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Stress psicologico e malattie allergiche

Psychological stress and allergic diseases

Estrés psicológico y patologías alérgicas

Diagnosi "no-biopsy" di celiachia nell'adulto

"No-biopsy" diagnosis of coeliac disease in adults

Diagnóstico "sin biopsia" de celiaquía en adulto

Update dell'allergia alla frutta a guscio

Update on nut allergy

Actualización sobre las alergias a los frutos secos

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Notiziario Allergologico

PDF VERSION

Notiziario Allergologico has been alive and well for over forty years. Today, it becomes international with a new layout that includes the translation of all content into three languages. The purpose remains unchanged if not implemented: to promote allergology culture by offering readers the possibility of an in-depth study and update on various allergology topics, also with a view to the future, thanks to the competence and authority of the authors of the articles published. The popular character of the articles contributes to making them accessible to a vast number of specialists, not only allergologists but also pulmonologists, paediatricians, dermatologists, etc.

ENGLISH

EDITORIAL

edited by **Gianni Mistrello**

The 2025 Nobel Prize in Medicine was awarded to three researchers, Shimon Sakaguchi, Mary E. Brunkow and Fred Ramsdell, who, through their research on different but complementary aspects, demonstrated that the control of immunological self-tolerance is not limited to the selection carried out by the thymus (central tolerance) but that this capacity also extends to the peripheral level (peripheral tolerance). In particular, Sakaguchi was among the first to identify the existence of a subclass of T lymphocytes capable of suppressing autoaggressive responses (autoimmune diseases), while Brunkow and Ramsdell, working on possible correlations between genetic mutations and autoimmune diseases, succeeded in identifying, first in a mouse model and subsequently in a severe and rare form of childhood autoimmunity (IPEX syndrome), the key gene of the Fox p3 (Forkhead Box p3) protein, which is essential for the development of the aforementioned subclass of T lymphocytes. The combination of these two discoveries has therefore contributed to the delineation of a new cell population involved in the regulation of the immune system, for which the term regulatory T lymphocytes (Treg) has been coined. As research progressed, Treg cells have been the subject of numerous scientific investigations that have improved our understanding of the mechanisms (release of specific cytokines) by which these cells play a fundamental role in homeostasis and immunological tolerance, as well as promoting the interruption of immune responses previously triggered by contact with invading agents. Today, Treg lymphocytes are seen both as possible targets (tumours) and as potential therapeutic tools (autoimmune diseases, transplants). Their involvement does not end there; there is a body of evidence suggesting that Treg lymphocytes are also crucial in allergic diseases, due to their ability to maintain peripheral tolerance to harmless substances such as allergens, preventing or inhibiting the production of specific IgE antibodies mediated by Th2 lymphocyte hyperreactivity. A deficiency or malfunction of Treg lymphocytes increases the risk of developing both respiratory and food allergies, and one of the mechanisms by which allergen-specific immunotherapy expresses its therapeutic efficacy is based precisely on its ability to enhance their activity, thus neutralising the allergic response.

After this necessary introduction for our journal, we now turn to the articles in this issue of Notiziario Allergologico, which, although not related to the topic discussed above, are no less important. We begin with a contribution from Dr Zunno, who reminds us that an individual's state of well-being is generally the result of a complex balance between mind and body and that psychological stress, which often occurs in comorbidity with numerous pathologies, can modify their severity. There is now ample evidence that allergic diseases can also be associated with psychological stress; the persistence of this stress in allergic patients could have a negative impact on their neuro-immunological system, altering the Th1/Th2 ratio in favour of the latter and consequently leading to a worsening of symptoms. Hence, the author concludes, it is important to assess the psychological component in patients with allergic diseases, especially if they are alexithymic, and, if necessary, to adopt a multidisciplinary approach that also includes psychotherapeutic support.

Nuts (dried fruit), or rather the edible seeds derived from them, are becoming, especially in the paediatric population, among the foods most likely to cause allergic reactions to certain proteins they contain. Dr Sarti and Dr Catamerò discuss this particular allergy in detail, pointing out that in recent years there has been a significant increase in its prevalence, most likely linked to greater consumption of dried fruit, which is also used as an ingredient in snacks and pastries. Walnuts, hazelnuts, almonds, pine nuts and pistachios are the most commonly consumed types of dried fruit. Although they belong to different families, as clearly stated in the article, they contain various allergens characterised by a certain degree of amino acid sequence homology both among themselves (*seed storage and lipid transfer proteins, oleosins*) and with pollen-derived allergens (Betulaceae) such as profilins and PR-10 (*pathogenesis-related proteins*)*. While the former are mainly responsible for so-called primary sensitisation, the latter are generally dependent on pollen sensitisation and therefore give rise, in the diagnostic phase, to false positive responses due to a phenomenon of cross-reactivity. Hence, as the authors point out, the difficulty of the diagnostic approach, which must be based on a combination of different tests (molecular characterisation is important) and, if necessary, on the performance of an oral provocation test. The clinical symptoms of nut allergy vary in severity (including anaphylaxis) and depending on the pattern of sensitisation to allergenic molecules. From a practical point of view, the observations on the therapeutic approach based on an elimination diet are very useful. Especially in children, this approach should not involve generalised and prolonged dietary restrictions unless necessary. Hence the importance of phenotyping patients to distinguish those at high risk of anaphylaxis from those with milder and more localised manifestations and to limit the negative impact on their quality of life, including any psychological stress, the effects of which, as mentioned in the previous article, could contribute to exacerbating symptoms.

We conclude this issue with a contribution from Prof. Caio and colleagues who, after clarifying the distinctive features of various gluten-related disorders, then focused their attention on coeliac disease. As is well known, the development of this disease is associated with the ingestion of gluten, which, in genetically predisposed individuals, triggers an inflammatory response in the small intestine to the gliadin component, which can lead to villous atrophy and malabsorption. The authors, with commendable clarity, enrich their contribution by supplementing it with a series of practical recommendations and take-home messages on the clinical management of coeliac disease and, in particular, on the diagnostic approach in accordance with the new guidelines that have revised the previous ones on the significance to be attributed to the various serological tests and histological/endoscopic profiles. Taken together, these may make it unnecessary to use invasive procedures such as duodenal biopsies for diagnostic purposes, at least in selected groups of adult patients. Among these, it is important to note the significance in the diagnostic phase of the serological titre of IgA anti-transglutaminase antibodies when particularly high (≥ 10 times the upper limit of normal). The authors conclude by noting that despite the significant improvements in recent years in the diagnosis, pathology and natural history of coeliac disease, further studies are needed to fill the gaps in knowledge that still remain.

**It should be noted that peanuts, contrary to what many may think, are not classified as nuts, because they are actually legumes. This does not exclude the possibility that the allergens present in them show a certain level of homology with those present in various types of nuts.*

ENG

Psychological stress and allergic diseases

Dr. Roberta Zunno

Psychologist specialising in neuroscience-based strategic psychotherapy, ASL Salerno

1. Psychological stress and health

The mind and body constantly exchange emotional information, which is why neuroscience increasingly refers to the 'psychosomatic perspective', i.e. the integration between psyche and soma, where psychosomatics can be understood as a 'world view' in which the mind and body are in constant and essential dialogue. Engel's studies on the bio-psycho-social model (1) have emphasised that health is not a static condition but the result of a dynamic balance between various individual, social and environmental factors, defined as determinants of health. From this perspective, it is important to note that our perception of our own state of health also influences our health. For example, expectations regarding the intensity of itching can play a role in the perception of itching itself, which can be modulated by the patient's cognition and behaviour, with the implementation, for example, of obsessive rituals characterised by scratching and constant manipulation of the skin (2). In turn, these skin lesions can worsen the emotional condition of patients with chronic itching, who report feeling embarrassed and stigmatised and having a more negative relationship with their body image than the control group (3). Various studies have shown a high comorbidity between itching, stress, anxiety-depressive symptoms and sleep disorders (4-6) (Figure 1). According to studies by Damasio (7), the perception of one's state of health is the overall result of physical conditions, such as current illnesses, genetic predispositions, immune-inflammatory activity, hormonal status, etc., and the

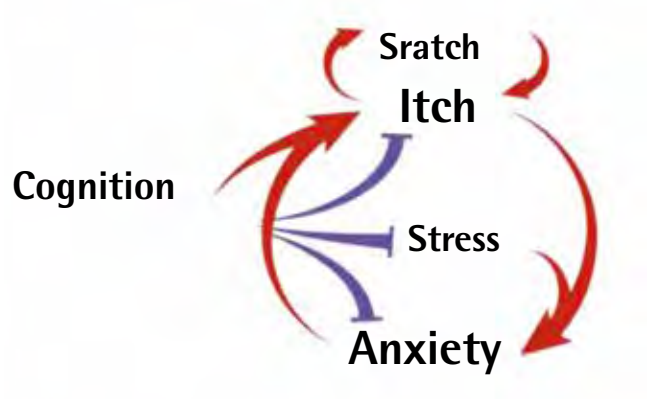
ABSTRACT

Keywords

• Alexithymia • Allergie • Anxiety • Depression • Immune system • Stress

Scientific research shows that psychological stress plays a significant role in the pathophysiological processes associated with allergic diseases, greatly affecting patients' quality of life and how they experience the disease. Data show a higher prevalence of stress, anxiety disorders, mood disorders and sleep disorders in allergic patients than in the general population. It is therefore important to assess the psychological component of allergic diseases and to provide multidisciplinary intervention that integrates pharmacological treatment with psychological support and psychotherapy, especially with an integrated mind-body approach.

Figure 1



Itching and anxiety create a vicious cycle, leading to a heightened perception of itch and related behaviour. Stress can worsen anxiety, and cognition can exert positive or negative feedback within this process. *Figure source: (5)*

mental processing of thoughts, emotions, memories, expectations, past experiences and fantasies. In this sense, the processes we experience as mental are actually representations of the body in the brain: the brain records internal or external stimuli by constructing body maps, i.e. mental images of both current events and information already stored in memory. Body maps are processed through a dual channel: *bottom-up* and *top-down*. The *bottom-up* direction concerns all physiological information that travels from the periphery of our body to the central nervous system, while the *top-down* direction concerns all higher cortical cognitive and emotional processes that connect the current psychophysical condition to the person's life history (7, 8). The two circuits are in constant dialogue with each other, and it is precisely these continuous exchanges that are considered to be at the basis of the state of health , which can act as both protective and risk factors, depending on their functionality. Adopting an integrated mind-body perspective is fundamental in the study of risk and protective factors that affect an individual's health throughout their life. One health risk factor that numerous studies have shown to be comorbid with many chronic diseases is psychological stress. The literature considers stress to be a complex process involving exposure to stressful environmental factors, subjective assessment of *the stressor*, activation of physiological response systems, and health consequences (9). The main stress axes, the sympathetic nervous axis, the hypothalamic-pituitary-adrenal axis and the neurogenic inflammation axis, have direct effects on the respiratory, cardiovascular and digestive systems and influence the functioning of the entire organism, from an emotional, mental and physical point of view, with continuous mutual interactions, interfering with the immune system (10). While acute stress causes a significant but transient neuro-endocrine-immune response, chronic stress has an inflammatory effect on the immune system, stimulating the activation of pro-inflammatory cells and altering cytokine production (10). A chronic stressful condition, characterised by a high psycho-emotional load, can alter the immune response by inducing inflammation, as evidenced by the latest research in the field of epigenetics (11). Environmental factors can generate significant and permanent alterations in phenotype, with immediate and long-term effects, not only in the exposed individual, but also in subsequent generations, in which case we could speak of 'transgenerational epigenetic inheritance' (12). Evidence has shown that maternal psychological stress during pregnancy can be one of the factors contributing to the modulation of the immune trajectories of offspring, with changes in the endocrine and immune regulatory systems observable in the postnatal period (13) (Figure 2). These alterations could translate, in the postnatal period, into increased vulnerability to the development of atopic conditions (9). A systematic review focusing on the effects of prenatal maternal stress showed that, in most of the available analyses, exposure to stress during pregnancy is associated with an

increased risk of asthma, atopic dermatitis, allergic rhinitis or elevated IgE levels in offspring (9). At the same time, the authors point out that factors such as the high methodological heterogeneity of the studies, differences in stress measurement methods and the presence of potential biases do not support causal conclusions (9).

2. Psychological stress and allergies

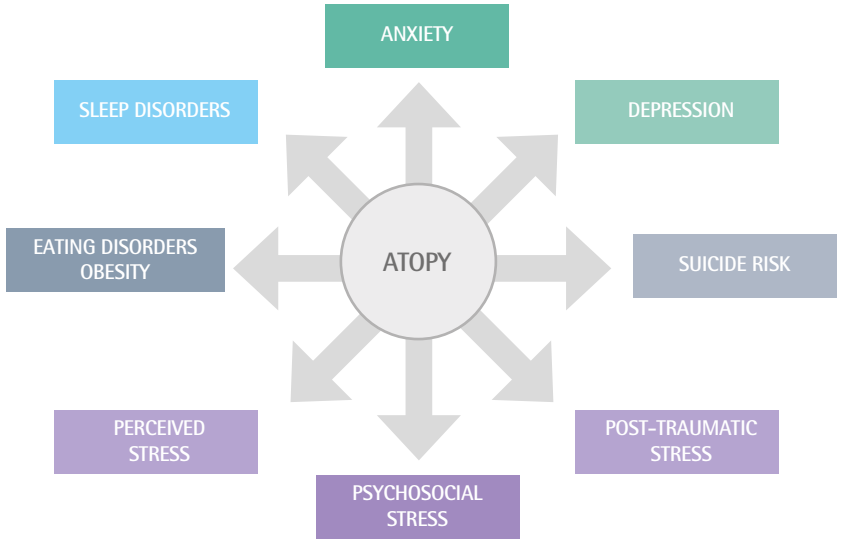
Scientific research shows that psychological stress and emotional distress play a significant role in the pathophysiological processes associated with allergic diseases, greatly affecting patients' quality of life and how they experience the disease (Figure 3). In particular, data show a higher prevalence of stress, anxiety disorders, mood disorders, sleep disorders and suicide risk in allergic patients compared to the general population (4, 5, 14-16) (Figure 4). Furthermore, some psychological disorders have higher than normal inflammatory indices (17), as the brain is connected to the immune system through endocrine, nervous and lymphatic pathways, including the stress axis. For example, depression has been confirmed as a pro-inflammatory state, in which some of the elevated inflammatory markers, including CRP and IL-12, show reduced variability, supporting greater homogeneity in terms of inflammatory phenotype in depression (18) (Figure 5). The presence of psychosocial stress modulates the immune and nervous systems and can act as a trigger for the onset or exacerbation of disease or can be generated by the low

Figure 2 Analyzed prenatal maternal stress (PMNS), factors and properties

Factor	Properties	Examples
Stressor Type	Neurogenic	Light Restraint Electric shocks Saline injection Rotation Tail-suspending Chronic mild unpredictable
	Psychogenic	Housing unfamiliar conspecific Crowded housing Resident-intruder confrontation Witness of stress induction (bystander) Conditioned stress
Timing (immune system development window of vulnerability, WOV)	Stem cell Hepatic Myeloid Immunocompetence Memory*	
Duration/frequency	Daily Intermittent Constant	
Animal Species	Non-human primate	*Macaca mulatta* *Saimiri boliviensis*
	Swine	*Sus scrofa*
	Murines	*Rattus norvegicus* *Mus musculus*
Sex	Male Female	
Age at assessment	Neonate Infant Puberty Adult	

**The Memory WOV is exclusively postnatal, thus it was not included in the analysis. Figure adapted from: (13)*

Figure 3 Summary representation of the psychological conditions influencing the manifestation of allergic phenomena



quality of life of patients, creating a vicious circle (4, 6) (Figure 6). The long-term course of the disease, the need for chronic treatment and repeated exacerbations are a major source of stress for patients, accompanied by feelings of anger, shame, embarrassment, social isolation and low self-esteem, which can lead to anxiety and/or depressive symptoms. In turn, stress and anxiety exacerbate these symptoms, affecting the patient's behaviour and worsening the prognosis of the disease and their quality of life (9, 14). A similar picture emerges in severe forms of asthma (19), atopic dermatitis (20), and urticaria (21), where high levels of perceived stress, anxiety, and depressive symptoms have been found. Most of these studies show that the decrease in clinical symptoms is correlated with a reduction in perceived stress levels and anxiety-depressive symptoms, without this necessarily implying a direct causal relationship, but rather a covariation between clinical and psychological dimensions (19-21).

Special attention should also be paid to anaphylaxis. During anaphylactic shock, people may experience fear and severe emotional stress and feel as though they are about to die, an experience that can be traumatic. This condition can have a significant impact on patients' quality of life, greatly affecting their physical and mental health. People who have experienced anaphylactic shock may develop psychiatric comorbidities, including anxiety, depression and post-traumatic stress disorder; therefore, it is important to be aware of the possible psychological distress of patients with anaphylaxis and to consider the psychological component (22, 23). Recently, following the development by Knibb et al. in 2022 of a psychometric scale to measure the impact of the risk of anaphylaxis on the quality of life of adult patients, we produced its Italian validation entitled *Anaphylaxis Quality of Life Scale for Adults-Italian Version* (A-QoL-Adults-I) (22). The aim was to provide Italian clinicians with a reliable tool to assess the perception of quality of life in patients at risk of anaphylaxis and the impact that this condition can have on it, thereby improving the overall management of the patient, considering both the clinical and psychological and social aspects (22).

3. A focus on alexithymia

Another interesting fact is that there seems to be a high correlation between allergic diseases and alexithymia (20, 24). The term alexithymia (25) refers to 'not having words for emotions' (from the Greek a = lack, *léxis* = word, *thymòs* = emotion), due to a lack of connection between the psychological component (*feelings*) and the biological component (*emotions*) of affect, i.e. between the cognitive-experiential level of feelings (subjective awareness and the possibility of verbal description of affective states) and the physiological (amygdala, hypothalamus, autonomic nervous system, neuroendocrine activation) and motor-expressive (e.g. facial expressions,

ENG

changes in posture and tone of voice) levels of *emotions*. Alexithymia seems to be a cross-cutting vulnerability factor underlying the onset of somatisation mechanisms, as it is present in all different personality organisations, medical pathologies and psychopathological disorders (8). The limited ability to process emotions in people with alexithymia cognitively predisposes them to have undifferentiated and poorly regulated affective states. In these cases, there is emotional dysregulation characterised by difficulty in mentalising, and therefore verbalising, one's internal mental states, which leads to regulating emotions through impulsive acts or compulsive behaviours (such as binge-eating, substance abuse, etc.), and a tendency towards somatisation, elements that worsen the person's quality of life and psycho-physical health. Since emotions are very weakly connected to images and words, they are experienced as somatic sensations, perceptions or poorly differentiated impulses, resulting in a mode of thinking that is more oriented towards the outside world and concrete content, which also makes it difficult to describe one's emotions to others. This emotional dysregulation is often at the root of psychosomatic illnesses, which directly involve the body, due to the frequent somatisation of aggressive and self-destructive tendencies (8). For example, people with alexithymia are at greater risk of developing certain dermatological conditions because their difficulties in managing stress and regulating emotions affect the neuroendocrine and immune systems, which are closely linked to the skin, which is densely innervated by neurons (26). In fact, patients with atopic dermatitis (20) and chronic spontaneous urticaria have been found to have high levels of alexithymia and severe difficulties in regulating emotions (27). The literature suggests that screening for alexithymia may be useful in defining the role of emotional dysregulation as a perpetuating and/or triggering factor in chronic skin diseases in some patients, and recommends psychotherapy, as a complement to therapeutic options, with the primary aim of helping them recognise their feelings and learn to use them as signals of emotional stress (26).

Figure 4 Illustration of what psychological interventions were shown to be or may be helpful in the treatment of chronic itch

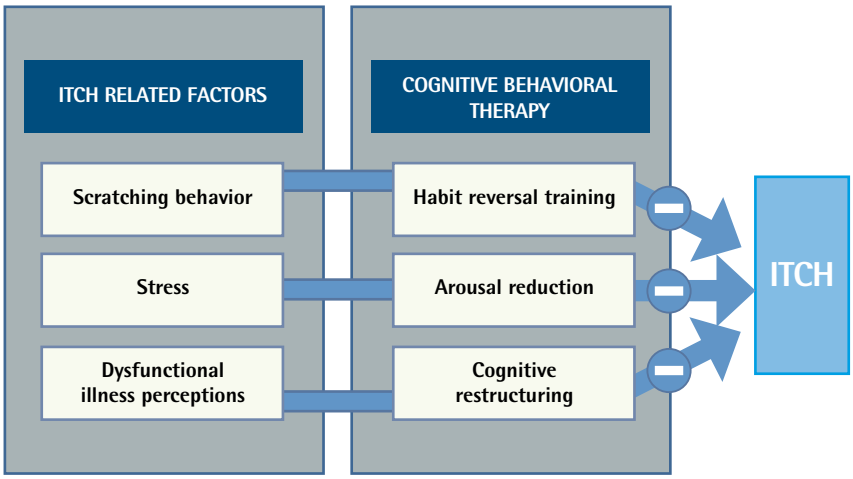


Figure source: (16)

4. Integrated mind-body therapies

The most recent data in the literature suggest that a multidisciplinary approach may be more effective in treating allergic diseases, with treatment that considers the person's overall emotional experience from a mind-body perspective (6). Proper *self-management* of the *disease requires* strong motivation to change and increased *disease awareness* on the part of the patient and their *caregivers*. *Disease awareness* refers to being aware of the disease, its characteristics, associated *health behaviours*, diagnosis and prognosis, and life expectancy, starting with the patient's personal re-elaboration of the information provided

to them (28). In this sense, the focus is on the patient, their emotional and relational context, and their personal way of conceiving and experiencing the disease, which influence their acceptance of it and adherence to treatment, and which also depends on the doctor-patient relationship that is structured through both verbal and non-verbal communication. The more patients are aware of the disease and its management, including exploring concerns about treatment options, the more likely they are to accept it and adhere to treatment in an active and collaborative manner. Various studies (4, 5, 16) indicate the importance of paying attention to psychological aspects as early as the diagnosis stage and of including psychological support to complement pharmacological treatment in order to ensure greater effectiveness in the care of allergic patients, especially due to the high comorbidity with psychological symptoms, suggesting, for example, relaxation and hypnosis techniques to both alleviate symptoms and reduce the use of drugs and their potential side effects, with significant savings in healthcare costs (29). Psychological support and psychotherapy, especially those with an integrated mind-body approach, whose techniques also involve the use of the body, such as hypnosis and *mindfulness*, help patients listen to their bodies and the emotional experiences associated with their symptoms, reducing psychological stress and redefining their life stories and relationships with their clinical symptoms in positive terms, focusing on enhancing the individual and placing full trust in their resources and self-healing processes (6, 11, 16, 30). Integrated mind-body therapies regulate the immune system, enhancing the immune and inflammatory response by modulating the areas of the brain involved in controlling the stress response, increasing the activity of the parasympathetic autonomous system, which stimulates slowing down, relaxation and recovery, and reducing the discharge of the Parasympathetic Autonomic Nervous System, which has the function of accelerating the body's internal processes and is hyper-activated when the body prepares to react to *stressors*, both external and internal (11). Mind-body techniques

Figure 5 Summary of Significant Findings

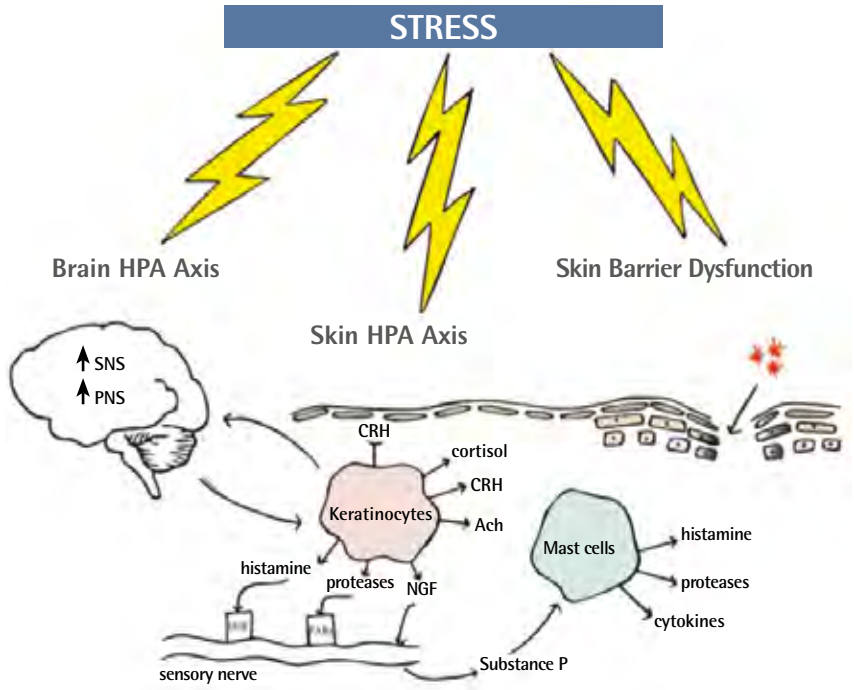
Marker	Meta-analysis of mean differences in immune parameters in depression compared with healthy controls	Meta-analysis of variability: CVR
CRP	▲ in patients g = 0.71; 95%CI: 0.50-0.92	▼ variability in patients CVR = 0.85; 95%CI: 0.75-0.98
IL-3	▲ in patients g = 0.60; 95%CI: 0.31-0.89	◄► CVR = 0.76; 95%CI: 0.56-1.04
IL-6	▲ in patients g = 0.61; 95%CI: 0.39-0.82	◄► CVR = 0.92; 95%CI: 0.81-1.05
IL-12	▲ in patients g = 1.18; 95%CI: 0.74-1.62	▼ variability in patients CVR = 0.61; 95%CI: 0.46-0.80
IL-18	▲ in patients g = 1.97; 95%CI: 1.00-2.95	◄► CVR = 0.86; 95%CI: 0.67-1.09
sIL-1RA	▲ in patients g = 0.53; 95%CI: 0.18-0.89	◄► CVR = 1.00; 95%CI: 0.84-1.20
sIL-2R	▲ in patients G = 0.71; 95% CI: 0.44-0.98	▼ variability in patients CVR = 0.85; 95%CI: 0.73-0.99
TNF α	▲ in patients g = 0.54; 95%CI: 0.32-0.76	◄► CVR = 0.96; 95%CI: 0.84-1.10

The following table summarises the findings of variability and mean differences meta-analyses of inflammatory markers in depression concordant between the main and sensitivity analyses

Figure adapted from: (18)

ENG

Figure 6 Mechanism of stress-induced itch



Mechanisms of stress-induced itch. Stress results in the activation of the hypothalamus-pituitary-ad-renal (HPA) axis at the level of the brain and at the level of the skin, and can also cause dysfunction of the skin barrier. In the brain HPA axis, acute stress causes sympathetic nervous system (SNS) elevation and compensatory elevation of the parasympathetic nervous system (PNS), while chronic stress causes SNS elevation and a dysfunctional PNS. Ach = acetylcholine; CRH = corticotrophin-releasing hormone; H1R = histamine 1 receptor; NGF = nerve growth factor; PAR2 = protease activated receptor.

Figure taken from: (4)

could be very useful in allergic diseases, even when combined with therapies that modify the patient's habits and lifestyle and accompany them in a cognitive and emotional restructuring of the weight that the disease has in their life, paying attention to the emotional, cognitive and behavioural aspects that act as perpetuating factors of the symptoms. The goal of integrated mind-body therapies is not therefore, only to reduce the effect of stress, but also to support the person in reconstructing their life story in a more adaptive and emotionally 'sustainable' way, through

Figure 7 The mediating role of anxiety and depression in the relationship between alexithymia and mental health

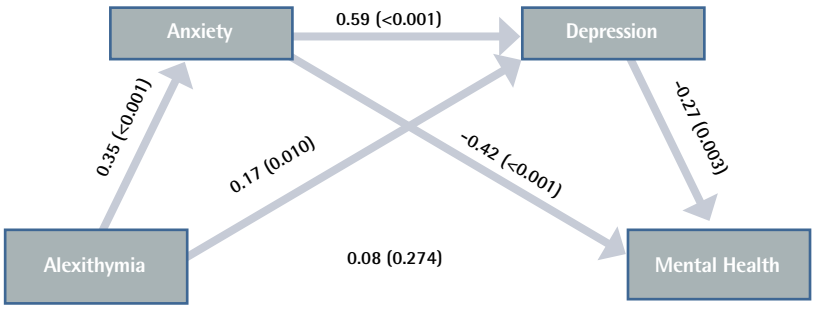


Figure source: (24)

processes of reworking their emotional experiences and emotional regulation, starting from the possibility of naming their emotions, thus reducing the alexithymic component and the tendency to somatisation. In summary, facilitating mind-body dialogue through mind-body therapies and giving patients the opportunity to verbalise this dialogue can enable patients with allergic conditions to draw on their internal resources and use them to discover new ways of connecting with their emotions in order to cope with daily stress, starting with conscious and accepting listening to their bodies, with a consequent reduction in clinical symptoms and improvement in their quality of life.

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Diagnosis of coeliac disease in adults: a 'No-biopsy' approach

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1. Introduction

Gluten-related disorders are a group of different medical conditions associated with gluten consumption, the three main forms of which are coeliac disease (CD), wheat allergy and non-coeliac gluten/wheat sensitivity (NCGWS).

CD is an immune-mediated disease characterised by a distinctive genetic and antibody profile, associated with the presence of specific lesions in the small intestine triggered by an environmental agent, gluten, introduced through the diet. Gluten is a group of alcohol-soluble proteins found in various cereals, including wheat, rye, barley and spelt (1, 2, 3). In recent years, we have witnessed profound changes in the diagnosis, pathogenesis and natural history of this condition.

Other conditions that fall within the spectrum of gluten-related disorders include:

Dermatitis herpetiformis (DH)

Dermatitis herpetiformis is the specific skin manifestation of coeliac disease. Both diseases develop in people who are

ABSTRACT

Keywords

• Coeliac Disease • Guidelines • Serological Tests • Gluten-Free Diet • 'No biopsy' Approach • Adults

Acronyms

• CD, Celiac disease • NCGWS, Non-celiac wheat sensitivity • DH, Dermatitis herpetiformis • Anti-TG2, anti-tissue transglutaminase 2 antibodies • GFD, gluten-free diet • IgA anti-EMA, anti-endomysial antibodies • AGA, IgA anti-gliadin antibodies • DGP, anti-deamidated gliadin antibodies • EGDS, esophagogastroduodenoscopy

The new updated guidelines on coeliac disease constitute a complete revision of the previous guidelines on the management of coeliac disease and other gluten-related disorders, promoting a patient-centred approach with the aim of optimising clinical outcomes and the use of diagnostic resources.

The most important change is the possible diagnostic approach without biopsy in selected adults with high serum IgA anti-TG2 titres (≥10 times the upper limit of normal). In addition to this, IgA anti-transglutaminase 2 antibodies remain the main serological test, while the routine use of IgA anti-endomysium antibodies is no longer recommended as a confirmatory test. Duodenal biopsy protocols are standardised, with at least four biopsies from the second portion of the duodenum and two from the duodenal bulb, and the modified Marsh classification is confirmed. The guidelines also propose structured approaches for the diagnosis of potential coeliac disease and seronegative coeliac disease. Finally, HLA-DQ2/DQ8 typing is recommended only in selected cases for diagnostic clarification.

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Figure 1 Approach to the diagnosis of NCGWS. FODMAP, fermentable oligo-, di-, monosaccharides and polyols; NCWS, non-coeliac gluten/wheat sensitivity

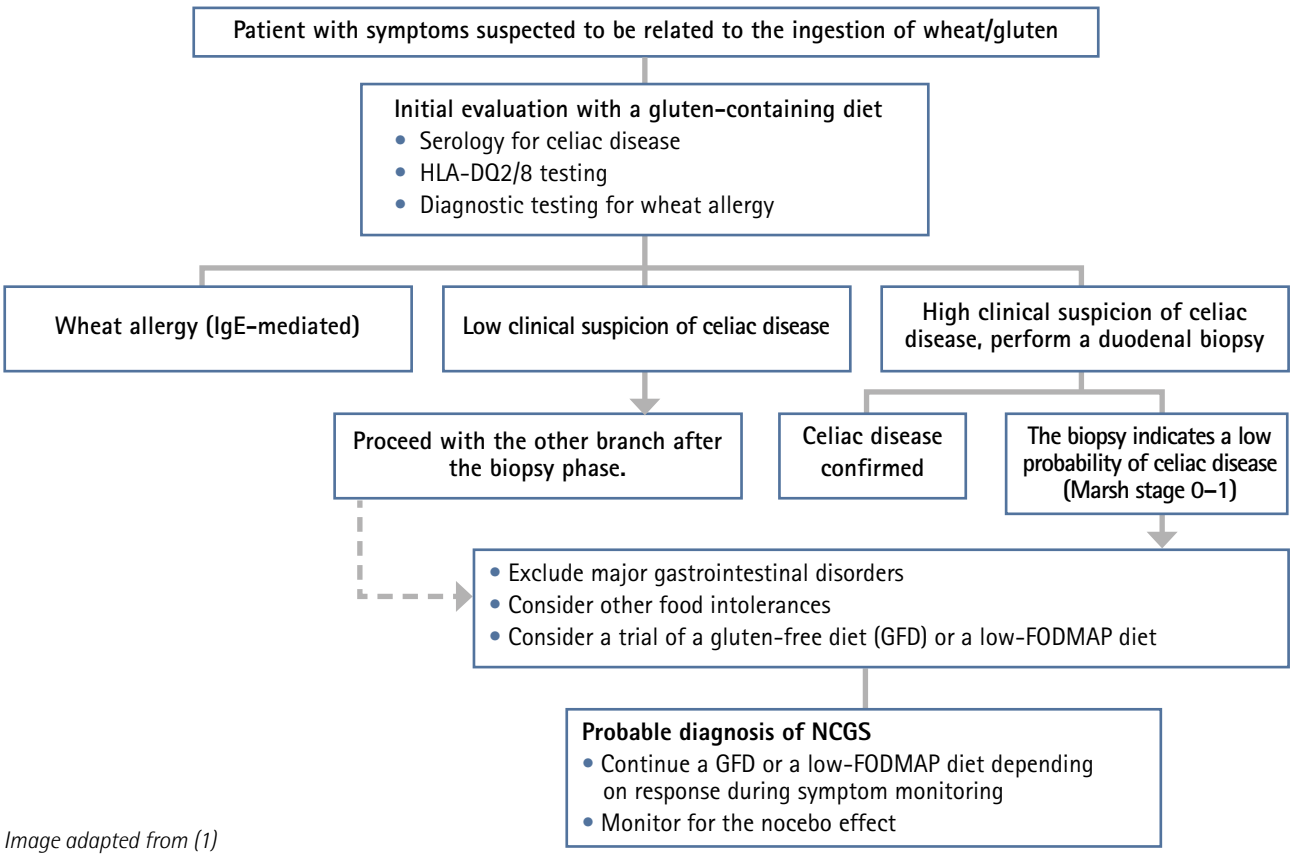

Image adapted from (1)

sensitive to gluten, who therefore share the same HLA haplotypes and improve with a gluten-free diet. The diagnosis of DH is confirmed by direct immunofluorescence on perilesional skin, which shows granular deposits of IgA in the papillary dermis, associated with positive serology for anti-tissue transglutaminase 2 (TG2) antibodies (4).

Gluten-related neurological manifestations

Neurological complications may be the first clinical manifestation of coeliac disease and are reported in 10–22% of affected adults; scientific evidence suggests a correlation with the activation of the immune system in response to gluten. The most common neurological manifestation is gluten ataxia. Less than 10% of these patients have gastrointestinal symptoms, but only one-third show signs of enteropathy in the intestinal biopsy. Other rare neurological disorders described in the literature include gluten neuropathy, gluten encephalopathy, and temporal lobe epilepsy.

Several patients also report mild cognitive impairment, often referred to as 'foggy mind', which improves with a

gluten-free diet but may reappear in the event of food contamination. Difficulty concentrating and paying attention are also common (1, 5).

Non-coeliac wheat sensitivity (NCWGS)

Non-coeliac wheat sensitivity is a condition characterised by symptoms similar to those of irritable bowel syndrome, associated with extra-intestinal manifestations. The disorders appear after gluten intake and improve rapidly with its elimination. In order to suspect this condition, it is essential to rule out coeliac disease, wheat allergy and other important gastrointestinal diseases while the patient is still following a gluten-containing diet (1). Figure 1 summarises the approach to diagnosing NCWGS.

2. Epidemiology and environmental triggers

Over the last 5–6 decades, the global prevalence of coeliac disease has increased significantly, although a significant proportion of cases remain undiagnosed. The diagnosis is more common in females, with a female:male ratio of between 2:1 and 1.5:1.

In Western countries, the prevalence is estimated at around 0.7% when the diagnosis is confirmed histologically, while it rises to 1–1.6% in serological screening studies of the general population (1, 6).

CD can occur at any age; however, in recent years, there has been a marked increase in diagnoses in children, especially older children and adolescents, increasing the median age at diagnosis (7). This change is probably linked to an increased ability to recognise mild or asymptomatic forms, facilitated by the widespread use of highly specific serological tests, such as anti-endomysium and anti-transglutaminase (anti-TG2) antibodies.

Exposure to gluten is essential for the development of CD: after ingestion, gluten peptides, which resist complete digestion in the gastrointestinal tract, give rise to immunogenic fragments. These fragments are presented to gliadin-specific T cells in a manner dependent on HLA-DQ2 or HLA-DQ8, triggering an inflammatory response in the small intestine that can lead to villous atrophy and malabsorption (1, 8). In fact, the presence of risk HLA alleles is a necessary but not sufficient factor for the development of coeliac disease. HLA genes account for only about 35–40% of the overall genetic risk, highlighting the important role of a large number of non-HLA genes involved in the immune mechanisms underlying the disease (9).However, loss of gluten tolerance can occur at any age as a result of additional triggers other than gluten itself, including gastrointestinal infections, certain medications, interferon alpha, and surgery (1, 10, 11).

3. Diagnostic approach

The new updated guidelines on coeliac disease (CD) (1) are a comprehensive revision of the 2019 Guidelines of the European Society for the Study of Coeliac Disease (ESsCD) on the management of coeliac disease and other gluten-related disorders (2).

The main changes in the diagnostic approach to coeliac disease in adults, compared to the 2019 version, are as follows:

Serological tests

IgA anti-transglutaminase 2 (anti-TG2) antibodies remain the main screening and diagnostic test. Routine use of anti-endomysium antibodies (IgA anti-EMA) is no longer recommended, but may be reserved for doubtful cases to improve diagnostic accuracy and cost-effectiveness.

Standardised biopsy and histological reporting protocols

It is mandatory to take at least four biopsies from the second portion of the duodenum and two from the duodenal bulb. The modified Marsh classification remains the gold standard.

Introduction of diagnosis without biopsy in adults

The possibility of diagnosing coeliac disease without performing endoscopy with duodenal biopsies in adults under 45 years of age with anti-TG2 IgA values ≥ 10 times the upper limit of normal (ULN) is introduced on a conditional basis. Confirmation by serology on a second blood sample is required.

Expanded indications for difficult-to-diagnose cases

New structured approaches are proposed for the management of potential coeliac disease, seronegative villous atrophy and cases diagnosed after the start of a gluten-free diet.

Clarification on the interpretation of Marsh I histological stage

In the presence of negative serology and Marsh I lesions, a diagnosis of coeliac disease is unlikely and alternative causes should be sought.

Role of HLA-DQ2/DQ8 typing

Although not routinely recommended, HLA-DQ2/DQ8 typing is indicated when there are diagnostic uncertainties (e.g. ambiguous results, gluten-free diet started before testing, potential coeliac disease or seronegative forms) and in the screening of certain risk groups.

Clarifications on the use of rapid tests and non-haematological tests

A positive result from rapid tests (POCT) must always be confirmed with standard serological tests and, if indicated, with a duodenal biopsy. The guidelines advise against the use of saliva and stool tests due to their poor diagnostic accuracy.

Patient-centred diagnostic approach

Emphasis is placed on shared decision-making with the patient, particularly the option of not performing a biopsy or choosing to carry out a gluten reintroduction test, with the aim of reducing unnecessary procedures while ensuring a reliable diagnosis.

Taken together, these updates outline an accurate diagnostic pathway that is better aligned with current clinical practice and emphasise the reduction of unnecessary procedures in appropriate patients (1).

4. Serological tests

The new guidelines recommend the following as the most suitable initial serological test for coeliac disease (1):

IgA anti-tissue transglutaminase (TG2) antibody as a single test for initial screening for CD at any age.

Concomitant measurement of total IgA to rule out selective IgA deficiency and avoid false-negative results.

Testing while the patient is on a gluten-containing diet, as markers tend to normalise with a gluten-free diet, which can lead to missed diagnoses.

Autoantibodies, such as anti-endomysium antibodies (IgA anti-EMA) and anti-TG2, have significantly improved the diagnostic accuracy of CD compared to older tests, such as IgA anti-gliadin antibodies (AGA) (12, 13). In terms of predictive values, the positive predictive value (PPV) and negative predictive value (NPV) of anti-TG2 IgA are 90% and 98%, respectively. In comparison, PPV and NPV are 100% and 97% for anti-EMA IgA, 94% and 90% for anti-AGA IgA, and 70% and 98% for anti-AGA IgG (14, 15). Although anti-EMA IgA is highly specific, the test is laborious and operator-dependent, making the immunoenzymatic or chemiluminescent test for anti-TG2 IgA technically simpler and allowing for greater standardisation and automation. However, they may be reserved for unclear cases to ensure better diagnostic accuracy and cost-effectiveness before proceeding to duodenal biopsy (1, 15). In patients with confirmed total IgA deficiency, serology for coeliac disease should be performed with IgG-based tests, such as IgG anti-TG2 or IgG anti-DGP antibodies. Due to the lower sensitivity of these tests, a negative IgG result does not rule out the diagnosis; therefore, oesophagogastroduodenoscopy (EGDS) with duodenal biopsies should be performed regardless of the IgG serology results. HLA-DQ2/8 typing is reserved for selected clinical cases in which both IgG-based serological tests and duodenal biopsy are inconclusive or un r impracticable. A negative result would effectively rule out CD and eliminate the need for further investigation (1).

Saliva and faecal tests for CD have low sensitivity and specificity; therefore, their use in clinical practice should be discouraged (1).

4.1 Who should be tested or screened for coeliac disease?

Although there is currently no strong evidence to recommend mass screening of the general population, in Italy, Law 130 of 15 September 2023 established a national screening programme for coeliac disease and type 1 diabetes in the paediatric population (0-17 years), with the aim of early detection of cases and individuals at risk, prevention of complications and improvement of prognosis. The programme provides for the establishment of a National Observatory and information campaigns, with gradual implementation following a pilot study currently underway in four regions (Campania, Lombardy, Marche and Sardinia). Regardless of whether this possibility is introduced in the near future, individuals of all ages who

should be screened for CD are those summarised in Table 1.

5. Histopathology

For the diagnosis of CD, it is recommended that at least four biopsies be taken from the distal duodenum, plus two from the duodenal bulb (1).

When coeliac disease is suspected, duodenal biopsies should be performed even if the endoscopic appearance of the duodenal mucosa is macroscopically normal. Mucosal lesions may be patchy, so multiple biopsies are necessary (16, 17); including biopsies from the duodenal bulb may improve the identification of early or localised involvement (ultra-short CD, which affects only the duodenal bulb) (18).

During endoscopy, the use of single-bite biopsy forceps is recommended to obtain optimal orientation of biopsy samples for histological examination. Subsequently, samples should be processed individually rather than combined into a single paraffin block and, in particular, bulb biopsies should be placed in a separate tube from those taken from the distal duodenum.

In particular, for optimal histopathological evaluation in CD, the following is recommended (1):

- The use of haematoxylin-eosin (H&E) staining;
- Histological interpretation should be carried out, where possible, in the context of clinical and serological information;

Pathology reports should explicitly state key parameters such as: number of biopsies received, quality of orientation,

Table 1 Individuals to be tested/screened for MC

Category	Indications for testing/screening
Individuals who should be tested for MC (symptomatic or with associated conditions)	
Symptoms and signs suggestive of MC	Chronic diarrhoea (non-bloody), steatorrhoea, unexplained weight loss, chronic iron deficiency and anaemia of unknown origin, postprandial bloating, dyspepsia, recurrent abdominal pain, constipation, ileostomy or colostomy with unexplained elimination of large amounts of fluid.
Gastrointestinal disorders	Autoimmune atrophic gastritis, irritable bowel syndrome, microscopic colitis, acute or chronic idiopathic pancreatitis, idiopathic liver enzyme abnormalities, autoimmune hepatitis, primary biliary cholangitis, hyposplenism or functional asplenia.
Neurological Disorders	Idiopathic ataxia, peripheral neuropathy, idiopathic epilepsy.
Dermatological and Oral Disorders	Dermatitis herpetiformis, refractory psoriasis, recurrent aphthous ulcers, dental enamel defects, hypomineralisation of molars and incisors.
Endocrine and Autoimmune Disorders	Type 1 diabetes mellitus, Hashimoto's thyroiditis, Graves' disease, Sjögren's syndrome.
Gynecological disorders	Delayed menarche, early menopause, unexplained infertility with recurrent miscarriages.
Other indications	Suspected coeliac disease associated with immune checkpoint inhibitors, chronic fatigue syndrome, selective IgA deficiency, pulmonary haemosiderosis, endoscopic capsule or radiological imaging findings suggestive of villous atrophy, 'early' osteoporosis with low-impact fractures, IgA nephropathy (perform the test if other features suggestive of coeliac disease are present; consider it in cases of early onset, atypical or refractory IgA nephropathy, or in the presence of a concomitant autoimmune disease or a family history of coeliac disease).
Individuals who should be screened for CD (high risk but asymptomatic or mildly symptomatic)	
Genetic conditions	Down syndrome, Turner syndrome, Williams syndrome.
Family history	First-degree relatives of individuals with coeliac disease, even if asymptomatic.

Table adapted from (1)

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Vh:Cr ratio, IEL count, and Marsh stage.

In cases of diagnostic uncertainty, a second opinion is encouraged to increase diagnostic confidence. Furthermore, the use of digital pathology platforms and artificial intelligence-based tools is increasingly recognised as supporting reproducibility and reducing inter-observer variability (19).

Finally, obtaining an adequate number of biopsies and correct orientation of the samples are essential for reliable histological evaluation.

Advanced endoscopic techniques cannot replace standard histopathology in the assessment of small intestinal mucosal damage in CD, but they are valuable and complementary tools that can reduce unnecessary biopsies and improve targeted sampling (1).

Radiological and nuclear medicine techniques play an important role in the evaluation of CD, particularly in cases with atypical presentations, suspected complications, or when endoscopic and histological findings are inconclusive. They provide valuable additional information for assessing structural changes, detecting complications, and estimating disease severity (1).

5.1 Subclassifications (A, B, C) of Marsh stage III in the modified Marsh classification

The Marsh classification was originally developed to study histological alterations in coeliac disease and was subsequently modified to subdivide stage III (villous atrophy) into three subcategories: 3A (partial), 3B (subtotal) and 3C (total). Although the subclassifications (3A–3C) provide a more detailed description of mucosal damage, their clinical relevance in daily practice is limited (1, 20). According to numerous studies, these substages do not significantly influence treatment decisions or long-term outcomes, but may be useful for monitoring disease activity and mucosal healing, particularly in patients with severe enteropathy (e.g. Marsh 3C), who are at increased risk of incomplete histological recovery and may benefit from closer follow-up (1, 21).

Morphometric analysis has been proposed as a more objective method for assessing mucosal damage. This approach involves quantitative assessment of the villus height/crypt depth ratio (Vh:Cr) and intraepithelial lymphocyte (IEL) density (19, 22).

A Vh:Cr ratio of less than 2 indicates villous atrophy and active disease, while patients with treated CD typically have ratios greater than 3 (19).

Despite its potential for objective histological assessment, morphometry faces significant difficulties in clinical practice due to limitations such as lack of standardisation and insufficient evidence of superiority over existing methods.

5.2 Confirmation of CD diagnosis in adults

The diagnosis of CM in adults is confirmed with positive specific serology in patients with Marsh stage II or Marsh stage III.

However, with these new guidelines, diagnostic confirmation of CM in adults can be based solely on positive serology (non-biopsy approach) when the initial level of anti-TG2 IgA is ≥10 times the upper limit of normal (ULN).

However, some considerations are necessary (1):

- The initial anti-TG2 IgA result must be confirmed on a second blood sample. The patient must remain on a gluten-containing diet until confirmation. In this independent sample, any positive result should be considered confirmatory of coeliac disease.
- Decisions about omitting duodenal endoscopy/biopsies and confirming the final diagnosis should be made in secondary care.

A shared decision with the patient on the potential benefits and limitations of omitting duodenal biopsies is essential.

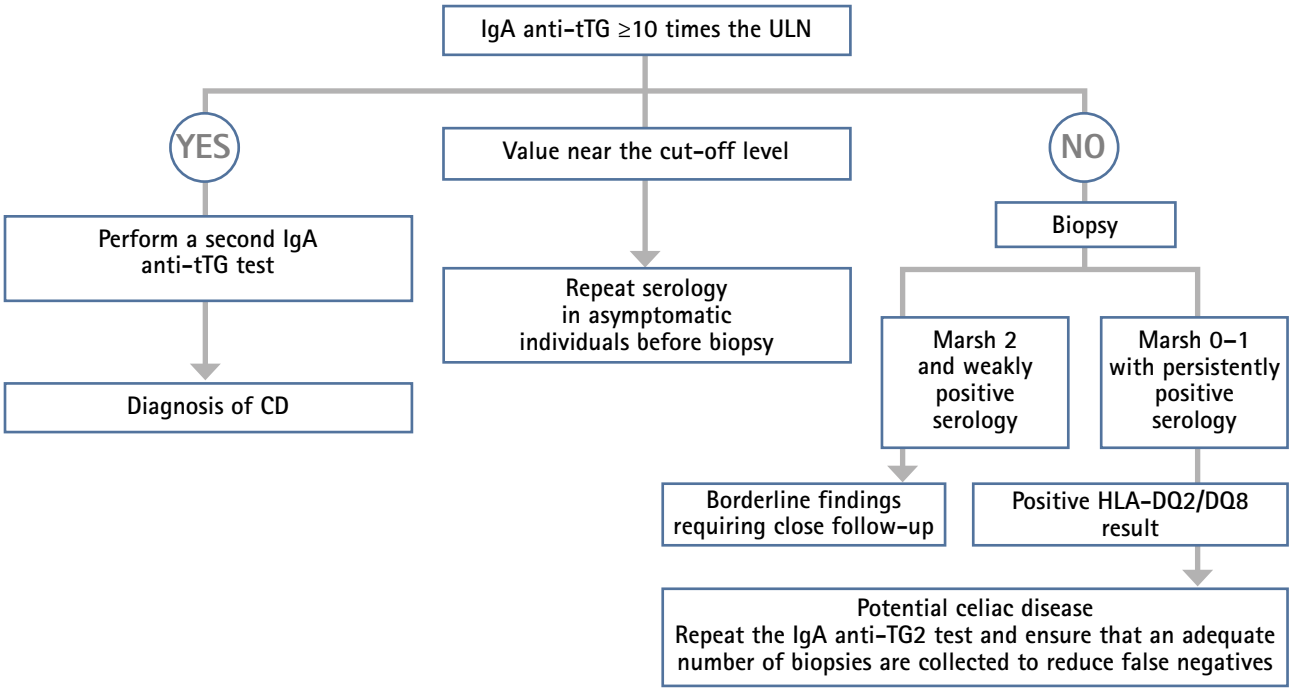
This approach is not appropriate in the presence of warning signs for alternative conditions (e.g., haematochezia, dysphagia, or signs of obstruction).

Pending further safety data, the biopsy-free approach should be limited to patients under 45 years of age. This threshold reflects concerns about an increased risk of complications with advancing age in CD.

For decades, small intestine biopsy has been central to confirming the diagnosis of CD. In the paediatric population, the non-biopsy approach is based on solid evidence and has become the standard diagnostic pathway for CD in children (23). In adults, however, the evidence supporting a non-biopsy diagnosis is emerging more gradually (24).

To confirm the diagnosis of CD using the non-biopsy approach, a second measurement of anti-TG2 IgA ≥10×

Figure 2 Flow chart for the 'no-biopsy' approach in patients <45 years of age who do not have warning symptoms suggestive of serious diagnoses or comorbidities

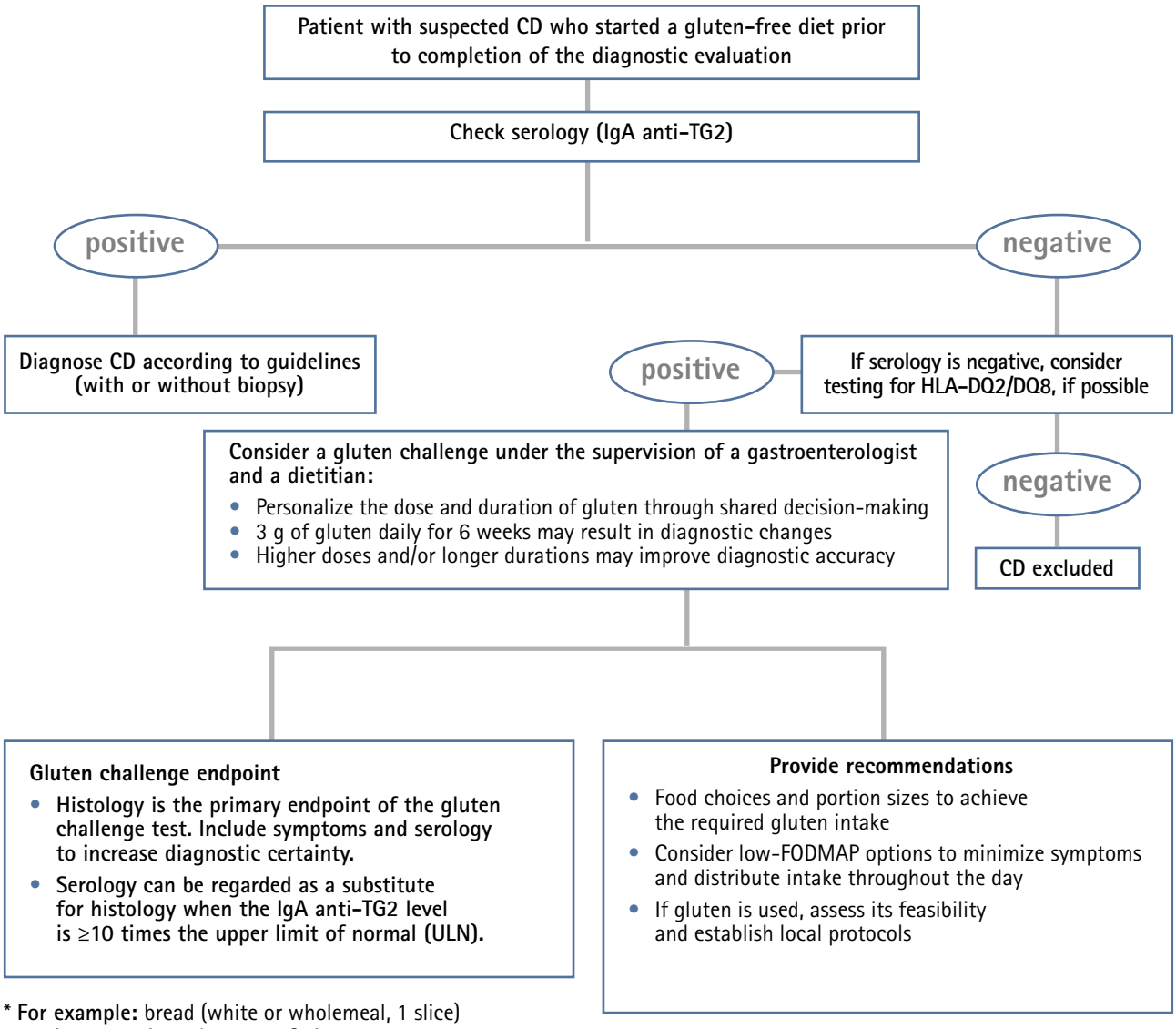


ULN on a new blood sample is conditionally recommended, where possible. This recommendation addresses practical issues such as potential pre-analytical errors and aims to ensure that the diagnosis is established within the context of second-level gastroenterological care. Although there is no direct evidence to support a clinical benefit of repeating the serological test, these pragmatic considerations have been emphasised by the expert working group in response to the diagnostic challenges of real-world practice. Establishing a lifelong diagnosis of CD, which requires strict and continuous adherence to a gluten-free diet (GFD), based solely on a single, non-repeated serological result may contribute to patient uncertainty and does not eliminate the risk of laboratory errors. However, the diagnostic accuracy of a single IgA anti-TG2 result ≥10× ULN is well documented, with high-quality studies demonstrating a PPV ≥98% (24).

Patients generally prefer the non-invasive option without biopsy over biopsy-based diagnosis (25); however, a Finnish questionnaire-based study found that patients diagnosed without biopsy had less frequent dietary follow-up, more persistent symptoms, and greater diet-related stress (26). This suggests a potential risk of suboptimal care in this group and reinforces the importance of diagnosis and initial management taking place in secondary gastroenterology services (1).

The requirements for safely adapting the non-biopsy approach are currently under investigation; however, factors such as age at initial diagnosis, severity of clinical and laboratory parameters, or the presence of warning symptoms suggestive of serious diagnoses or comor-

Figure 3 Approach to the diagnosis of CD in adults using gluten challenge testing



* **For example:** bread (white or wholemeal, 1 slice) contains approximately **3.5 g of gluten.**

Image adapted from (1)

bidities must be taken into account (1).
In the case of Marsh II histology, the diagnosis is generally supported by high-titre serology; however, the combination of low-titre positive anti-TG2 IgA and Marsh II histology represents a diagnostic 'grey area' that requires careful follow-up. These subjects may represent evolving CD and should remain under observation in specialist care settings (1).
In patients with positive but low-titre IgA anti-TG2 (<10× ULN), small intestine biopsy is still necessary for the diagnosis of coeliac disease, as lower antibody titres are less specific and may overlap with other conditions. In particular, in asymptomatic individuals with low-titre anti-TG2 positivity (close to the cut-off), a prudent strategy may be to repeat serology after a few weeks before proceeding with biopsy, especially if immediate histological confirmation is not essential. This approach helps to reduce unnecessary procedures while monitoring serological evolution, which may clarify the clinical picture.
In adults who are persistently positive for IgA anti-TG2 antibodies but have architecturally normal duodenal histology (Marsh 0–I), a definitive diagnosis of CD cannot be established. However, if these individuals have the HLA-DQ2 and/or DQ8 haplotype, they can be classified as having potential coeliac disease.
In these cases, it is recommended that IgA anti-TG2 serology be repeated to rule out false-positive or transient results and to ensure that a sufficient number of biopsies are collected to reduce false negatives (27). Add HLA-DQ2/DQ8 typing in high-resource settings to evaluate patients with potential coeliac disease and consult a coeliac disease specialist for complex cases.
In cases of Marsh stage I with negative serology for coeliac disease, CD is unlikely and other causes should be explored, including other gluten-related disorders, wheat allergy, Helicobacter pylori infection and drug reactions. More rarely, it may be secondary to inflammatory bowel disease, autoimmune conditions, immunoglobulin deficiencies, haematological malignancies, infections, and irritable bowel syndrome (28). Figure 2 summarises the above indications.

5.3 The role of HLA-DQ typing in screening and diagnosis of CD

The HLA test has a low PPV but a high NPV for CD; therefore, guidelines recommend that HLA-DQ2/8 typing should not be used routinely in the initial diagnosis of CD.
HLA-DQ2/8 testing is indicated in the following scenarios (29):
Suspected CD:

- In patients who are already following a gluten-free diet (GFD) before diagnosis has been established, with disappearance of symptoms, mostly normalised duodenal histology ( ) and negative coeliac serology; in this situation, a definite diagnosis of CD is impossible without a gluten challenge test. However, HLA-DQ2/8 typing, if negative, is useful for ruling out coeliac disease.
- In the evaluation of patients with CD and persistent symptoms, particularly when reassessing the accuracy of the original diagnosis.
- When there is a discrepancy between serology and biopsy, or when biopsy changes are mild in the presence of low-titre positive serology.
- To rule out coeliac disease in the evaluation of patients with disorders suspected to be related to gluten/wheat ingestion.

Screening of groups at risk of developing CD:

- Children (first-degree relatives of patients with coeliac disease).
- The HLA-DQ2/8 test is useful in individuals with IgA deficiency, in patients with chromosomal abnormalities associated with an increased risk of CD (e.g. Down syndrome, Turner syndrome, Williams syndrome) and in those with Hashimoto's thyroiditis or type 1 diabetes mellitus (T1DM). In these groups, the absence of HLA genetic risk allows the need for further serological testing to be ruled out.

5.4 Gluten challenge test in the diagnosis of CD in adults

A gluten challenge test is necessary if a patient with suspected CD has reduced or eliminated gluten from their diet prior to appropriate diagnostic evaluation, as this may have led to false negative serological and histological results. Re-

sponses to the challenge vary considerably; a minimum intake of 3 g/day of gluten for 6 weeks represents a compromise between diagnostic accuracy and symptom tolerability. The endpoint of the challenge test is duodenal histology, while symptoms and serology may provide additional diagnostic support (30, 31). Figure 3 summarises the approach to diagnosing CD in adults using gluten challenge tests.

6. Conclusions, limitations of the guidelines and future perspectives

Important knowledge gaps remain, including the diagnosis of complex subgroups, the validation of non-biopsy approaches, and the clinical significance of Marsh III subclassifications. Further prospective studies are needed to improve risk stratification, personalisation of care, and allocation of healthcare resources, with a focus on resource-limited settings (1).

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Update on nut allergy

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1. Introduction

Nut allergy is a significant public health issue, as it is a potentially life-threatening condition and, if not properly treated, persists in most cases throughout life (1–3). It is responsible for an estimated 18% to 40% of deaths related to food anaphylaxis (1, 4, 5). Unlike other food allergies, the probability of spontaneous resolution of nut allergy is extremely low, with rates below 10% in most longitudinal studies (3, 6).

The chronic nature of the condition entails a significant clinical and psychosocial burden: the constant risk of possible severe reactions following accidental exposure leads to a marked reduction in quality of life with associated severe dietary restrictions involving not only the patient but the entire family (7, 8).

2. Epidemiology

The global prevalence of nut allergy in the general population varies widely, with estimates ranging from 0.05% to 4.9% (9). Epidemiological data indicate a significant increase in recent decades, particularly in the paediatric population. In the United States, for example, the self-reported prevalence of nut allergy in children increased from 0.2% in 1997 to 1.1% in 2008 (10, 11).

A crucial aspect is the high variability of estimates depending on the diagnostic criteria adopted. In Europe, the self-reported prevalence of hazelnut allergy reaches about 4.0%, while the prevalence confirmed by oral food challenge (OFC), considered the gold standard for diagnosis, drops dramatically to 0.04% (9).

There are also marked geographical differences, influenced by local eating habits and environmental exposure. Hazelnuts are the main allergen in continental European countries, often in association with cross-reactivity with birch pollen (9). In the United States, walnuts and cashews are the most frequently involved nuts, while in the United Kingdom, Brazil nut allergy is more common (12). In Australia and New Zealand, cashews are the predominant allergen, with a prevalence of up to 3% in 6-year-old children (13).

In Italy, nut allergy ranks second as a cause of food anaphylaxis (after milk) and develops with a peak onset at 36 months (2-5 years) (10, 11).

Recent data from the European Anaphylaxis Registry have shown that cashews are an emerging allergen of growing clinical relevance, currently recognised as the leading cause of food-induced anaphylaxis in the paediatric population (14).

Another important epidemiological factor is the tendency for polysensitisation to increase with age. Specifically, allergy to multiple tree nuts increases from 2% in children under two years of age to 47% at age 14, likely as a result of cumulative exposure over time (15).

3. Taxonomy, co-allergy and cross-sensitisation

From a botanical point of view, nuts are defined as dry, hard, indehiscent fruits that grow on trees and do not open spontaneously to release their seeds, as in the case of chestnuts, hazelnuts and acorns (16). In common parlance, however, the term is used more broadly to refer to a variety of edible seeds derived from drupe-type fruits, such as walnuts, almonds and pistachios (16). The main types of nuts consumed in Europe in-

ABSTRACT

Keywords
• Peanut • nuts • OFC (oral food challenge)
• *Pollen-Food Allergy Syndrome* (PFAS) • Lipid Transfer Protein LTP

Nut allergy is an IgE-mediated allergic condition that is steadily increasing in prevalence, characterised by a low probability of spontaneous resolution and a significant clinical and psychological impact. It is one of the main causes of food anaphylaxis in children and shows wide epidemiological variations related to geographical and diagnostic factors. Clinical manifestations range from mild oral symptoms to severe systemic reactions, especially in cases of sensitisation to storage proteins, molecules that are stable to heat and digestion. Diagnosis requires an integrated approach based on accurate medical history, skin tests, specific IgE and molecular diagnostics, with possible recourse to oral provocation testing. The allergenic component allows individual risk to be defined and management to be guided. Treatment is based on avoiding the responsible food and using self-injectable adrenalin, while oral immunotherapies and biologics such as omalizumab are promising emerging options for improving safety and quality of life.

clude almonds, hazelnuts, walnuts, pecans, cashews, pistachios, Brazil nuts and macadamia nuts (2, 9, 12).

It is essential to distinguish these foods from peanuts, which are legumes and grow underground but, despite this taxonomic distinction, are commonly considered together with nuts due to their allergenic characteristics and clinical risk profile (16). The botanical relationships are directly reflected in the similarity of allergenic protein sequences, which partly explains the clinically relevant cross-reactivity phenomena (1).

In fact, cross-reactivity is the end result of a complex interaction between the molecular structure of allergens, botanical phylogenetic relationships and IgE-mediated effector mechanisms (12).

A preliminary and crucial element in understanding these mechanisms is the conceptual distinction between cross-sensitisation and clinical cross-reactivity (co-allergy). Cross-sensitisation is defined by the presence of specific IgE or positive skin tests to related food s, in the absence of clinical manifestations upon ingestion. In contrast, co-allergy implies a reproducible symptomatic response after oral exposure (1).

Although co-sensitisation rates are extremely high, ranging from 60.6% to 96.7%, clinically confirmed co-allergy is significantly less frequent, with an estimated prevalence of between 12% and 60.7% (8, 10, 18, 19).

From a mechanistic point of view, cross-reactivity is strongly driven by phylogenetic relationships between different plant species. Nuts belonging to the same botanical family share high sequence identity and three-dimensional conservation of major allergens, creating the molecular conditions for the recognition of shared epitopes by IgE (16). The main families involved include:

- *Juglandaceae*: including walnuts and pecans, which have up to 95% sequence identity in 11S globulins (Jug r 4 and Car i 4) and approximately 88% in 2S albumins (Jug r 1 and Car i 1), explaining the high probability of clinical co-allergy (1, 20, 21).
- *Anacardiaceae*: including cashew and pistachio, characterised by 79% homology between vicilins (Ana o 1 and Pis v 3), an association so close that it is commonly referred to as 'pistachio–cashew nut allergic syndrome' (20–22).
- *Betulaceae*: including hazelnuts, whose allergy is frequently secondary to cross-reactivity with birch pollen proteins (homologues of Bet v 1) (8).

The most severe systemic reactions are mainly mediated by seed storage proteins, in particular 2S albumins, 7S globulins (vicilins) and 11S globulins (legumins), characterised by high thermal stability and resistance to enzymatic digestion, which allows them to pass through the gastrointestinal tract in an immunologically active form (8, 9).

In addition to 'primary' cross-reactiv-

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ity, mediated by homologous storage proteins, there are forms of secondary cross-reactivity, supported by pan-allergens widely distributed throughout the plant kingdom. Among these, the following play a central role:

- PR-10 proteins (Cor a 1 in hazelnuts, Jug r 5 in walnuts and Ara h 8 in peanuts), structurally homologous to Bet v 1 in birch pollen (23); primary sensitisation typically occurs through inhalation, with subsequent clinical expression of Pollen-Food Allergy Syndrome (PFAS). Unlike storage proteins, these molecules are heat-labile and susceptible to digestion, which is why clinical manifestations are often limited to the oral cavity, although systemic reactions have been reported in adults (1).

- Non-specific lipid transfer proteins (nsLTPs) (Cor a 8, Jug r 3, Ara h 9), which are particularly relevant in Mediterranean areas, are more heat-stable and more resistant to proteolytic digestion than other pan-allergens and, as a result, can induce severe and systemic clinical reactions (1).

A key aspect of cross-reactivity mechanisms is the fact that not all cross-reactive IgE are functionally relevant. The onset of symptoms requires the allergen to be able to effectively cross-link two or more adjacent IgE molecules on the surface of mast cells and basophils, leading to cell degranulation and the release of pro-inflammatory mediators such as histamine, leukotrienes and prostaglandins. When the IgE-allergen binding is of low affinity, or the epitope does not allow adequate cross-linking, the patient remains in a clinically silent state of sensitisation, despite positive allergy tests.

4. Clinical aspects

IgE-mediated clinical manifestations to nuts present a wide spectrum of severity, ranging from mild and localised symptoms, such as itching and oropharyngeal discomfort, to rapidly evolving systemic conditions characterised by respiratory compromise and cardiovascular collapse, typically occurring within minutes of exposure (3).

From a clinical point of view, nut allergy can be characterised by different phenotypic patterns based on the sensitisation of individuals to different molecular allergens contained in nuts, their biochemical nature and structural stability (Fig. 2).

The primary form of nut allergy is characterised by direct sensitisation to storage proteins, such as Ana or 3, Cor a 14, Jug r 1, Ana o 1, Jug r 2, Cor a 9 and Jug r 4, highly thermostable molecules resistant to proteolytic digestion, capable of passing through the gastrointestinal tract in an immunologically intact form and inducing a severe systemic response (2, 6, 8). In this context, clinical studies have shown that paediatric patients can experience reactions upon their first known exposure to the food, and that monosensitisation to specific components, such as Ana or 3 (from cashew nuts) or Cor a 14 (from hazelnuts), is strongly associated with a high risk of an r severe cardiovascular and respiratory symptoms, requiring a strict elimination diet and constant availability of self-injectable adrenalin (3, 8, 24). In this context, clinical manifestations can range from isolated skin involvement (urticaria, angioedema), respiratory involvement (bronchospasm, cough, dyspnoea, throat tightness) and gastrointestinal involvement (vomiting, abdominal pain) to potentially fatal anaphylaxis (20-50% of paediatric patients) (25).

PFAS, on the other hand, is a secondary allergic reaction that develops in individuals who are primarily sensitised to environmental pollens, particularly birch pollen, and is mediated by PR-10 proteins and profilins that are structurally homologous to the major allergen Bet v 1, such as Cor a 1, Jug r 5 and Cor a 2.1 These allergens, being thermolabile and easily degradable by digestive enzymes, cause symptoms limited to the oral cavity and pharynx in most cases, explaining the discrepancy observed between the high prevalence of self-reported allergy and the low frequency of clinically confirmed allergy by oral provocation testing, especially in areas with high birch endemicity.22,23 PFAS is more common than primary nut and peanut allergy and increases with patient age (26).

Finally, another clinical phenotype is represented by LTP syndrome, which is more common in Mediterranean regions and characterised by sensitisation to non-specific lipid transfer proteins, such as Cor a 8 and Jug r 3, which are

Figure 1 Taxonomic classification of nuts and nut products

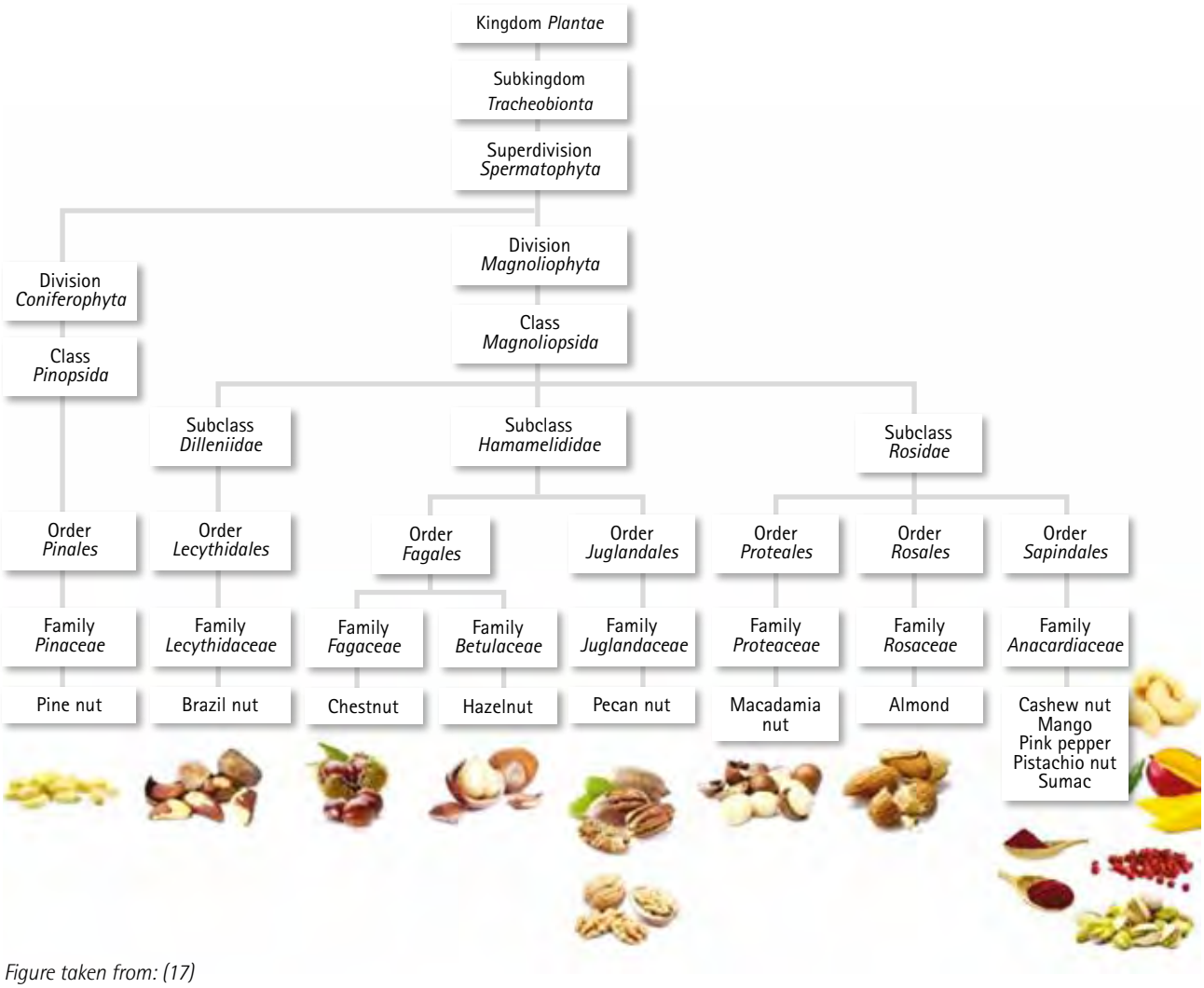
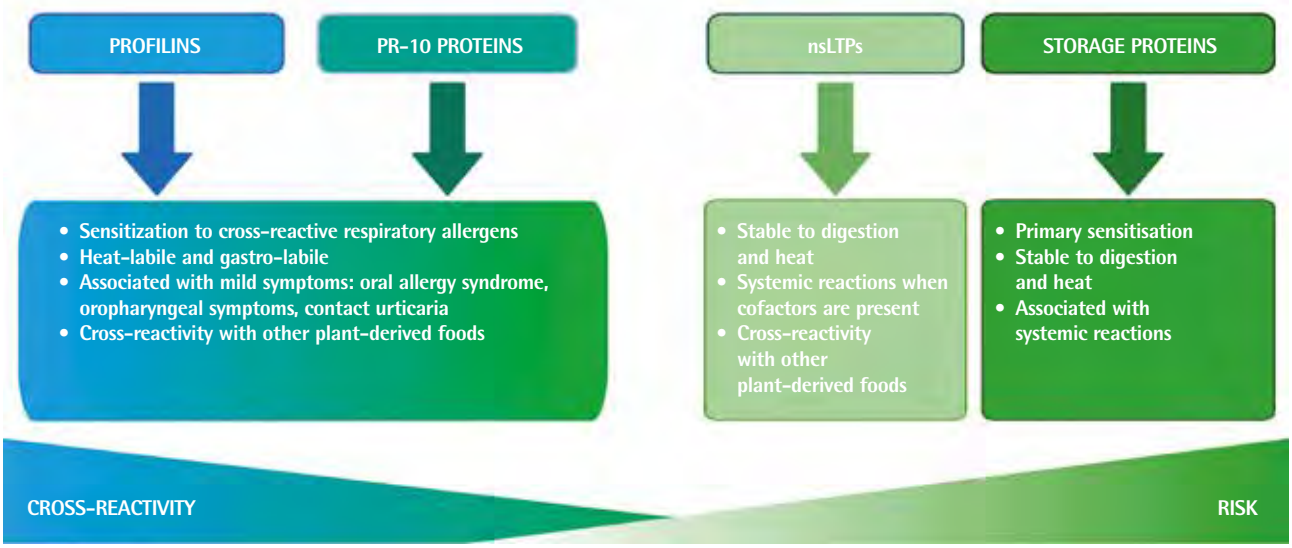


Figure taken from: (17)

small molecules but highly stable to heat and digestion. In these patients, the primary sensitiser is often Pru p 3, the LTP of peaches, which can cause cross-reactivity with nuts, even in the absence of a concomitant pollen allergy (8, 9, 16). Clinically, these patients may exhibit a wide variety of clinical pictures: from oral allergy syndrome to anaphylaxis. A distinctive feature is the possible dependence of symptoms on cofactors (physical exercise, non-steroidal anti-inflammatory drugs and alcohol) that can increase the severity or likelihood of an allergic reaction (27).

Figure 2 Severity grading and characteristics of the different classes of proteins contained in nuts



5. Diagnosis

The diagnosis of nut allergy is complex and gradual, based on the critical integration of clinical history, skin tests, serological determinations of specific IgE (to the whole food and its molecules) and, when necessary, oral provocation tests.

The medical history is the first fundamental step that guides the rest of the diagnostic process. The clinical history must investigate the symptoms, the timing of onset in relation to ingestion, the amount of food consumed, the presence of any contributing factors, the repeatability of reactions over time and the presence of allergic comorbidities, including rhinitis, asthma or atopic dermatitis.

The anamnestic data is then confirmed or not, and the type of allergy is characterised through in vivo and in vitro tests.

Skin prick tests (SPTs) are a first-level test, considered positive when the diameter of the wheal is ≥3 mm. However, the predictive ability of specific cut-offs varies significantly between studies and between different types of nuts.

In some studies, a wheal ≥8 mm has been associated with a high probability of clinical allergy to walnuts, hazelnuts and cashews, with positive predictive values above 95%. In other studies, for example on hazelnuts, the same cut-off showed a positive predictive value of only 74%, requiring a diameter ≥17 mm to achieve 100% diagnostic certainty. Conversely, for Brazil nuts, highly predictive values have been reported even with wheals ≥6 mm (28–30).

The use of prick-by-prick with fresh food can increase diagnostic accuracy compared to commercial extracts, which may be deficient in labile allergens or lipid proteins such as oleosins (30).

The determination of specific IgE (sIgE) to whole extracts, with a standard cut-off of ≥0.35 kU/L, is highly sensitive for identifying sensitisation but has limited specificity, with a high frequency of false positives (3). To predict clinical reactivity with high certainty, much higher cut-offs and highly variable c s between different foods are required, such as values ≥15–18.5 kU/L for walnuts, highly discordant thresholds for cashews (from 8 to over 100 kU/L in different studies) and relatively low levels for Brazil nuts,

for which a positive predictive value of 100% has been reported at ≥3.5 kU/L (28–31).

In this context, molecular diagnostics (CRD) represents a crucial advance, allowing for more accurate risk stratification through the measurement of IgE to individual allergenic components.

Sensitisation to Ana or 3, cashew 2S albumin, has been shown to be the most accurate marker for predicting clinical allergy to cashew (96% sensitivity and 94% specificity) and pistachio, with high accuracy even at low concentrations and allowing effective discrimination between tolerant and allergic individuals (Table 1) (7).

Similarly, positivity for Cor a 14 and Cor a 9 in hazelnuts identifies individuals with primary allergy to hazelnuts and at risk of severe systemic reactions, with a high negative predictive value that allows primary allergy to be reliably ruled out in the case of negativity, although the positive predictive value may be limited in some paediatric cohorts (28, 30, 32, 33).

For walnuts, Jug r 1 has higher values in allergic children than in tolerant children and is a better predictor than the complete extract, while Jug r 4 plays a key role in identifying patients with combined walnut-pecan allergy. In addition, patients sensitised to walnut LTP (Jug r 3) may also react to LTPs from other nuts (7, 8).

For peanuts, the severity of the reaction is related to the number of sensitisations to storage proteins (Ara h 1, 2, 3, 6). Ara h 2 and Ara h 6 are the most relevant markers of primary peanut allergy; of

Table 1 Cutoffs divided by food type for SPT and sIgE values

Food	Cutoffs for skin prick tests	Cutoffs for IgE
Hazelnut	≥ 8-17 mm: 74-100% PPV >5 mm: sensitivity 82% specificity 78%	≥ 0.7-15 kU/L: 57-92% PPV 2.34 kU/L: sensitivity 79%, specificity 62%
Walnut	≥ 8 mm: 95% PPV >3 mm: sensitivity 86% specificity 42% PPV 59% NVP 76%	5.07-18.5 kU/L 95-99% PPV 2.50 kU/L sensitivity 67% specificity 60% PPV 62% NVP 66% 2.8 kU/L: sensitivity 87% specificity 82%
Pecan	≥ 7 mm 75% PPV	/
Cashew	>5 mm: sensitivity 93% specificity 92% ≥ 8 mm: 95% PPV >10-12 mm: 95% PPV	≥ 8-14.9 kU/L: 95% PPV 1.1 kU/l: sensitivity 94% specificity 97%
Brazil nut	≥ 6 mm: PPV 100% ≥ 9 mm: accuracy >= 95%	≥3.5 kU/L: 100% PPV
Pinenut	>7 mm: sensitivity 28% specificity 100% PPV 100% NPV 79%	>0.60 kU/L: sensitivity 56% specificity 68% PPV 36% NPV 83%
Almond	/	0.8 kUA/L e ≥ 7,6 kUA/L: sensitivity and specificity 90%
Pistachio	/	≥ 88 kU/L: 90% accuracy

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Table 2 Classification of currently available and measurable protein classes

Source	Heat- and digestion-stable allergens				Heat- and digestion-labile allergens	
	11S globulins	7S globulins	2S globulins	LTP	PR-10	Profilins
Hazelnut *Corylus avellana*	**Cor a 9 ****	Cor a 11	**Cor a 14***	**Cor a 14***	Cor a 1**	Cor a 2*
Almond *Prunus dulcis*	Pru du 6	-	-	Pru du 3	-	Pru du 4
Cashew nut *Anacardium occidentale*	**Ana o 2****	Ana o 1	**Ana o 3***	**Ana o 3***	-	-
Pistachio nut *Pistacia vera*	Pis v 2	Pis v 3	Pis v 1	Pis v 1	-	-
Walnut *Juglans regia*	Jug r 4	**Jug r 2****	**Jug r 1*****	**Jug r 3****	-	-
Pecan nut *Carya illinoinensis*	Car i 2	-	Car i 1	-	-	-
Pecan nut *Carya illinoinensis*	Car a 2		**Ber e 2****	**Ber e 1****	-	-
Pine nut *Pinus pinea*	**Pin p 1****	-	-	Pin p 1**	Coc n 1*	Coc n 5
Coconut *Cocos nucifera*	Coc n 4	Coc n 2	-	-	-	Coc n 5

In bold: available commercially (* ISAC, ** ImmunoCAP)

Figure adapted from: (48)

these, Ara h2 is the most specific, while Ara h6 contributes to improving diagnostic accuracy, as studies have shown that in patients with a history of allergic reaction to peanuts, in the absence of sensitisation to Ara 1,2,3, IgE to Ara h6 may be present (30, 31, 34, 35).

Overall, the molecular characterisation of sensitisation is not merely a diagnostic exercise, but an essential tool for risk stratification, prognosis and personalised management of patients with nut allergies (Fig. 3).

In selected situations, especially in complex or discordant cases, the Basophil Activation Test (BAT) can be used to distinguish between asymptomatic IgE sensitisation and clinically relevant al-

lergy by evaluating the ex vivo cellular response to allergen exposure. The main clinical benefit of the BAT is the reduction in the use of oral food challenge (OFC) tests, which are high-risk and time-consuming procedures: the use of the BAT in a stepwise diagnostic algorithm allows up to 75% of positive challenge tests to be avoided, while maintaining a diagnostic accuracy of 96-100% (36-38).

In cases where clinical data and allergy tests are discordant or inconclusive, OFC in a protected environment remains the diagnostic gold standard, allowing the clinical relevance of sensitisation to be confirmed or ruled out with certainty. According to PRACTALL recommendations, the test is conducted with incremental administrations every 20–30 minutes and interrupted based on standardised safety criteria, often supported by a 'traffic light' system for evaluating reactions. OFC must be performed in a specialist setting, with experienced personnel and equipment for managing severe allergic reactions, including anaphylaxis.

6. Treatment overview: elimination diet vs specific immunotherapy

The treatment of nut allergy is currently based on a combination of avoidance strategies, management of accidental reactions and, in selected contexts, interventions to modulate the immune response (2, 39). The standard of care remains strict avoidance of the responsible food, combined with the availability of emergency therapy for the treatment of acute reactions (39). Historically, this approach has resulted in 'blanket avoidance', i.e. the indiscriminate exclusion of all nuts from the diet; However, more recent evidence and the use of advanced diagnostic tools have gradually shifted management towards selective consumption of individual fruits, based on individual clinical tolerance demonstrated through appropriate diagnostic tests and, when indicated, oral challenge tests in a protected environment (7, 8, 12, 16, 26, 30).

The elimination diet simplifies the daily management of allergies and reduces the immediate risk of reactions linked to cross-contamination or misidentification of foods by the patient or their family. However, this approach also has significant disadvantages, including marked dietary restriction, a negative impact on quality of life and increased anxiety in patients and caregivers due to the possibility of unpredictable accidental reactions (2, 3, 7). In children, prolonged elimination can also lead to nutritional risks, interfere with growth and promote the development of a true clinical allergy to previously tolerated fruits following a period of complete avoidance (2).

Oral immunotherapy (OIT) is currently the most studied desensitisation approach with the best results in nut allergy. It consists of the daily administration of progressively increasing doses of the allergen, with the aim of increasing the reaction threshold and protecting the patient from accidental exposure (2, 3). Clinical studies have reported high success rates, particularly for walnuts and cashews. An additional advantage is the phenomenon of cross-desensitisation, whereby treatment for a particular fruit can also confer protection against botanically related fruits (39–42). However, adverse events can occur during OIT, sometimes requiring the use of adrenaline during the dose escalation phase, and the food must continue to be consumed at home to maintain desensitisation. In addition, there are reports of possible (albeit very rare) cases of gastrointestinal complications, including eosinophilic oesophagitis or other forms of eosinophilic inflammation induced by immunotherapy (2, 8).

Alternative approaches, such as sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT), are attracting growing interest. SLIT has a more favourable safety profile, with mainly local side effects affecting the oral cavity, but it is less effective than OIT and data are currently limited mainly to certain forms of allergy, such as hazelnut allergy and LTP syndrome (43). EPIT, based on the transcutaneous application of the allergen via patches, offers an additional option with a good safety profile, but with generally more modest efficacy and insufficient evidence for routine use in nuts (44, 45).

In this therapeutic scenario, omalizumab, an anti-IgE monoclonal antibody, has taken on an increasingly important role. Recently approved by the Food and Drug Association (FDA) for use in children over one year of age as a monotherapy to reduce the risk of allergic reactions from accidental exposure to multiple foods (46), omalizumab is

particularly interesting as an adjuvant to OIT, as it allows for a more rapid escalation of doses and a significant reduction in the frequency and severity of adverse reactions during the initial phase of treatment (2, 8). The OUTMATCH study showed that a significant number of patients treated with omalizumab are able to tolerate significantly higher amounts of allergenic protein than those typically involved in accidental exposure, making this strategy a promising option for improving the safety and efficacy of nut allergy treatment (47).

7. Conclusion

In conclusion, nut allergy is an allergic disease whose prevalence is increasing. This epidemiological growth has been accompanied over time by increasingly accurate studies of diagnostic and therapeutic methods. In particular, when used in a targeted manner based on anamnestic data, CRM allows the patient to be phenotyped and thus distinguishes those at high risk of potentially fatal anaphylaxis from those with mild and localised manifestations, thereby guiding therapeutic decisions appropriate to each individual patient.

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Comorbidity of histamine intolerance in a case of polyvalent allergy

Comorbidity of Histamine Intolerance and Polyvalent Allergy: A case Report and literature review

Wojas O. et al. Healthcare 2025, 13, 94.
https://doi.org/10.3390/healthcare13020094

The importance of histamine intolerance (HIS) is well known, but the lack of diagnostic protocols and specific therapies makes it difficult to manage. Endogenous histamine is present in mast cells and basophils, while exogenous histamine is present in certain foods, especially in fish of the Scombridae family (mackerel, tuna); Symptoms of histamine intolerance can occur when histamine concentrations in the body exceed its ability to break it down. This intolerance can result from low activity of the enzyme responsible for its degradation (diamine oxidase, DAO), a condition present in some people for genetic reasons (e.g. SNP on the coding gene), inflammation of the intestine (where DAO is most expressed) or taking drugs that compromise the expression or functioning of DAO and stimulate the release of endogenous HIS.

The case reported by Wojas and colleagues concerns a 30-year-old man with a clinical picture characterised by allergic rhinitis and asthma previously diagnosed by SPT; the patient was subsequently subjected to specific immunotherapy for grasses, birch, *D. farinae* and *D. pteronyssinus*, to which he reacted positively, with a 30% reduction in symptoms. Nevertheless, the subject experienced reactions such as facial erythema, urticaria, pruritus, abdominal pain, and tachycardia after meals containing various types of food. The symptoms usually resolved with a

Figure 1 — Histamine-releasing foods

Image source: Dr Valentina Cuomo, 'Histamine intolerance: foods to avoid and symptoms', SempreFarmacia.it

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double dose of antihistamines; the patient was also prescribed epinephrine via auto-injector. Following the patient's report of difficulty swallowing large or hard pieces of food, the subject underwent gastroscopic observation and oesophageal biopsy, which led to the hypothesis of eosinophilic oesophagitis.
The patient was then prescribed an exclusion diet for milk, eggs, wheat, soy, fish and seafood, together with pantoprazole (proton pump inhibitor) at a dose of 40 mg/day, with minimal improvement in his condition. A subsequent complete physical examination revealed no noteworthy pathological signs other than mild hypertrophy of the inferior turbinates; the patient also confessed that he had abandoned the prescribed diet due to difficulties in adhering to it.
The patient therefore underwent a DAO enzyme activity test: an activity of 7.5 U/mL, compared to a reference range of 14-33 U/mL, confirmed the reduced activity of the enzyme, and a normal level of tryptase activity (3.78 ng/mL, with a reference range of < 10 ng/mL). A spirometry test ruled out bronchial obstruction.
The symptoms of eosinophilic oesophagitis led clinicians to perform an oesophagogastroduodenoscopy with oesophageal biopsy: the examination revealed narrowing of the oesophagus along its entire length, lack of peristalsis, slightly enlarged, friable mucosa with local ruptures following insufflation, and an irregular Z line. A colonoscopy was also performed to investigate the possibility of other inflammatory conditions or gastrointestinal tract disorders (coeliac disease, lactose intolerance, and Crohn's disease), with negative results.
The evidence thus gathered led to the confirmation of the diagnosis of eosinophilic oesophagitis and histamine intolerance. The patient was therefore prescribed a new diet excluding various foods such as milk, eggs, soy, wheat, fish and seafood, cheese, alcohol, various cold cuts, spinach, aubergines, avocados, tomatoes, ketchup, chocolate, cucumbers and yeast. He was also prescribed budesonide (1 mg b.i.d.) for 12 weeks and a DAO preparation (DAOSiN, one tablet t.i.d.) before meals. After one month of therapy, the patient no longer required epinephrine and his symptoms of histamine intolerance had almost resolved; however, the patient had difficulty following the prescribed diet and resumed alcohol consumption. A second endoscopic examination also revealed worsening eosinophilic oesophagitis. The patient was finally referred to a specialist clinical centre to undergo treatment with Dupilumab, while continuing DAO supplementation and pre-existing drug therapy.
In this case report, the authors demonstrated the possible intrinsic complications associated with the coexistence of histamine intolerance and IgE-dependent allergies, due to the possibility of overlapping symptoms of the two different clinical conditions.
In general, the coexistence of allergic and non-allergic comorbidities makes both diagnosis and treatment particularly difficult, given the absence of widely approved therapeutic standards. The authors conclude by expressing their hope that their experience will be useful to anyone faced with similar cases.

Acute pancreatitis following food-induced anaphylaxis

A Case Report of Acute Pancreatitis in Food-Induced Anaphylaxis

Wiese J et al. Cureus. 7 October 2024;16(10):e71017. doi: 10.7759/cureus.71017. PMID: 39525265; PMCID: PMC11548797.

In *the case* report described here, Wiese et al. emphasise the link between certain health problems whose origin can be associated with the onset of an anaphylactic phenomenon.
This is the case of a 54-year-old woman who developed acute pancreatitis (AP) following food-induced anaphylaxis. The woman was admitted to hospital as an emergency following the consumption of a meal rich in meat and cheese (*'steak alfredo'*); immediately after the meal, the patient felt nauseous, followed by vomiting and the onset of symptoms such as itching, hives, dyspnoea, chest tightness, and increased bowel movements. The patient's medical history included asthma, hypothyroidism, and allergies to oxycodone-acetaminophen, latex, milk, azithromycin, and certain contrast agents; however, the woman reported no previous cases of anaphylaxis or recent changes in her medications.
Upon admission, initial treatment consisted of one litre of Rin-

ger's lactate, intramuscular epinephrine, diphenhydramine, and methylprednisone; the woman's vital signs quickly improved, with stabilisation of blood pressure, heart rate, and respiratory rate. The patient received an additional litre of Ringer's lactate and was kept under observation.

About twelve hours after the anaphylactic event, the patient experienced severe abdominal pain; an ultrasound scan ruled out the possibility of kidney stones, while a CT scan revealed fatty thickening and oedema in the pancreatic area; together with evidence of significantly elevated lipase levels (558 units/L), the patient was diagnosed with acute pancreatitis and therefore underwent therapy based on analgesics and continuous intravenous Ringer's lactate at 1.5 ml/kg/h for 24 hours; the treatment prevented the development of complications of the clinical picture, with improvement in abdominal pain. No further therapeutic or diagnostic interventions were necessary, and after five days the patient was discharged from the clinic.

The authors' suspicion of a possible correlation between pancreatitis and allergic phenomena is based on the patient's overall condition, *imaging* results, and response to treatment. In general, the authors point out that it is known that numerous pro-inflammatory cells (neutrophils, eosinophils, h r mast cells, etc.) play a crucial role in promoting specific allergic responses following food intake in cases of pancreatitis (e.g., inflammation of the ampulla of Vater leading to bile reflux into the pancreatic ducts; vasodilation and increased vascular permeability with consequent hypotension and reduced blood flow in the pancreas) play a crucial role in specifically promoting allergic responses following food intake. Possible correlations between the drugs taken by the patient and the development of AP were also ruled out, based on known evidence (e.g. the potential role of GLP-1 RA on cell hyperplasia and the genesis of inflammatory environments).

The authors conclude by emphasising the importance of also considering possible allergic factors in the onset of seemingly unrelated pathological conditions, however counterintuitive this may appear. The management of AP requires adequate risk stratification and a multidisciplinary approach, which in cases such as this could be developed from what the patient brings to the table.

Fish allergy: fish allergenicity ladder and predictive role of parvalbumin epitopes in the Chinese population

Fish Allergenicity Ladder and Parvalbumin Epitopes for Predicting Clinical Cross-Reactivity and Reintroduction in Chinese Population.

Wai CYY et al.
Allergy 2025;80(10):2810-2823

Fish are one of the most important food allergens, and individuals who are allergic to one type of fish are often advised to avoid all types of fish, regardless of species. This is based on IgE positivity to the major allergen present in fish, namely parvalbumin (12-kDa sarcoplasmic calcium-binding protein). In reality, as previously observed by the authors of the article under review, there have been recent reports of patients with mono-allergy to a single type of fish, who are able to tolerate the ingestion of others. This makes the clinical management of patients with this allergy rather complex due to the considerable variety of edible fish species, whose sensitising effects may depend on various factors such as allergenicity (which, as will be seen, depends on the amount of parvalbumin present in them) and the different eating habits and cooking methods used in the population. As the authors have widely emphasised, a more accurate diagnosis of fish allergy would make it possible to identify patients at greater risk of adverse reactions, while at the same time avoiding the exclusion of fish species that less sensitive patients can tolerate from their diet. Therefore, with the aim of improving the diagnosis of this specific allergy, the authors have promoted a large-scale study taking into account clinical reactions and specific IgE levels observed in the serum of patients allergic to different fish species (tuna, salmon, cod, carp, catfish, halibut, herring, grouper and tilapia, as well as recombinant parvalbumin) and the correlation of these parameters with detectable levels of parvalbumin. In

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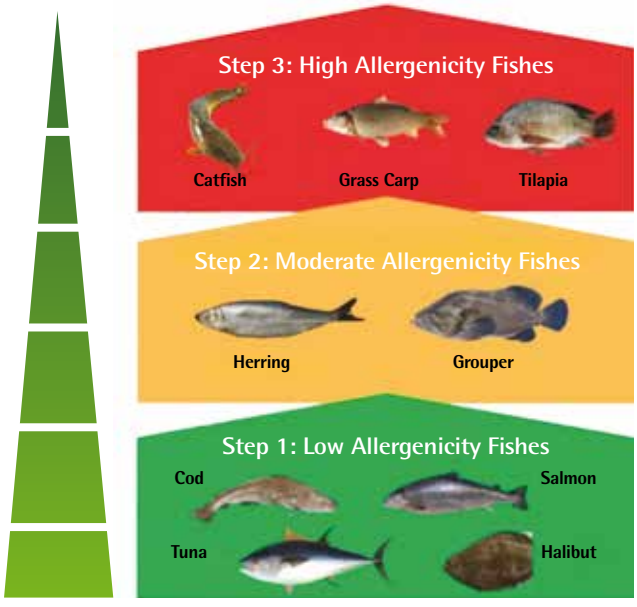
addition, the study was extended with the aim of identifying specific IgE-binding epitopes of parvalbumin, which are in some way predictive of a possible cross-reactivity phenomenon. To this end, 166 fish-allergic subjects were enrolled, recruited from five hospitals in Hong Kong on the basis of immediate allergic reactions after fish ingestion. They were then asked to complete a questionnaire indicating all the fish species in their diet, both those that had caused an allergic reaction and those that were tolerated without any symptoms. These patients then underwent a series of clinical tests to assess the level of specific IgE in their serum against the fish species under consideration, the intensity of the skin response to the prick test and the oral provocation test. At the same time, the parvalbumin content was determined in terms of both protein content and transcriptome, identifying parvalbumin homologous transcripts using an appropriate procedure. Based on the self-reported history of the enrolled patients and the distribution of IgE levels in their serum towards the above samples, 98 of the 166 patients tested positive for all fish extracts, unlike the others (68), who tested oligo- or mono-positive. A close correlation was then observed between IgE levels to fish extracts and those to recombinant parvalbumin, and above all that the amounts of parvalbumin determined in various fish by proteomic and transcriptomic analysis were correlated with greater allergenicity. Taking into account that parvalbumin is involved in muscle contraction, the authors observed that their findings were consistent with other reports according to which large migratory fish, in which dark muscle fibres are more developed due to continuous swimming activity, show significantly lower levels of parvalbumin than fish that, having much less intense swimming activity, have greater development of white muscle fibres and consequently higher levels of parvalbumin. Once all the data had been subjected to a very complex statistical analysis, the authors constructed an allergenicity scale for the various fish species considered. More precisely, starting from the lowest level of allergenic potential, we find: step 1 (tuna, halibut, salmon and cod); step 2 (herring and grouper); step 3 (catfish, carp and tilapia) (Figure 1).

Figure 1 Allergenicity scale of the fish species considered



The investigation was then extended to verify the possible existence, in parvalbumin, of specific IgE-binding epitopes capable of predicting clinical cross-reactivity, i.e. tolerance or allergic sensitisation to certain fish species. To this end, an epitope mapping approach was carried out on parvalbumin from four different fish species (salmon, cod, grouper and carp) using sera from individuals allergic to fish (n=11), partially tolerant individuals (n=12) or fully tolerant individuals (n=5), based on an oral provocation test. This identified an IgE-binding epitope (Epi c, 64–78) in the amino acid sequence of grouper parvalbumin that was specifically recognised by sera from subjects allergic to grouper and carp. At the same time, an IgE-binding epitope (Sal s β,119–33) was identified in salmon parvalbumin, which can be considered a biomarker capable of differentiating between individuals allergic to carp and grouper and those tolerant to salmon. The identification of these two epitopes is of great importance in terms of 'precision diagnosis' of fish allergy; being able to predict which patients with a specific allergy to fish in general are tolerant to certain fish species would allow them to be reintroduced into the diet, with beneficial effects especially in the case of salmon, which is particularly rich in

omega-3. The authors conclude their interesting contribution by emphasising that the data obtained need further confirmation in studies involving a more significant number of patients who are allergic or tolerant to fish, possibly on a multinational scale, given that their study was carried out on the Chinese population.

Are we sure that intestinal epithelial impairment is solely responsible for sensitisation to food allergens?

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

Asero R et al. Eur Ann Allergy Clin Immunol Vol 57, N.4, 147-153, 2025.

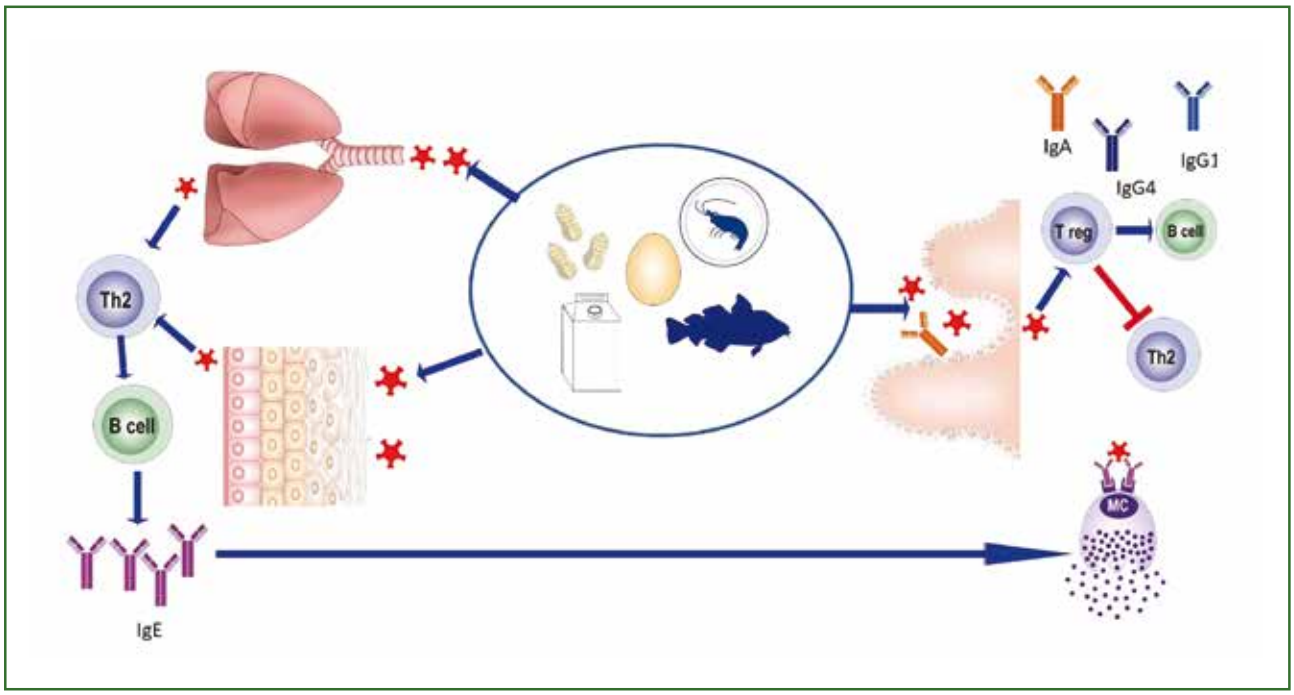
As is well known, epithelial barriers act as a protective shield against external agents such as pathogens, pollutants and allergens, and there is ample evidence that their impairment, particularly in the skin or respiratory tract, is associated with the development of allergic diseases such as asthma, rhinitis, atopic dermatitis and eosinophilic oesophagitis, as well as other chronic diseases. However, as the authors of the article point out, the role of the gastrointestinal epithelium in *food allergy* is not yet well-defined. They remind us that under normal conditions, the intestinal epithelium, by virtue of its structure, allows the absorption of nutrients and *food proteins*, but there is no clear evidence that its impairment is the main cause of food allergy, since the latter can also develop when the integrity of the gastrointestinal barrier remains intact. Furthermore, it is emphasised that contact between *food allergens* and the immune system following their intestinal absorption generally leads to the development of specific tolerance mediated by the induction of various immunological mechanisms, including the stimulation of regulatory T cells (Treg cells) and the production of specific IgA antibodies. The hypothesis that allergic sensitisation to milk and egg allergens, observed in infancy or early childhood, is attributable to immaturity of the intestinal tract is contradicted by the many cases in which these specific allergies appear at a later age, such as in children and adults.

The authors' reference to studies in animal models (mice in particular) in which primary allergic sensitisation to ovalbumin (one of the most clinically relevant allergens) can be induced subcutaneously or peritoneally, but rarely orally, and to reports in the literature, has led them to consider the hypothesis that 'food allergy/sensitisation' may also originate outside the intestinal tract and occur, for example, via the skin or respiratory tract. This observation is consistent with others that question traditional paradigms on food allergies sensitisation' may also originate outside the intestinal tract and occur, for example, via the skin or respiratory tract. This observation is consistent with others that challenge traditional paradigms on food allergy, while highlighting the complexity of the mechanisms that induce allergic sensitisation. To confirm this, the authors, drawing on the literature, cite a series of very particular and intriguing situations, including the following: LEAP study (*Learning Early About Peanut Allergy*). In this study, the authors observed that peanut allergy develops more frequently in Jewish children living in the UK (who avoid consuming peanuts in the early years of life) than in those living in Israel, who, on the contrary, introduce peanuts into their diet at a relatively early age. Hence, the claim that early introduction of peanuts into the diet reduces the risk of allergic sensitisation by modulating the immune response in a tolerogenic direction.

Other interesting examples concern cases in which primary sensitisation is not linked to the ingestion of food allergens but is caused by extra-intestinal exposure to homologous allergens present in other substances. One of these concerns the allergen galactose-alpha-1,3-galactose (alpha-Gal) oligosaccharide, discovered following cases of anaphylaxis after the first administration of Cetuximab (a drug consisting of a chimeric monoclonal antibody used in oncology), i.e. after ingestion of red meat. Both events are caused by primary sensitisation to alpha-Gal, which developed following bites from parasites such as *Ixodes ricinus*.

Other examples involve primary sensitisation caused by

Figure 1 — Primary exposure to food allergens



Primary exposure to food allergens ingested through the digestive tract leads to anergy, i.e. the production of IgG1, IgG4 and/or IgA antibodies. Exposure of the immune system to food allergens via the respiratory tract or damaged skin (as in patients with atopic dermatitis) leads to a Th2-type response and ultimately to the production of IgE antibodies, which then spread throughout the body. Subsequent ingestion of the same food allergens can potentially cause severe allergic reactions.

molecules present in pollen, which then extends to cross-reactive homologous molecules present in food (*pollen-food syndrome*). The allergen responsible for primary sensitisation is peamaclein, a minor allergen in cypress pollen belonging to the *Gibberellin-Regulated Proteins* (GRP) family, which cross-reacts with a homologous molecule found in peaches (Pru p 7) and other plant-derived foods. Another similar case known as *Mugwort-Celery-Spice Syndrome* is represented by defensins (specifically Art a 1, Amb a 4), molecules present in Asteraceae pollen responsible for primary allergic sensitisation that then extends to homologous molecules of food origin present in peanuts (Ara h 12 and 13) and celery (Api g 7).

The authors conclude by expressing their hope that future research will continue to explore the interaction between the gastrointestinal barrier, immunological tolerance and environmental factors in order to improve preventive and therapeutic strategies for patients with food allergies on a global scale.

Provide information, create a profession

Edited by **Franco Frati**
Specialist in Paediatrics, Allergology and Clinical Immunology
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Specific immunotherapy in paediatrics

Dr. Chiaretta Trincianti
Gaslini Institute, Genoa

Allergen-specific immunotherapy is currently the only treatment capable of permanently modifying the natural history of allergic diseases. It plays a particularly important role in paediatrics, as it reduces allergic symptoms and can also help prevent the development of asthma in children and adolescents with allergic rhinitis.

Specific immunotherapy for inhalant allergens is widely used in children with rhinitis and/or allergic asthma and can be administered subcutaneously (SCIT) or sublingually (SLIT). In paediatrics, SLIT is often chosen because it is easy to administer at home, less invasive and generally has a high safety profile.

Patient and family compliance is crucial to the effectiveness of the treatment, as immunotherapy requires regular and prolonged administration. It is therefore essential, when prescribing, to provide clear and complete information on the methods of administration and the characteristics of the drug, emphasising how therapeutic adherence and the child's motivation are crucial to the success of the immunotherapy programme. In this context, it is advisable to address the main critical issues related to the daily management of SLIT in advance, during the specialist visit.

Although sublingual immunotherapy has a well-documented safety profile, the prescribing doctor's willingness to engage in ongoing dialogue with parents and patients, including through remote contact, especially in the early stages of treatment, helps to consolidate the therapeutic alliance and contributes to improving adherence to therapy. In this scenario, the development of digital technologies and telemedicine tools can provide valuable support in the management and monitoring of patients undergoing desensitisation, enabling more timely and continuous care and facilitating access to clarification and clinical guidance.

Numerous scientific studies show that immunotherapy for inhalant allergens, when correctly prescribed and adequately monitored, can reduce the symptoms of rhinitis and allergic asthma, decrease the need for drug therapy and significantly improve the quality of life of allergy sufferers, with benefits that can persist for several years even after treatment has been discontinued.

ENG

Eosinophilic inflammation: clinical experience

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Eosinophilic inflammation is an inflammatory process characterised by tissue accumulation, activation and degranulation of eosinophils, effector cells of innate and adaptive immunity. This phenomenon is mainly supported by a Th2-type immune response, mediated by cytokines such as interleukin-5 (IL-5), essential for the maturation and survival of eosinophils, and IL-4 and IL-13, involved in tissue remodelling and allergic response (1, 2, 3).

During my clinical experience, while specialising at the Centre for Allergology and Clinical Immunology at the Monserrato University Hospital (CA), directed by Professor Stefano Del Giacco, I observed different forms of eosinophilic inflammation, especially in patients with eosinophilic asthma and EGPA (Eosinophilic Granulomatosis with Polyangiitis).

During clinical practice with patients suffering from eosinophilic asthma, we first carried out a complete assessment, collecting the clinical history and verifying the severity of the symptoms. We performed blood tests to count eosinophils, spirometry to assess lung function, FeNO and, when indicated, allergy tests. In these patients, it is customary to first perform skin prick tests and, if necessary, measure specific IgE levels, with the aim of assessing the possible indication for allergen-specific immunotherapy, which is essential in the management of asthma. In certain patients, ITS plays a crucial role as it not only treats the symptoms but also modifies the natural course of the disease (4).

The basic treatment consists of inhaled corticosteroids and bronchodilators; in more severe or unresponsive patients, we have introduced targeted biological therapies (Anti-IL-5, Anti-IL-5Rα, Anti-IL-4/IL-13, Anti-TSLP mAbs), carefully monitoring the clinical response. This approach has allowed us to personalise therapy and improve both symptom control and quality of life, significantly reducing inflammation and flare-ups.

In patients with EGPA, eosinophilic inflammation involves not only the respiratory tract but also small and medium-sized blood vessels, causing vasculitis and multi-organ damage. Clinically, these patients often present with bronchial asthma, marked peripheral eosinophilia, and systemic symptoms such as peripheral neuropathy and skin lesions. Management still requires systemic corticosteroids and, in severe cases, immunosuppressants, but today biological therapies are taking on a central role: in our patients treated with anti-IL-5 monoclonal antibodies, we have observed a marked reduction in eosinophilia, less need for systemic corticosteroids and an overall improvement in quality of life.

This experience has allowed me to understand how eosinophilic inflammation is a cross-cutting phenomenon that can manifest itself both in predominantly respiratory diseases, such as eosinophilic asthma, and in systemic and vasculitic forms, such as EGPA, and, above all, how targeted biological therapies are now a fundamental tool for modulating eosinophilic inflammation and personalising patient care, significantly improving their quality of life.

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