria to overt anaphylaxis requiring medical intervention at the emergency room with antihistamine, steroid, or adrenaline therapy. We subsequently assessed the IgE reactivity profile towards key food allergens using a macroarray method: "Act d 1 Kiwi (*Actinidia deliciosa*) Cysteine protease, Act d 2 Kiwi (Actinidia deliciosa) Thaumatin-like protein, Act d 5 Kiwi (*Actinidia deliciosa*) Kiwellin, Act d 10 Kiwi (*Actinidia deliciosa*) 9kDa nsLTP, Ana o 2 Cashew nut (*Anacardium occidentale*) 11S Globulin, Ana o 3 Cashew nut (*Anacardium occidentale*) 2S Albumin, Ani s 1 Anisakis (*Anisakis simplex*) Serine protease inhibitor, Ani s 3 Anisakis (*Anisakis simplex*) Tropomyosin, Api g 1 Celery (*Apium graveolens*) PR-10, Api g 2 Celery (*Apium graveolens*) 9kDa nsLTP, Api g 6 Celery (*Apium graveolens*) 7kDa nsLTP, Ara h 1 Peanut (*Arachis hypogaea*) 7S globulin, Ara h 2 Peanut (*Arachis hypogaea*) 2S Albumin, Ara h 3 Peanut (*Arachis hypogaea*) 11S Globulin, Ara h 6 Peanut (*Arachis hypogaea*) 2S Albumin, Ara h 8 Peanut (*Arachis hypogaea*) PR-10, Ara h 9 Peanut (*Arachis hypogaea*) 9kDa nsLTP, Ara h 15 Peanut (*Arachis hypogaea*) Oleosin, Ber e 1 Brazil nut (*Bertholletia excelsa*) 2S Albumin, Bos d 2 Cow epithelium (Bos domesticus) Lipocalin, Bos d 4 Cow's milk (*Bos domesticus*) Alpha-lactalbumin, Bos d 5 Cow's milk (*Bos domesticus*) Beta-lactoglobulin, Bos d 6 Cow's milk/meat (*Bos domesticus*) Serum albumin, Bos d 8 Cow's milk (*Bos domesticus*) Casein, Clu h 1 Atlantic herring (*Clupea harengus*) β-Parvalbumin, Cor a 8 Hazelnut (*Corylus avellana*) 9kDa nsLTP, Cor a 9 Hazelnut (*Corylus avellana*) 11S Globulin, Cor a 11 Hazelnut (*Corylus avellana*) 7/8S Globulin, Cor a 12RUO Hazelnut (*Corylus avellana*) Oleosin, Cor a 14 Hazelnut (*Corylus avellana*) 2S Albumin, Cra c 6 Brown shrimp (*Crangon crangon*) Troponin C, Cuc m 2 Muskmelon (*Cucumis melo*) Profilin, Dau c 1 Carrot (*Daucus carota*) PR-10, Fag e 2 Buckwheat (*Fagopyrum esculentum*) 2S Albumin, Fra a 1|Fra a 3 Strawberry (*Fragaria ananassa*) PR-10|LTP, Gad m 1 Atlantic cod (*Gadus morhua*) β-Parvalbumin, Gad m 2/3 Atlantic cod (*Gadus morhua*) β-Enolase/Aldolase, Gal d 1 Egg white (Gallus domesticus) Ovomucoid, Gal d 2 Egg white (*Gallus domesticus*) Ovalbumin, Gal d 3 Egg white (*Gallus domesticus*) Conalbumin/Ovotransferrin, Gal d 4 Lisozyme C, Gal d 5 Egg yolk/chicken meat (*Gallus domesticus*) Livetin/Serum albumin, Gly m 4 Soybean (*Glycine max*) PR-10, Gly m 5 Soybean (*Glycine max*) 7S globulin, Gly m 6 Soybean (*Glycine max*) 11S Globulin, Gly m 8 Soybean (Glycine max) 2S Albumin, Jug r 1 Walnut (*Juglans regia*) 2S Albumin, Jug r 2 Walnut (*Juglans regia*) 7/8S Globulina, Jug r 3 Walnut (*Juglans regia*) 9kDa nsLTP, Jug r 4 Walnut (*Juglans regia*) 11S Globulin, Jug r 6 Walnut (*Juglans regia*) 7/8S Globulina, Mac i 2S Albumin Macadamia integrifolia 2S Albumin, Mal d 1 Apple (*Malus domestica*) PR-10, Mal d 2 Apple (*Malus domestica*) TLP, Mal d 3 Apple (*Malus domestica*) 9kDa nsLTP, Pap s 2S Albumin Poppy seed (*Papaver somniferum*) 2S Albumin, Pen m 1 "Black-Tiger shrimp (*Penaeus monodon*)" Tropomiosina, Pen m 2 "Black-Tiger shrimp (*Penaeus monodon*)" Arginine kinase, Pen m 3 "Black-Tiger shrimp, (*Penaeus monodon*)" Myosin LC, Pen m 4 "Black-Tiger shrimp (*Penaeus monodon*)" Sarc CBP, Pis v 1 Pistachio (*Pistacia vera*) 2S Albumin, Pis v 2 Pistachio (*Pistacia vera*) 11S Globulin, Pis v 3 Pistachio (*Pistacia vera*) 7/8S Globulin, Pis v 4RUO Pistachio (*Pistacia vera*) Mn-SOD, Pru p 3 Peach (*Prunus persica*) 9kDa nsLTP, Pru p 7RUO Peach (*Prunus persica*) GRP, Raj c α-Parvalbumin Thornback ray (*Raja clavata*)

Table I *- Food allergens investigated for specific IgE reactivity.*

	Sensitized		FDEIA		SOA		Systemic reaction		Anaphylaxis	
Act d 1 (Pectate lyase)	*11*	0.9%	*6*	0.5%	*39*	3.2%	*45*	3.7%	*22*	1.8%
Act d 10 (nsLTP)	*25*	2.1%	*18*	1.5%	*85*	7.1%	*119*	9.9%	*51*	4.2%
Act d 2 (TLP)	*8*	0.7%	*8*	0.7%	*21*	1.7%	*32*	2.7%	*13*	1.1%
Act d 5 (Kiwellin)	*0*	0.0%	*0*	0.0%	*0*	0.0%	*2*	0.2%	*2*	0.2%
Ana o 2 (11S Globulin)	*3*	0.2%	*0*	0.0%	*3*	0.2%	*3*	0.2%	*1*	0.1%
Ana o 3 (2S Albumin)	*4*	0.3%	*1*	0.1%	*11*	0.9%	*20*	1.7%	*8*	0.7%
Ani s 1 (Kunitz Serin PI)	*7*	0.6%	*2*	0.2%	*9*	0.7%	*16*	1.3%	*2*	0.2%
Ani s 3 (Tropomyosin)	*16*	1.3%	*5*	0.4%	*23*	1.9%	*38*	3.2%	*12*	1.0%
Api g 1 (PR-10)	*11*	0.9%	*3*	0.2%	*30*	2.5%	*29*	2.4%	*6*	0.5%
Api g 2 (nsLTP)	*23*	1.9%	*16*	1.3%	*74*	6.2%	*97*	8.1%	*52*	4.3%
Api g 6 (nsLTP)	*13*	1.1%	*5*	0.4%	*30*	2.5%	*40*	3.3%	*16*	1.3%
Ara h 1 (7/8S Globulin)	*5*	0.4%	*1*	0.1%	*19*	1.6%	*23*	1.9%	*9*	0.7%
Ara h 15 (Oleosin)	*0*	0.0%	*1*	0.1%	*2*	0.2%	*2*	0.2%	*0*	0.0%
Ara h 2 (2S Albumin)	*4*	0.3%	*0*	0.0%	*8*	0.7%	*14*	1.2%	*4*	0.3%
Ara h 3 (11S Globulin)	*5*	0.4%	*0*	0.0%	*10*	0.8%	*13*	1.1%	*3*	0.2%
Ara h 6 (2S Albumin)	*5*	0.4%	*1*	0.1%	*13*	1.1%	*16*	1.3%	*3*	0.2%
Ara h 8 (PR-10)	*16*	1.3%	*4*	0.3%	*33*	2.7%	*26*	2.2%	*7*	0.6%
Ara h 9 (nsLTP)	*32*	2.7%	*55*	4.6%	*138*	11.5%	*193*	16.0%	*83*	6.9%
Ber e 1 (2S Albumin)	*1*	0.1%	*0*	0.0%	*4*	0.3%	*4*	0.3%	*1*	0.1%
Bos d 2 (Lipocalin)	*2*	0.2%	*0*	0.0%	*2*	0.2%	*3*	0.2%	*2*	0.2%
Bos d 4 (α-Lactalbumin)	*2*	0.2%	*0*	0.0%	*5*	0.4%	*12*	1.0%	*8*	0.7%
Bos d 5 (β-Lactoglobulin	*2*	0.2%	*0*	0.0%	*6*	0.5%	*14*	1.2%	*8*	0.7%
Bos d 6 (Serum Albumin)	*3*	0.2%	*0*	0.0%	*5*	0.4%	*9*	0.7%	*5*	0.4%
Bos d 8 (Casein)	*2*	0.2%	*0*	0.0%	*8*	0.7%	*16*	1.3%	*10*	0.8%
Can s 3 (nsLTP)	*15*	1.2%	*10*	0.8%	*43*	3.6%	*58*	4.8%	*33*	2.7%
Clu h 1 (β-ParvAlbumin)	*6*	0.5%	*1*	0.1%	*9*	0.7%	*21*	1.7%	*6*	0.5%
Cor a 1.0401 (PR-10)	*38*	3.2%	*9*	0.7%	*84*	7.0%	*82*	6.8%	*21*	1.7%
Cor a 11 (7/8S Globulin)	*14*	1.2%	*3*	0.2%	*23*	1.9%	*28*	2.3%	*12*	1.0%
Cor a 12RUO (Oleosin)	*1*	0.1%	*0*	0.0%	*0*	0.0%	*1*	0.1%	*0*	0.0%
Cor a 14 (2S Albumin)	*4*	0.3%	*2*	0.2%	*13*	1.1%	*23*	1.9%	*10*	0.8%
Cor a 8 (nsLTP)	*24*	2.0%	*39*	3.2%	*101*	8.4%	*155*	12.9%	*64*	5.3%
Cor a 9 (11S Globulin)	*6*	0.5%	*3*	0.2%	*14*	1.2%	*21*	1.7%	*9*	0.7%
Cra c 6 (Troponina C)	*4*	0.3%	*0*	0.0%	*6*	0.5%	*7*	0.6%	*1*	0.1%
Cuc m 2 (Profilin)	*30*	2.5%	*4*	0.3%	*74*	6.2%	*71*	5.9%	*18*	1.5%
Dau c 1 (PR-10)	*11*	0.9%	*1*	0.1%	*33*	2.7%	*27*	2.2%	*7*	0.6%
Fag e 2 (2S Albumin)	*2*	0.2%	*0*	0.0%	*3*	0.2%	*3*	0.2%	*0*	0.0%
Gad m 1 (β-Parvalbumin)	*5*	0.4%	*1*	0.1%	*9*	0.7%	*20*	1.7%	*7*	0.6%
Gad m 2/3 (Enolase/Aldolase)	*1*	0.1%	*0*	0.0%	*2*	0.2%	*4*	0.3%	*1*	0.1%
Gal d 1 (Ovomucoid)	*4*	0.3%	*0*	0.0%	*4*	0.3%	*13*	1.1%	*8*	0.7%

→

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	Sensitized		FDEIA		SOA		Systemic reaction		Anaphylaxis	
Gal d 2 (Ovalbumin)	*4*	0.3%	*0*	0.0%	*5*	0.4%	*17*	1.4%	*11*	0.9%
Gal d 3 (Ovotransferrin)	*4*	0.3%	*0*	0.0%	*5*	0.4%	*10*	0.8%	*6*	0.5%
Gal d 4 (Lisozima C)	*10*	0.8%	*0*	0.0%	*4*	0.3%	*11*	0.9%	*4*	0.3%
Gal d 5 (Serum Albumin)	*1*	0.1%	*0*	0.0%	*2*	0.2%	*3*	0.2%	*3*	0.2%
Gly m 4 (PR-10)	*14*	1.2%	*2*	0.2%	*31*	2.6%	*26*	2.2%	*8*	0.7%
Gly m 5 (7/8S Globulin)	*0*	0.0%	*0*	0.0%	*2*	0.2%	*2*	0.2%	*2*	0.2%
Gly m 6 (11S Globulin)	*9*	0.7%	*2*	0.2%	*10*	0.8%	*15*	1.2%	*8*	0.7%
Gly m 8 (2S Albumin)	*1*	0.1%	*0*	0.0%	*0*	0.0%	*3*	0.2%	*3*	0.2%
Jug r 1 (2S Albumin)	*7*	0.6%	*5*	0.4%	*33*	2.7%	*44*	3.7%	*16*	1.3%
Jug r 2 (7/8S Globulin)	*12*	1.0%	*9*	0.7%	*32*	2.7%	*42*	3.5%	*14*	1.2%
Jug r 3 (nsLTP)	*22*	1.8%	*51*	4.2%	*95*	7.9%	*145*	12.1%	*55*	4.6%
Jug r 4 (11S Globulin)	*8*	0.7%	*3*	0.2%	*23*	1.9%	*30*	2.5%	*13*	1.1%
Jug r 6 (7/8S Globulin)	*12*	1.0%	*1*	0.1%	*27*	2.2%	*23*	1.9%	*7*	0.6%
Mac i 2S Albumina	*1*	0.1%	*1*	0.1%	*9*	0.7%	*11*	0.9%	*6*	0.5%
Mal d 1 (PR-10)	*35*	2.9%	*9*	0.7%	*80*	6.7%	*70*	5.8%	*15*	1.2%
Mal d 2 (TLP)	*0*	0.0%	*0*	0.0%	*1*	0.1%	*5*	0.4%	*2*	0.2%
Mal d 3 (nsLTP)	*32*	2.7%	*31*	2.6%	*139*	11.6%	*195*	16.2%	*87*	7.2%
Pap s 2S Albumin	*3*	0.2%	*0*	0.0%	*4*	0.3%	*5*	0.4%	*1*	0.1%
Pen m 1 (Tropomyosin)	*14*	1.2%	*3*	0.2%	*21*	1.7%	*30*	2.5%	*11*	0.9%
Pen m 2 (Arginin chinasi)	*15*	1.2%	*1*	0.1%	*13*	1.1%	*19*	1.6%	*6*	0.5%
Pen m 3 (Myosin light chain)	*3*	0.2%	*1*	0.1%	*3*	0.2%	*8*	0.7%	*1*	0.1%
Pen m 4 (Sarcoplasmic CBP)	*0*	0.0%	*0*	0.0%	*3*	0.2%	*5*	0.4%	*2*	0.2%
Pis v 1 (2S Albumin)	*6*	0.5%	*1*	0.1%	*11*	0.9%	*17*	1.4%	*6*	0.5%
Pis v 2 (11S Globulin)	*2*	0.2%	*1*	0.1%	*9*	0.7%	*10*	0.8%	*5*	0.4%
Pis v 3 (7/8S Globulin)	*3*	0.2%	*0*	0.0%	*10*	0.8%	*12*	1.0%	*7*	0.6%
Pru p 3 (nsLTP)	*49*	4.1%	*70*	5.8%	*204*	17.0%	*284*	23.6%	*108*	9.0%
Pru p 7RUO	*4*	0.3%	*0*	0.0%	*8*	0.7%	*14*	1.2%	*9*	0.7%
Raj c α-Parvalbumin	*2*	0.2%	*1*	0.1%	*4*	0.3%	*5*	0.4%	*1*	0.1%
Sal s 1 (β-Parvalbumin)	*7*	0.6%	*1*	0.1%	*11*	0.9%	*24*	2.0%	*9*	0.7%
Sco s 1 (β-Parvalbumin)	*7*	0.6%	*1*	0.1%	*10*	0.8%	*26*	2.2%	*9*	0.7%
Ses i 1 (2S Albumin)	*9*	0.7%	*3*	0.2%	*17*	1.4%	*20*	1.7%	*10*	0.8%
Sin a 1 (2S Albumin)	*1*	0.1%	*0*	0.0%	*2*	0.2%	*2*	0.2%	*1*	0.1%
Sola l 6 (nsLTP)	*15*	1.2%	*4*	0.3%	*21*	1.7%	*33*	2.7%	*19*	1.6%
Thu a 1 (β-Parvalbumin)	*8*	0.7%	*1*	0.1%	*13*	1.1%	*25*	2.1%	*8*	0.7%
Tri a 14 (nsLTP)	*3*	0.2%	*13*	1.1%	*12*	1.0%	*24*	2.0%	*9*	0.7%
Tri a 19 (ω-5-Gliadin)	*1*	0.1%	*16*	1.3%	*6*	0.5%	*30*	2.5%	*7*	0.6%
Tri a 30 (α-amylase inhibitor)	*2*	0.2%	*0*	0.0%	*0*	0.0%	*4*	0.3%	*2*	0.2%
Vit v 1 (nsLTP)	*28*	2.3%	*23*	1.9%	*99*	8.2%	*130*	10.8%	*63*	5.2%
Xip g 1 (β-Parvalbumin)	*11*	0.9%	*1*	0.1%	*17*	1.4%	*28*	2.3%	*11*	0.9%
Zea m 14 (nsLTP)	*36*	3.0%	*29*	2.4%	*135*	11.2%	*182*	15.1%	*84*	7.0%

Parvalbumin, Sal s 1 Salmon (*Salmo salar*) β-Parvalbumin, Sco s 1 Atlantic mackerel (*Scomber scombrus*) β-Parvalbumin, Ses i 1 Sesame seed (*Sesamum indicum*) 2S Albumin, Sin a 1 Mustard (Brassica/Sinapis spp.) 2S Albumin, Sola l 6 Tomato (*Solanum lycopersicum*) 7kDa nsLTP, Thu a 1 Tuna (*Thunnus albacares*) β-Parvalbumin, Tri a 14 Wheat (*Triticum aestivum*) 9kDa nsLTP, Tri a 19 Wheat (*Triticum aestivum*) ω-5-Gliadina, Tri a aA_TI Wheat (*Triticum aestivum*) α-AmilasiTI, Vit v 1 Grape (*Vitis vinifera*) 9kDa nsLTP, Xip g 1 Swordfish (*Xiphias gladius*) β-Parvalbumin, Zea m 14 Corn, cereals (*Zea mays*) 9kDa nsLTP" (**table I**). Additionally, we recorded the foods associated with the occurrence of reactive episodes as gathered from the medical history.

Variables

The initial variables considered were age, gender, and total IgE levels. Additionally, we assessed specific reactivity to key food allergens, both plant-based and animal-derived.

Data sources/measurement

Serum IgE reactivity was assessed using the Allergen ExplorerALEX® system (Macroarray Diagnostics, Vienna, Austria). In this method, a large number of allergens and extracts are applied to a nitrocellulose membrane within a cartridge chip. The chip is incubated with 0.5 mL of patient's serum, diluted 1:5 and containing a CCD (cross-reactive carbohydrate determinants) inhibitor, with continuous agitation. Following a two-hour incubation, the chips undergo three washings and a pre-titrated dilution of anti-human IgE labeled with alkaline phosphatase is introduced and incubated for 30 minutes. After another thorough washing cycle, the enzyme substrate is added, and the reaction is halted after eight minutes by the addition of 100 µL of ALEX Stop Solution. The membranes are dried, and a charge-coupled device camera measures the color reaction intensity for each allergen spot. The dedicated software digitizes the images and generates a report listing the allergens and components along with their scores in kUA/L. Finally, an arbitrary calibration curve is established by reacting four spots with decreasing concentrations of specific IgE (<0.3 kUA/L, 0.3-1 kUA/L, 1-5 kUA/L, 5-15 kUA/L, and >50 kUA/L). A concentration of ≥ 0.3 kUA/L is considered positive.

Bias

The diagnosis of food allergy was not confirmed through blinded or open oral food challenges but relied solely on anamnestic findings, supported by records of admissions to the Emergency Room and the administration of therapies aimed at addressing clinical presentations of generalized urticaria or anaphylaxis.

Quantitative variables

We examined the quantitative differences in specific IgE levels, comparing them with observations in individuals characterized by clinical conditions distinct from FDEIAR.

Statistical methods

All data underwent analysis utilizing the SPSS/PC + statistical package for statistical assessment (IBM SPSS, version 29, Chicago, IL). Demographic (age and gender), clinical, and laboratory data for patients attending the outpatient Allergy clinic and undergoing specific IgE testing were sought and compiled using the TD-Synergy Laboratory Information System.

In the univariate analysis, the non-parametric Mann-Whitney U-test (for two groups) was initially employed to compare continuous IgE values among males, females, and subjects with or without specific clinical involvement. Subsequently, each variable of interest was dichotomized into negative or positive categories to scrutinize the proportion of subjects exhibiting symptoms in the resulting two groups.

For the assessment of paired observations on two variables expressed in a contingency table, Pearson's χ^2 test or Fisher's exact test (utilized for two-by-two contingency tables with fewer than 50 cases) was employed to ascertain independence between them.

Ethical issues

The study received approval from the Ethical Committee of IDI-IRCCS (IDI-IRCCS CE | 495-17). Data collection was carried out in an anonymous manner, utilizing solely information gathered from routine specialist surveys. Enlisted patients granted informed consent for the use of their clinical data in an anonymized format.

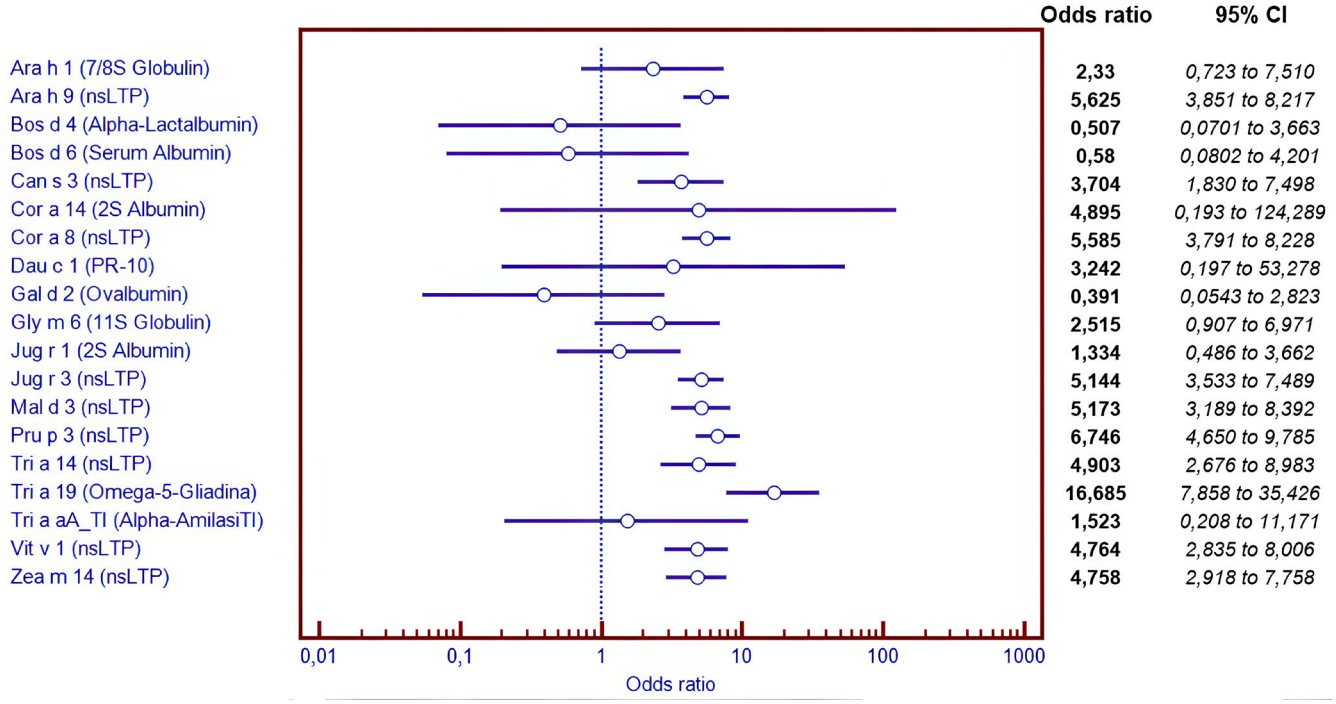
Results

A total of 1,203 patients (804 [66.8%] females, mean age 36.9 ± 18.6), diagnosed as having food allergy or hypersensitivity, were included in the analysis. Among them, 116 participants (9.6%, 75 females, mean age 34.3 ± 14.7) had exercise-induced allergic reactions to foods (FDEIAR). Patients with and without FDEIAR did not differ in terms of mean age and sex distribution.

Focusing on the subset of participants with FDEIAR, 77 (66.3%) of these individuals showed both a positive clinical history and IgE reactivity to at least one of the non-specific Lipid Transfer Proteins (nsLTPs) included in the proteomic test, whereas 16 individuals exhibited reactivity to Tri a 19 (omega-5 gliadin), 16 to PR10, 8 to profilins, 8 to Tropomyosin, 7 to seed storage proteins, 6 to Act d 1 from kiwi, while none showed reactivity to egg or milk molecules. Participants reactive to nsLTPs affected by FDEIAR reported adverse reactions mainly correlated with the intake of Rosaceae (peach, apricot, and more rarely cherry) or walnut.

Figure 1 illustrates the association of allergy to various food allergens with exercise as a co-factor. Different Lipid Transfer Proteins (LTPs) along with omega-5-gliadin emerged as the sole allergens clearly associated with FDEIAR. Molecules not significantly associated with the occurrence of a reactive episode due to physical exercise after food intake are not depicted in the figure.

Figure 1 *- Forest diagram depicting the correlation between sensitization to various food allergens and Food-Dependent Exercise-Induced Allergic Reactions. The association is present for various Lipid Transfer Proteins (LTPs) such as Ara h 9, Can s 3, Cor a 8, Jug r 3, Mal d 3, Pru p 3, Tri a 14, and Zea m 14 as well as with Tri a 19 (omega-5-gliadin).*



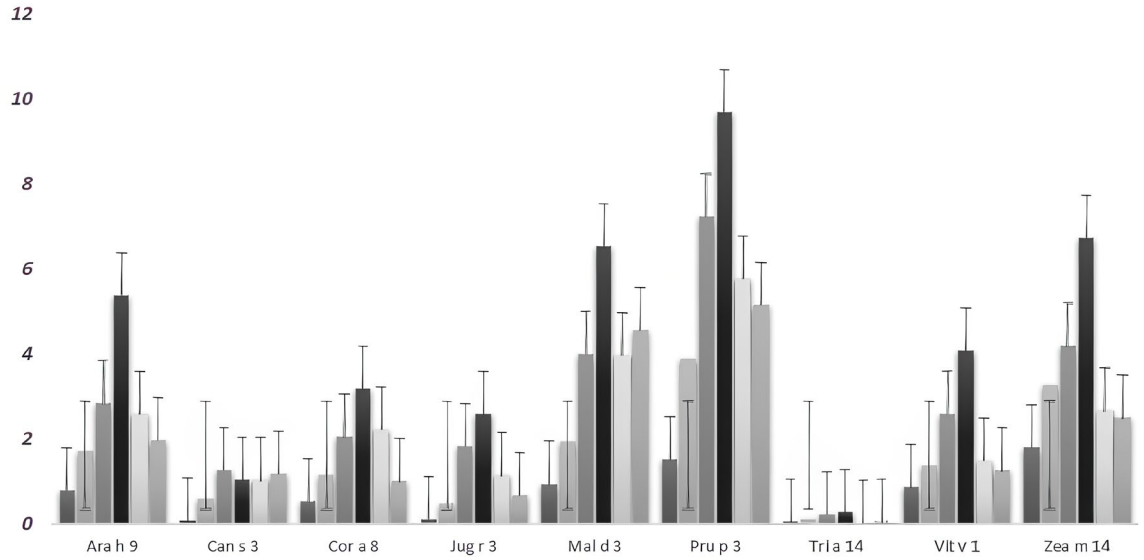
The subgroup of patients hypersensitive to LTPs (631 individuals, 52.4% of participants with food allergy) was specifically investigated. These patients were categorized into: a) sensitized but not allergic (18.6%); b) allergic with only local symptoms (oral allergy syndrome) (33.5%); c) allergic with urticaria at rest (31.4%); d) allergic with anaphylaxis (4.3%) and e) allergic with FDEIAR (n = 77; 12.2%). Among FDEIAR patients, 42.8% had experienced an anaphylactic reaction requiring the use of adrenaline, while the remaining had a history of generalized urticaria with or without angioedema that responded to steroids and antihistamines. As illustrated in **figure 2**, the severity of allergic reactions was associated with an increase in specific IgE to LTPs. Interestingly, patients with FDEIA exhibited reduced IgE levels compared to those with anaphylaxis at rest. Further, IgE levels in FDEIA were in several cases lower than in patients with urticaria/angioedema at rest (Pru p 3, Vit v 1, Zea m 14) and similar in the other cases (**figure 2**). Finally, notably, FDEIAR patients displayed nearly identical IgE levels regardless of the severity of allergic reactions induced by exercise (**figure 2**).

Discussion and conclusions

Several lines of evidence indicate that patients with Food-Dependent Exercise-Induced Allergic Reactions (FDEIAR) are clinically similar to those with classical food allergy at rest. In studies of Wheat-Dependent Exercise-Induced Anaphylaxis (WDEIA), Christensen and colleagues demonstrated that exercise significantly lowered the threshold of the offending dose (22, 23). Importantly, they also found that a substantial proportion of patients with a history of WDEIA react to the offending food also at rest if they are challenged with a sufficiently elevated dose of allergen (23). Furthermore, they observed that exercise causes a drop in the offending dose of food and an increase in the severity of the reaction (23). Reactivity also at rest by WDEIA patients was confirmed in another study by the same group (24), which also showed that exercise and nonsteroidal anti-inflammatory drugs (NSAID) act synergistically in reducing the offending food dose and increasing the severity of allergic reactions. Interestingly, exercise does not cause any increase in circulating gliadin in healthy subjects (6), suggesting that patients with WDEIA may have a predisposition to the additional effect of cofactors, such as hyperresponsivity of the intestinal epithelium, possibly secondary to a specific damage (6).

Surprisingly enough, studies on FDEIAR have rarely addressed the other two main variables in this type of food allergy: the nature and characteristics of the offending allergen(s) and specific IgE levels. This is now feasible thanks to the widespread availability

Figure 2 - *Mean specific IgE levels to Lipid Transfer Protein (LTP) in patients who sensitized but tolerant to plant-derived foods or experiencing allergic reactions of varying severity, with or without exercise as a cofactor. Individuals with a history of Food-Dependent Exercise-Induced allergic reactions (FDEIAR) or Anaphylaxis (FDEIA) exhibit reduced IgE levels compared to those experiencing food anaphylaxis at rest.*



	T-Test	Ara h 9	Can s 3	Cor a 8	Jug r 3	Mal d 3	Pru p 3	Tri a 14	Vit v 1	Zea m 14
FDEIAR *vs*	***Tolerant***	P = 0.02	P = 0.03	P = 0.02	P = 0,01	P = 0,001	P = 0,0001	*ns*	*ns*	*ns*
	Oral allergy Syndrome	*ns*	*ns*	*ns*	P = 0,04	P = 0,005	*ns*	*ns*	*ns*	*ns*
	Urticaria - Angioedema	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*	*ns*
	Anapylaxys	P = 0,01	*ns*	*ns*	P = 0.03	P = 0,03	P = 0,006	*ns*	*ns*	P = 0,01

of recombinant food allergens for component-resolved diagnosis. It is evident that the intrinsic nature of the allergen plays a relevant role if most cases of FDEIAR are reported in patients hypersensitive to omega-5-gliadin worldwide or lipid transfer protein in the Mediterranean area, as also clearly shown in the present study. The relevance of specific, particular food allergens is supported by studies of patients with FDEIA induced by crustaceans, whose clinical reactions rarely seem to involve the major allergens of this food source (25, 26). Similarly, an old study by one of us showed that a patient with egg and poultry-induced FDEIA reacted to a common, cross-reacting allergen at about 77 kDa, possibly conalbumin (27). Another emerging food allergen as a possible cause of FDEIA is gibberellin-regulated protein, a recently discovered cause of pollen-food allergy syndrome that occurs in patients primarily sensitized to Cup a 7, a minor allergen in cypress pollen (28-30). Taken together, the study of a wide range of components related to food allergy has unequivocally demonstrated that only LTPs and Tri a 19 may have a correlation as factors favoring an adverse reaction induced by physical exertion. All other tested foods do not exhibit this behavior. It will be interesting to evaluate and understand the biological, metabolic, or catabolic reasons that may underlie what has been observed. To date, only certain plant-based foods, specifically LTPs and omega-5-gliadin, are capable of eliciting an adverse reaction induced by physical exertion, both compartmental and anaphylactic.

Regarding the levels of IgE specific for the offending foods, older studies already noted that these were generally lower than usual (9), a finding that was confirmed at a molecular level in our patients hypersensitive to Lipid Transfer Protein (LTP). We did not observe any difference in the dosage of IgE synthesized towards different LTP when comparing values in patients with non-anaphylactic FDEIAR to those with post-prandial exertion-induced anaphylaxis. Interestingly, IgE levels observed in cases of anaphylaxis directly related to food intake without the need for any cofactor (neither physical exertion nor the use of anti-inflammatories, data not shown) were significantly higher in the case of reactivity to LTP from peanuts, nuts, apples, peaches (notably the most significantly different), and corn.

In conclusion, food allergic reactions induced by exercise appear to be preferentially associated with specific allergens. Patients produce a limited amount of IgE that demonstrate an intermediate titer between subjects simply sensitized but tolerant and patients with a classic food allergy. Based on literature data, FDEIAR and classic food allergy seem capable to coexist in patients sensitized to these allergens.

Fundings

This study was funded, in part, by the Italian Ministry of Health, Current Research Program 2021-2023.

Contributions

RA: conceptualization, methodology, supervision, writing – original draft, writing – review & editing. VV: data curation, formal analysis, writing – review & editing. ES: conceptualization, data curation, methodology, supervision, writing – review and editing.

Conflict of interests

The authors declare that they have no conflict of interests.

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ORIGINAL ARTICLE

Eur Ann Allergy Clin Immunol Vol 58, N.1, 41-45, 2026

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Co-sensitizations to gibberellin regulated proteins (GRPs) in Italy: results of a polycentric study

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Key words

Gibberellin regulated proteins (GRPs); co-sensitization; PR-10; nsLTP; profilin.

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Doi
10.23822/EurAnnACI.1764-1489.356

Impact statement

A high percentage of co-sensitizations to PR-10, Profilin, and nsLTP is present in patients sensitized to GRPs, and PR-10 appears to be a protective factor against anaphylaxis.

Summary

Background. *Gibberellin regulated proteins (GRPs) are small glycoproteins that induce allergy to various types of fruit. This study aimed to evaluate co-sensitization to cypress pollen and other molecules responsible for fruit allergy, such as nsLTP (Pru p 3), PR-10 (Bet v1), and Profilin (Bet v2).* ***Methods.*** *Sixty subjects sensitized to peach GRP (Pru p 7) were consecutively recruited from four Italian centers: 28 males and 32 females (mean age 37.9 years; range 11-79). Specific IgE for Pru p 7, Pru p 3, Bet v 1, Bet v 2, cypress pollen extract (Cup s), and Cup a 1 were determined in all subjects.* ***Results.*** *Sensitization rates to Cup s, Cup a 1, Pru p 3, Bet v 1, and Bet v 2 in the entire studied population were 90.0%, 83.3%, 45.8%, 40.0%, and 30.0%, respectively. In subjects residing in Northern Italy, the respective sensitization rates were 96.4%, 80.0%, 50.0%, 73.3%, and 40.0%, while in those residing in Southern Italy they were 83.3%, 86.7%, 40.0%, 6.7%, and 20.0%. The only significant difference was observed for PR-10 ($p < 0.0001$). Co-sensitization to PR-10 was found to be associated with a reduced risk of anaphylaxis (OR: 0.125). Allergic reactions were most commonly triggered by peach (26/40), followed by orange (12/40), with other foods being less frequently implicated.* ***Conclusions.*** *This study confirms a high association between sensitization to Pru p 7 and cypress pollen and highlights a high percentage of co-sensitization to nsLTP, PR-10, and profilin. PR-10 emerged as a protective factor against anaphylaxis.*

Introduction

Gibberellin regulated proteins (GRPs) are a class of small glycoproteins consisting of 63 amino acids with a low molecular weight of 7 kDa. They possess an isoelectric point (pI) around 9, are water-soluble, and are characterized by a high cysteine content, resulting in the formation of 6 disulfide bridges. This structural feature confers high stability to GRPs, rendering them resistant to proteolysis and heat. Consequently, they have the potential to induce systemic allergic reactions, whether consumed in raw or heat-treated forms. The name of this protein family derives from their regulation by gibberellin, a phytohormone produced by plants in response to various environmental stresses. Gibber-

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ellin is also applied exogenously in agriculture to modulate plant growth and fruit ripening. However, the impact of such treatments on the content of GRPs and their allergenic properties remains only partially elucidated.

Although the first identified molecule belonging to GRPs was potato snakin-1 (1), it never demonstrated allergenicity. Thus, the first true allergen belonging to GRPs was identified in peach (*Prunus persica*) and named peamaclein (Pru p 7) (2). Subsequently, allergens belonging to GRPs were identified in other fruits: apricot (*Prunus mume*, Pru m 7) (3), pomegranate (*Punica granatum*, Pun g 7) (4), orange (*Citrus sinensis*, Cit s 7) (5), cherry (*Prunus avium*, Pru av 7) (6), and more recently in pepper (*Capsicum annuum*, Cap a 7) (7). Allergens belonging to this family have also been described in the pollen of *Cupressaceae*, particularly in *Cupressus sempervirens* (Cup s 7) (8), *Juniperus ashei* (Jun a 7) (9), and *Cryptomeria japonica* (Cry j 7) (10). Considering the ubiquity of GRPs, it is highly probable that the list of proteins belonging to this family is destined to expand.

A high sequence identity of amino acids among GRPs has been demonstrated (11), responsible for a high probability of IgE cross-reactivity towards such molecules. In particular, cross-reactivity between Cup s 7 and Pru p 7 (12) and between Cup s 7 and Cit s 7 (13) has been well established. This lead to the hypothesis that GRPs allergy is a pollen/fruit allergy syndrome (PFAS), wherein primary sensitization occurs via the respiratory route through *Cupressaceae* pollen. This hypothesis has been corroborated by epidemiological studies and experimental cross-inhibition studies (14). However, not all individuals with symptoms attributable to sensitization to GRPs exhibit concurrent sensitization to *Cupressaceae*, showing that primary sensitization in some cases occurs not through the respiratory route but directly through dietary intake.

The aim of this multicenter study was to evaluate, in an Italian population sensitized to Pru p 7 (the only GRP currently commercially available), the percentage of co-sensitization to cypress pollen, particularly to the major molecular allergen Cup a 1, which defines its role as the primary sensitizer. Furthermore, co-sensitizations to non-specific Lipid Transfer Protein (nsLTP) of peach (Pru p 3), birch pollen PR-10 (Bet v1), and profilin (Bet v 2) were evaluated to assess whether different profiles exist between Northern and Southern Italy and whether different co-sensitizations may modulate the severity of symptoms in individuals sensitized to GRPs.

Materials and methods

Patients

This study employed a consecutive enrolment design across four Italian centers from Northern (Udine, Pordenone, Florence-Prato) and Southern Italy (Palermo) to recruit subjects sensitized to Pru p 7, identified based on clinical suspicion of fruit allergy. Recruitment occurred from January 2002 to December 2023. Sixty subjects were enrolled, comprised of 28 males and 32 females, with a mean age of 37.9 years (range 11-79). There were no significant demographic differences between Northern Italy (30 subjects, 13 males, and 17 females, mean age 35.7 years, range 11-79) and Southern Italy (30 subjects, 15 males, and 15 females, mean age 40.2 years, range 11-77). Clinical history data were collected from 40 subjects, including foods associated with symptoms and their severity. Symptoms were categorized as "anaphylaxis", defined as the presence of urticaria combined with at least one other symptom affecting the respiratory, gastrointestinal, or cardiovascular systems, or "non-anaphylaxis" (oral allergy syndrome, urticaria, gastrointestinal symptoms, or isolated respiratory symptoms).

Methods

Specific IgE (sIgE) levels for Pru p 7, Pru p 3, Bet v 1, Bet v 2, Cup a 1, and cypress pollen extract (*Cupressus sempervirens*, Cup s) were measured using the ImmunoCAP system (Thermo Fisher Scientific, Uppsala, Sweden) following the manufacturer's instructions. Data were expressed in kUA/L, with a cut-off set at 0.1 kUA/L.

Statistics

Statistical analysis was performed using MedCalc version 9.3.9.0 (Mariakerke, Belgium). Percentages of positivity for specific allergens were calculated for all subjects sensitized to Pru p 7 and separately for those from Northern and Southern Italy. Quantitative variables, such as sIgE levels, were analyzed using Student's t-test for unpaired data. Odds ratios (OR) were calculated for the risk of anaphylaxis in relation to co-sensitization towards nsLTP, PR-10, and profilin, individually and collectively. Significance was set at $p < 0.05$.

Ethics

This is a retrospective observational study, therefore no statement regarding studies conducted on humans and animals is required. Informed consent was obtained from all patients included in the study.

Results

The mean sIgE level for Pru p 7 in the entire studied population was 4.3 ± 5.43 kUA/L, with no significant difference between Northern (3.17 ± 6.21 kUA/L) and Southern Italy (5.43 ± 6.7 kUA/L) (p = ns). Sensitization percentages to Cup s, Cup a 1, nsLTP (Pru p 3), PR-10 (Bet v 1), and profilin (Bet v 2) are detailed in **table I**. Significant differences between Northern and Southern Italy were observed for PR-10 co-sensitization (73.3% *vs* 6.7%; $p < 0.0001$).

Among Pru p 7 sensitized individuals, 83.3% showed primary sensitization to *Cupressaceae* pollen, with 90.0% testing positive for the extract. The associations between Pru p 7 and Cup s/Cup

Table I *- IgE values for Pru p 7 (mean and range) in all tested samples, divided by origin (Northern and Southern Italy), and percentage of co-sensitization towards cypress extract (Cup s), major cypress allergen (Cup a 1), peach nonspecific lipid transfer protein (Pru p 3), birch PR-10 (Bet v 1), and Profilin (Bet v 2).*

	Pru p 7 (GRP) Mean (range)	**Cup s n (%)**	**Cup a 1 n (%)**	**Pru p 3 (nsLTP) n (%)**	**Bet v1 (PR-10) n (%)**	**Bet v 2 (Profilin) n (%)**
All (n = 60)	4.3 kUA/L (0.15-27.6)	54/60 (90%)	50/60 (83.3%)	27/60 (45.8%)	24/60 (40%)	18/60 (30%)
Nord (n = 30)	3.17 kUA/L (0.15-27.6)	29/30 (96.7%)	24/30 (80%)	15/30 (50%)	22/30 (73.3%)*	12/30 (40%)
Sud (n = 30)	5.43 kUA/L (0.41-24.5)	25/30 (83.3%)	26/30 (86.7%)	12/30 (40.0%)	2/30 (6.7%)*	6/30 (20%)

*p < 0.0001.

a 1 positivity/negativity are shown in **table II**. Clinical reactions to Pru p 7-associated foods are illustrated in **figure 1**. Peach was the most common trigger for clinical reactions (26/40), followed by orange (12/40), kiwi, lemon, tomato (5/40), strawberry (3/40), and other foods. Anaphylaxis occurred in 55.0% of patients, with no significant difference in sIgE levels between those with and without anaphylaxis. Patients co-sensitized to PR-10 had significantly lower anaphylaxis frequency (p = 0.0278; OR 0.125). Conversely, those with anaphylaxis showed a higher prevalence of Pru p 3 co-sensitization (45.5% *vs* 22.2%; OR 2.916), although not reaching significance (**table III**).

Table II *- IgE profile (mono-positive and double-positive) towards cypress extract (Cup s) and its major allergen (Cup a 1) in subjects sensitized to Pru p 7.*

		n	**%**
	Cup s^{Pos}	54	90
	Cup a 1^{Pos}	50	83.3
Cup s^{Pos}	Cup a 1^{Pos}	49	81.6
	Cup a 1^{Neg}	5	8.3
Cup s^{Neg}	Cup a 1^{Pos}	1	1.7
	Cup a 1^{Neg}	5	8.3

Figure 1 *- Foods associated with allergic reactions in subjects sensitized to Pru p 7.*

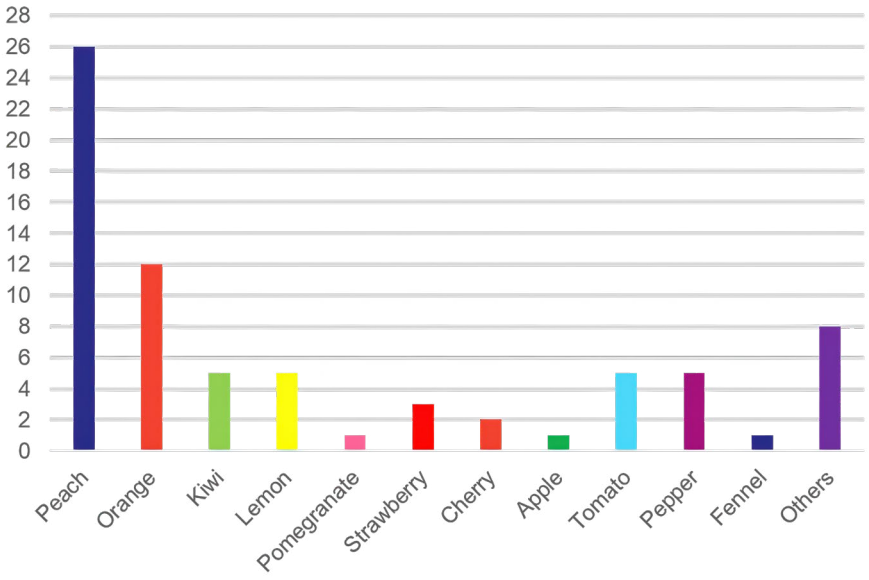


Table III *- Percentage of patients with anaphylaxis and non-anaphylaxis in co-sensitized to nsLTP (Pru p 3), Bet v 1 (PR-10), profilin (Bet v 2), individually and in combination.*

Co-sensitizations	Anaphylaxis (n = 22)	Non-anaphylaxis (n = 18)	OR (95%CI)	Statistical significance (P)
Pru p 3 (nsLTP)	10/22 (45.5%)	4/18 (22.2%)	2.916 (0.724-11.739)	ns
Bet v 1 (PR-10)	2/22 (9.1%)	8/18 (44.4%)	0.125 (0.022-0.702)	**< 0.03**
Bet v 2 (Profilin)	6/22 (27.2%)	6/18 (33.3%)	0.750 (0.193-2.913)	ns
Bet v 1 and Bet v 2	1/22 (4.5%)	6/18 (33,3%)	0.095 (0.010-0.888)	**< 0.05**
Pru p 3 and Bet v 1	1/22 (4.5%)	1/18 (5.5%)	0.809 (0.047-13.92)	ns
Pru p 3 and Bet v 2	3/22 (13.6%)	1/18 (5.5%)	2.684 (0.254-28.31)	ns

OR: odds ratio; ns: not significant.

Discussion and conclusions

In accordance with previous studies (14, 15), our investigation also revealed that sensitization to Pru p 7 is predominantly associated (83.3%) with primary cypress pollen sensitization, with no significant differences between Northern and Southern Italy, thus confirming the pollen-fruit allergy syndrome (PFAS) hypothesis. However, it remains a 16.7% subset of patients sensitized to Pru p 7, but not to Cup a 1, likely representing cases where the primary sensitizing agent is not cypress pollen but directly the food. Among the 10 negative Cup a 1 sera, 5 tested positive for cypress extract. This sIgE profile may be explained by the fact that cypress contains GRPs cross-reactive with those present in the fruits that act as a primary sensitizer. Another 5 subjects were negative for both Cup a 1 and cypress extract. In these cases, the lack of cross-reactivity with cypress GRPs may be due to either low sIgE values towards GRPs (4 cases had values < 2 kUA/L of Pru p 7) or IgE reactivity towards epitopes not shared between Pru p 7 and Cup s 7.

The remarkably high number of patients co-sensitized to peach non-specific Lipid Transfer Protein (nsLTP) (Pru p 3), with no significant difference between Northern and Southern Italy, is unexpected considering the higher prevalence of nsLTP sensitization in Southern Italy (16). Whether this is a bias related to the selected population and the small sample size, or a genuine finding, needs to be evaluated in future studies on larger populations. Despite the higher percentage of subjects co-sensitized to Pru p 3 in the anaphylaxis group (45.5%) compared to those without (22.2%) and the OR was 2.916, statistical significance was not achieved, likely due to the wide confidence interval (95%CI 0.724-11.739). Thus, further studies with larger samples are necessary to assess the real role of Pru p 3 co-sensitization in GRP-sensitized individuals.

In contrast, IgE positivity for PR-10 was significantly higher in patients enrolled from the North, which is expected given the higher prevalence of *Fagales* sensitization in Northern Italy. Similarly to previous studies on nsLTP (17-18), PR-10 co-sensitization was found to be protective against anaphylaxis (OR 0.125), whereas profilin co-sensitization alone was not consistent with findings by Pastorello *et al.* (17). Therefore, PR-10 co-sensitization should be considered a prognostic factor for less severe reactions in clinical practice, although it cannot entirely exclude the risk of anaphylaxis.

Lastly, as demonstrated in a recent study conducted in Italy on 23 GRP-sensitized subjects, peach was the most associated food with GRPs sensitization, followed by citrus fruits. This may be explained by the dietary habits in our country, where these fruits are commonly consumed. However, it is noteworthy that only 3 subjects (7.5%) presented symptoms with a single food (peach, strawberry, and orange, respectively). This percentage is lower compared to the 30% reported in the recent study by Cecchi *et al.* (19), which may be due to the high number of subjects co-sensitized to nsLTP in our study compared to the study in question, where cases were selected for Pru p 3 negativity. The peculiarity of our study lies in consecutively evaluating all GRP-sensitized cases, not just those selected for monosensitization, making the data more reflective of what is observed in everyday clinical practice. However, a limitation of the study is that Pru p 3 co-sensi-

tized subjects were not subjected to oral challenges with peach pulp, which theoretically contains only GRPs, to assess the different roles of GRPs and nsLTP in symptom genesis.
In conclusion, this study, conducted on a consecutive case series of Pru p 7-sensitized subjects, confirmed the high association with cypress sensitization, supporting the PFAS hypothesis, and highlighted high percentages of co-sensitizations to nsLTP, PR-10, and profilin. Only PR-10 co-sensitization differed between Northern and Southern Italy. Although a higher prevalence of Pru p 3 co-sensitization was observed in subjects with anaphylaxis, significance was not reached, while PR-10 co-sensitization was found to be protective against anaphylaxis. Peach and citrus fruits are the most associated foods with GRPs sensitization in Italy.
Although our study provides valuable insights into GRPs sensitization, the findings should be cautiously interpreted due to the study's limitations and the need for confirmation in larger, more diverse populations. The study's consecutive enrolment approach enhances its applicability to real-world clinical practice, but further research is warranted to validate these findings.

Fundings

None.

Contributions

DanVil, DanVis, VG, LC, DM, IB, MB, PF, OR: methodology, data curation. DanVil, ES: formal analysis. DanVil, IB: conceptualization, data curation. DanVil, ES: 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 58, N.1, 46-48, 2026

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The future of telemedicine after COVID-19 pandemic

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Key words

COVID-19; pandemic; practice; telehealth; telemedicine.

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Doi
10.23822/EurAnnACI.1764-1489.364

To the Editor,

the COVID-19 pandemic was responsible for many changes in the healthcare sector as social distancing and restriction measures forced healthcare professionals to find alternatives to continue the follow-up of chronic patients and respond to acute conditions. The COVID-19 epidemic was a breakthrough in telemedicine (1, 2). Telemedicine, already practiced earlier on a much smaller scale, underwent exponential growth during the pandemic period, showing its benefits and advantages but also revealing its needs and obstacles which had been previously overlooked. After COVID-19, telemedicine globally became widely accepted (1-3).

However, not everything is foolproof. For example, Justvig *et al.* (4) warned about the limitations in physical examination and the difficulties in learning and accessing technology, as well as the need for administrative support as challenges to be improved. Gilkey *et al.* (5) also investigated the relationship between telemedicine and costs for patients and concluded that although costs were reduced in most cases, some families reported increased spending on medication. Physicians need to adapt their practice to this innovation, similar to how they adapted to using computers. The strict privacy policy, regulations, and licenses must be addressed as they were facilitated during the pandemic due to unusual necessity (6). For the future, the necessary conditions for institutions, including the platforms to be used, remain to be clarified.

In our hospital, virtual consultations were implemented within two weeks in response to the pandemic situation. These consultations were conducted through a dedicated platform, ensuring that physicians were in the hospital to uphold standards of privacy and professionalism and to facilitate administrative procedures. When clinically indicated (*e.g.*, doubts in diagnostic evaluation or in cases of greater severity), patients were referred to face-to-face appointments, which occurred in less than 5% of cases. This demonstrates the clinical value of telemedicine (7, 8). As also found in Portugal, even though patients with asthma were slightly more satisfied with face-to-face consultations, remote consultations were considered a valid alternative in follow-up services for these chronic patients (9).

The COVID-19 pandemic began to gain weight in Portugal in February 2020 and culminated in a state of emergency twice: March 19, 2020 to May 2, 2020 and November 9, 2020 to April 30, 2021. Teleconsultation had its greatest relevance in the first month of emergency status, occupying 74% of all consultations in our department. When the measures were lifted, in the summer of 2020, we observed a significant decrease in its adherence that grew again as the number of cases increased in Octo-

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ber 2020, peaking again in January and February 2021 during the second state of emergency. After that, the use of teleconsultation stabilized at low levels, averaging between 2% and 6% of total consultations per month (**figure 1**). This period of stability was followed by a continued decline in the following years. In 2021, teleconsultations accounted for 7% of all consultations, decreasing to 4% in 2022 and further dropping to 2% in early 2023. These trends indicate a clear shift back to in-person consultations as pandemic-related restrictions were eased, as shown by the gray areas in **figure 1** (SE – State of Emergency), which correspond to periods of COVID-19-related isolation in Portugal, specifically from March 19 to May 2, 2020, and from November 9, 2020, to April 30, 2021.

Analyzing the more adherent to video appointments population, we found that younger patients (under 40) and those with chronic conditions like asthma were more likely to use teleconsultations during the pandemic. Post-pandemic, this trend shifted, with older patients and those requiring frequent in-person assessments (*e.g.*, for complex conditions) reverting to face-to-face appointments. Comparing our data with studies from other countries reveals similar trends. For example, studies from the US and UK also show a decline in telemedicine use post-pandemic, though the rates of decline vary. These international comparisons highlight common challenges such as technology access, patient preferences, and regulatory issues.

Table I (A and **B)** summarizes the number of appointments (in-person *vs* teleconsultation) from 2020 to 2023, and the difficulties and unmet needs in telemedicine, along with possible strategies to address them.

The future of telemedicine may be promising, but it depends on the effort to solve the issues addressed, need to involve all stakeholders including healthcare professionals, patients, payers, and administrative sectors working together and is likely to benefit from new technologies enhancing patient remote examination and monitoring with artificial intelligence.

More studies and data are emerging in order to improve its practice, making it accessible to a greater number of people, prioritizing quality and patient privacy, but telemedicine is here to stay, extending beyond the pandemic crisis, as an important tool to improve both the efficiency and the capacity of the healthcare systems (1-3, 10).

Now is the time. We must not lose this unique opportunity.

Fundings

None.

Contributions

MMA, RP: conceptualization, writing – original draft. HP: writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

Figure 1 *- Virtual appointments percentage by month.*

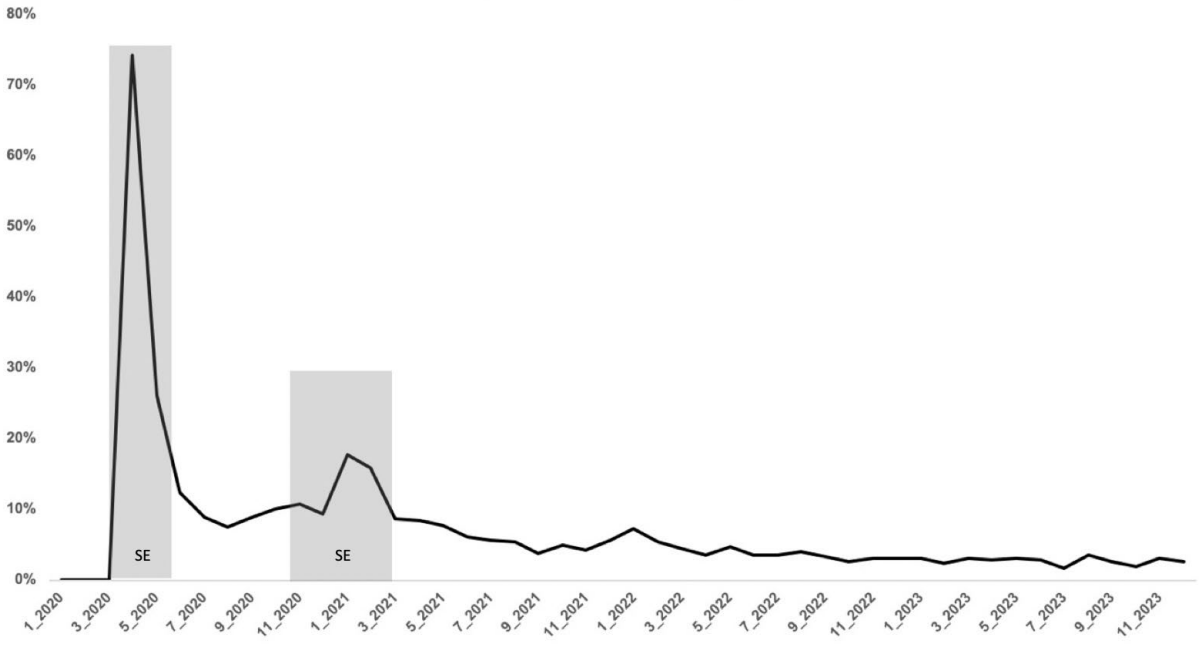


Table I - (A) *Number of appointments (in-person vs teleconsultation) by semester from 2020 to 2023;* ***(B)*** *Challenges and proposed strategies in telemedicine.*

(A)

Semester	In-person	Teleconsultation	Total	% Teleconsultation
Jan-Jun 2020	7,783	1,126	8,909	12.64%
Jul-Dec 2020	9,767	1,007	10,774	9.35%
Total 2020	17,550	2,133	19,683	10.84%
Jan-Jun 2021	11,096	1,248	12,344	10.11%
Jul-Dec 2021	11,964	602	12,566	4.79%
Total 2021	23,060	1,850	24,910	7.43%
Jan-Jun 2022	12,646	634	13,280	4.77%
Jul-Dec 2022	12,960	433	13,393	3.23%
Total 2022	25,606	1,067	26,673	4.00%
Jan-Jun 2023	14,340	427	14,767	2.89%
Jul-Dec 2023	12,576	323	12,899	2.50%
Total 2023	26,916	750	27,666	2.71%
Total	**186,264**	**11,600**	**197,864**	**5.86%**

(B)

Challenge	Strategy
Technology access	Improve digital literacy programs
Patient preferences	Offer hybrid models (in-person and telemedicine)
Regulatory issues	Standardize telemedicine regulations
Privacy and security concerns	Enhance cybersecurity measures
Cost of implementation	Provide financial incentives for telemedicine

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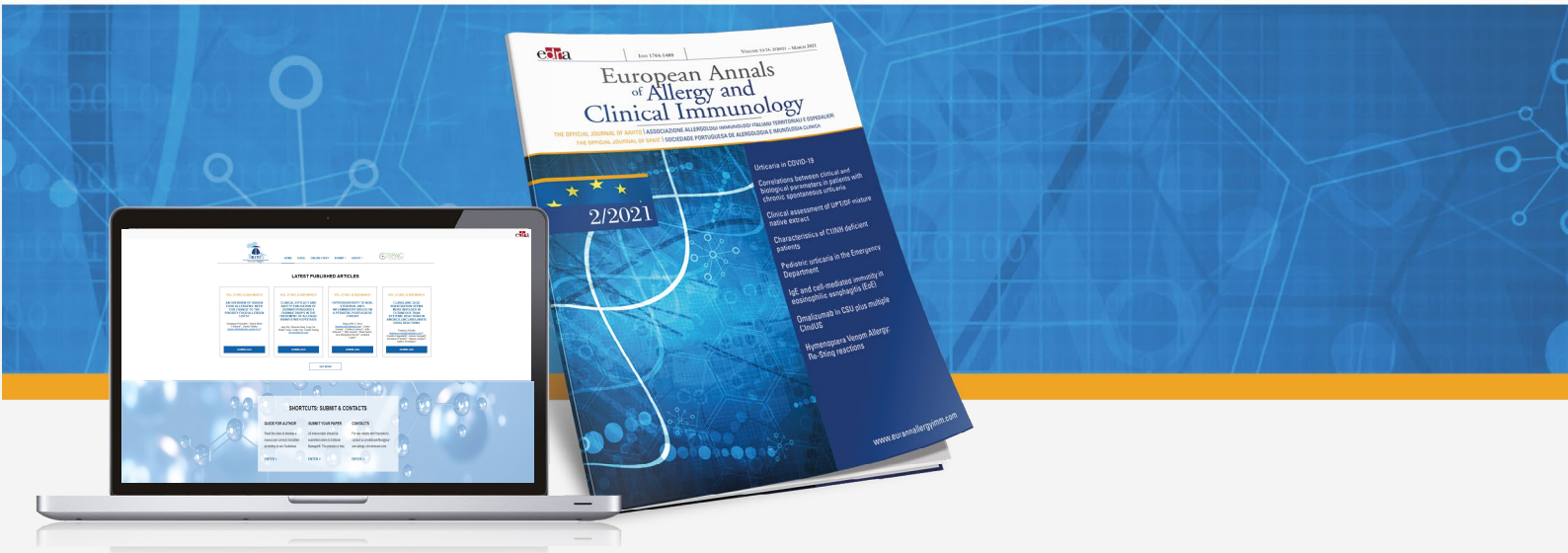
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