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Patologie dell'orecchio e immersione subacquea
Ear conditions and scuba diving
Patologías del oído e inmersión subacuática

Dieta vegana e allergie
Vegan diets and allergies
Dieta vegana y alergias

METTITI ALLA PROVA IN CUCINA

TEST YOURSELF IN THE KITCHEN

PONTE A PRUEBA EN LA COCINA

Allergia alimentare alla pesca
Food allergy to peach
Alergia alimentaria al melocotón

La memoria silenziosa dell'allergia
The silent memory of allergy
La memoria silenciosa de la alergia

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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**

Scuba diving, particularly recreational diving, is a fascinating activity and, thanks in part to technological advances in equipment that make it increasingly accessible, is attracting a growing number of enthusiasts.

In this issue of the Notiziario, Prof. di Donato's article—written prior to the recent news reports concerning five Italian divers who fell victim to a tragic diving accident in the Maldives— highlights the importance of adequate education and training for novice divers in order to prevent the risks associated with potential adverse events during a dive.

The author, after highlighting the risks to the auditory system – which, precisely because it is the organ most heavily stressed during this activity, is subject to a higher incidence of problems – went on to provide an overview of ear conditions associated with scuba diving. Particular attention was paid to barotrauma, ear damage caused by a failure to equalise or delayed equalisation of the ear cavity during changes in dive depth, which can permanently impair hearing when the inner ear is affected. The author then focused on methods of preventing barotrauma, with particular reference to the equalisation manoeuvres that every diver must learn to maintain normal Eustachian tube function. In this regard, the article concludes with interesting observations on allergic rhinitis, which, as it can compromise the aforementioned function due to chronic changes in the nasopharyngeal mucosa, requires those affected to undergo regular specialist check-ups and to avoid diving when the condition is in an acute phase.

Food allergies have a significant impact on the daily quality of life of those affected, as they must pay close attention to their dietary choices in order to prevent potentially dangerous reactions. This situation is further complicated for those who choose to follow a vegan diet. The authors of the second article (Dr. Villalta and Dr. Parrinello) therefore focus their attention on the possible implications from an allergological perspective that people who deliberately choose this dietary style may encounter. As is well known, a diet is defined as vegan when all animal-derived products are excluded in favour of plant-based substitutes, and we have already outlined the reasons behind this choice in the text accompanying the cover of this issue of the Notiziario. Many 'ready-to-eat' vegan products are industrially prepared and contain various ingredients, often making it difficult for people with allergies to identify the right product for them, partly because not all ingredients are subject to mandatory labelling and can therefore act as 'hidden allergens'. On the other hand, many of the plant-based foods (described in detail by the authors) that form the basis of a vegan diet are characterised by significant allergenic potential and therefore, in themselves, pose a greater risk of allergic sensitisation in individuals intending to follow this dietary approach. The authors conclude their article with a recommendation for these individuals: to carefully plan the foods to be included in their diet, ideally with the support of an expert nutritionist, to avoid any nutritional deficiencies, whilst also bearing in mind the potential allergic reactions associated with the consumption of certain types of plant-based foods. It should be noted that the authors have deliberately chosen not to consider any implications related to nickel allergy (found in many of the staple foods of a vegan diet) because the subject remains highly controversial.

The following article by Dr. Asero, whilst forming part of the overview of food allergies mentioned earlier, focuses on peach allergy.

As is well known, peaches, along with other fruits such as apples, apricots, plums, pears, cherries, strawberries, medlars… belong to the Rosaceae family; although it shares most of the general characteristics with the other members of this family, in the field of allergology, as the author points out, the peach is something of *a unique case*, representing, on the one hand, one of the most frequent causes

of allergic sensitisation (at least in Italy and Mediterranean countries) and, on the other, a crossroads for potential primary or secondary sensitisation, giving rise to various clinical presentations that are not easily interpreted in clinical practice. This variability depends mainly on the different chemical-physical/genetic characteristics of the individual allergenic components; a deeper understanding of the various components that trigger allergic symptoms can help establish a management plan for the condition, and the article details their specific characteristics. Some of these, due to structural homology with components present in pollen, may be responsible for *the* so-called *pollen-food syndrome* and the symptoms associated with it. Certainly, as the author points out, the *lipid transfer protein* (LTP, or Pru p 3) component—which is also present in plant foods botanically distant from the Rosaceae family (it acts as a defence mechanism against pest infestations)—is the one most frequently involved in primary sensitisation, representing one of the causes of food anaphylaxis, at least in Mediterranean countries. Given the importance of LTP as a potential allergen, the author suggests that, following a skin prick test with peach extract, a positive result should be followed by a molecular investigation to specifically determine whether or not it is relevant.

We conclude this double issue of the Notiziario with a highly intriguing article on the complex immunological mechanisms underlying the production of IgE antibodies. As is well known, this antibody isotype mediates allergic reactions, having the lowest serum concentration and the shortest half-life; despite this, levels of specific IgE in an allergic individual can persist for years or decades, regardless of re-exposure to the responsible allergen, representing a sort of immunological paradox. In other words, this means that avoiding the allergen is essential to reduce the risk of triggering symptoms, but does not necessarily lead to the disappearance of sensitisation. The author of the article (Dr. Perino), drawing on recent scientific findings, offers an interpretative framework for this aforementioned paradox. Until recently, this phenomenon was attributed to a periodic reactivation of IgE-producing plasma cells, resulting from recurrent antigenic stimulation even when not clearly demonstrable, all within a context of impaired regulatory circuit function, The author provides a detailed account of the experimental evidence suggesting the existence, at least in mouse models, of a persistent population of plasma cells (type 2 memory B cells) that are programmed to rapidly differentiate into specific IgE-producing plasma cells following contact with the allergen. These cells would constitute the *long-lived plasma cells* (LLPCs) capable of continuously producing IgE (IgE+ LLPCs), thereby contributing to the long-term maintenance of IgE-mediated humoral immunity without the need for repeated exposure to the antigen, as has already been demonstrated for the IgG and IgA antibody isotypes against pathogens. These cells are thought to reside preferentially in the bone marrow, distinguishing themselves from the *short-lived* IgE+ *plasma cell* component, which remains localised in peripheral lymphoid organs and subsequently undergoes rapid apoptosis, facilitated by the presence of a series of specific markers on their membrane. The existence in humans of type 2 memory cells and IgE+ LLPCs, although indirectly supported, nevertheless requires further biological evidence for precise confirmation. Of interest are the references to the potential effects of certain biologics and to a sequential therapeutic combination of biologics and allergen-specific immunotherapy on the two different populations. At present, as the author points out, these data are of conceptual relevance only; however, if confirmed, they would open up new therapeutic scenarios targeting not only the effects of IgE antibodies on the allergic response, but also those relating to the cellular sources of these antibodies.

I wish everyone a good read.

Ear conditions and scuba diving: understanding to prevent

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1. Introduction

There is no doubt that the auditory system is the one most affected by scuba diving and the one at greatest risk of accidents. The scientific literature, which is not particularly extensive on the subject, agrees that there is a high incidence of barotraumatic events affecting the middle ear following scuba diving (1) and free diving (2), but reports little or nothing regarding barotrauma of the inner ear, which is certainly less frequent but decidedly more serious, as it can permanently compromise the auditory perception of the affected ear (3). To understand the mechanisms that can lead a diver to suffer from ear barotrauma and how to prevent it, one must understand the fundamentals of the physics and pathophysiology of scuba diving and be familiar with the anatomy and physiology of the ear.

ABSTRACT

Keywords
• Ear barotrauma • Scuba diving • Middle ear • Inner ear • Equalisation • Eustachian tube • Hydrostatic pressure • Equalisation manoeuvres • Sensorineural hearing loss • Prevention

This article analyses ear conditions associated with scuba diving, with particular attention to barotrauma, which frequently affects the middle ear and, more rarely, the inner ear, but is potentially more serious. The physical principles underlying pressure changes (Boyle's law) and their impact on the auditory system are explained, highlighting how the greatest risks are concentrated in the first few metres of depth.
From a pathophysiological perspective, the ear requires effective pressure equalisation, made possible by the Eustachian tube, the proper functioning of which is essential to prevent damage. The article describes the main equalisation manoeuvres and emphasises the importance of performing them correctly and promptly.
Barotrauma is classified according to severity and occurs mainly during descent due to failure to equalise, but can also occur during ascent, with possible consequences for the inner ear such as vertigo and sensorineural hearing loss.
Finally, prevention strategies are highlighted, based on two pillars: adequate technical preparation and maintenance of Eustachian tube function, avoiding dives in the presence of respiratory tract conditions and resorting, if necessary, to therapeutic and rehabilitative support.

2. Notes on the physics and pathophysiology of scuba diving

Elements in nature can exist in a solid, liquid or gaseous state.

Gases have the distinctive property of being compressible, meaning that their volume varies in response to the pressure exerted upon them, as described by Boyle's and Mariotte's Law: "at constant temperature, the pressure and volume of a gas are inversely proportional – PV=K"; therefore, if the pressure of a given quantity of gas doubles, its volume is halved.

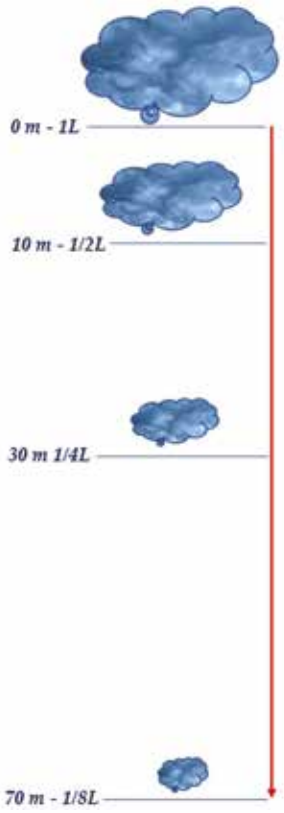
At sea level, atmospheric pressure is the pressure exerted by the mass of gases that make up the Earth's atmosphere and is equal to 1 atmosphere (1 ATA) or, expressed in other units of measurement, 1 kg/cm2, which is the weight of a 760 mm high column of mercury with a base of 1 cm² or that of a 10-metre column of water, again with a base of 1 cm². It is therefore clear that as one descends underwater, the pressure increases by 1 ATM every 10 metres; thus, following the progressive increase in pressure recorded as one descends, we find a pressure of 2 ATA at -10m, 3 ATA at -20m, 4 ATA at -30m and so on. Note that the progressive increase in hydrostatic pressure in the sea means that in the first 10 metres of depth, the ambient pressure doubles, rising from 1 to 2 ATA, and that to observe a further doubling—that is, to go from 2 to 4 ATA—one must descend not 10 but 20 metres, down to a depth of -30m, and that for a further doubling, one must reach -70m, where the ambient pressure is 8 ATA. Therefore, if we were to take a balloon inflated at the surface with 1 litre of air to a depth of -10 m, we would see it reduce to ½ litre; at -30 m to ¼ litre; and at -70 m to 1/8 litre; hence: changes in depth near the surface result in percentage changes in gas volume that are more significant than the same changes in depth occurring at greater depths. The above provides a clear and evident explanation for the fact that ear barotrauma is most likely to occur in the first few metres below the water's surface, and is less likely at greater depths (Figure 1).

3. Pathophysiology of the ear in an underwater environment

The ear functions as a mechano-electric transducer that converts changes in ambient pressure, i.e. sound waves, into bioelectric impulses, and is responsible for hearing and the sense of balance. It consists of a mechanical part (the outer and middle ear) and a neurological part (the inner ear), situated on either side of the head and connected to one another from the outside inwards (Figure 2).

Each part of the ear has specific anatomical and functional characteristics that make it particularly vulnerable to the underwater environment. The external auditory canal, the passage connecting the outer ear to the eardrum, becomes flooded, losing much of its ability to protect the middle ear from infections due to the loss of earwax and the persistence, after surfacing, of a warm, humid environment which, particularly in hot weather, promotes the onset

Figure 1 Ratio of the variation in volume of anatomical gases to underwater pressure



As one descends underwater, the pressure increases by 1 ATA for every 10m of depth. The gases contained within anatomical cavities reduce in volume in direct proportion to the change in pressure, in accordance with Boyle–Mariotte's law. Changes in depth near the surface result in greater changes in gas volume than those recorded for similar changes in depth at greater depths.

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of external ear infections. The middle ear, the anatomical cavity between the eardrum and the inner ear, requires effective and continuous 'equalisation' (see next paragraph) during changes in depth, otherwise barotraumatic damage may occur to the eardrum itself or, worse still, to the inner ear.
The inner ear, in addition to being affected by barotrauma, can become a target for gas embolism (a problem we will not address in this article).

4. Ear equalisation

As a diver descends, they are subjected to a rapid increase in ambient pressure, which leads to a sudden reduction in the volume of air contained within the anatomical cavities, creating an immediate need to 'equalise'.
Equalisation means achieving pressure equilibrium between an anatomical cavity and the surrounding environment (4); in other words, ensuring that air enters the cavity during compression (descent) and allowing it to escape during decompression (ascent). Whilst it is true that most anatomical cavities undergo spontaneous equalisation—that is, air enters them during descent and exits during ascent without the need for any action—the tympanic cavity is an exception during the descent phase, and to equalise it, appropriate active manoeuvres, known as 'equalisation manoeuvres' (EM), must be performed. This distinctive behaviour is a direct consequence of the physiological function of the Eustachian tube (ET), the anatomical system that connects the middle ear cavity with the nasopharynx. The ET must allow ventilation of the tympanic cavity and the drainage of physiological (or pathological) secretions, whilst simultaneously protecting the cavity itself from viral and bacterial infections. To fulfil these functions, the Eustachian tube is physiologically closed and opens intermittently once or twice a minute, through the action of specific muscles (the levator veli and tensor veli) activated by swallowing and yawning. Under conditions of stable ambient pressure, ventilation of the tympanic cavity involves the passage of minimal amounts of air throughout the day (approximately 2 cc over 24 hours) and normally a closed/open state is never achieved; instead, the air passes as a small gas bolus, propelled into the tubal lumen by a sort of peristalsis generated by the velar muscles. The rapid increase in ambient pressure characteristic of scuba diving disrupts the physiological function of the Eustachian tube and places the ear under a state of stress that is unparal-

Figure 2 Anatomy of the ear

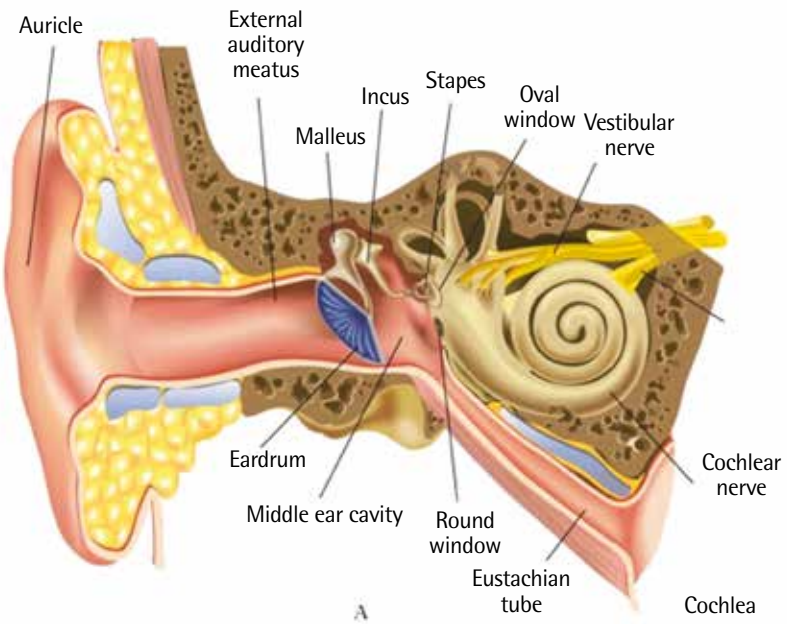
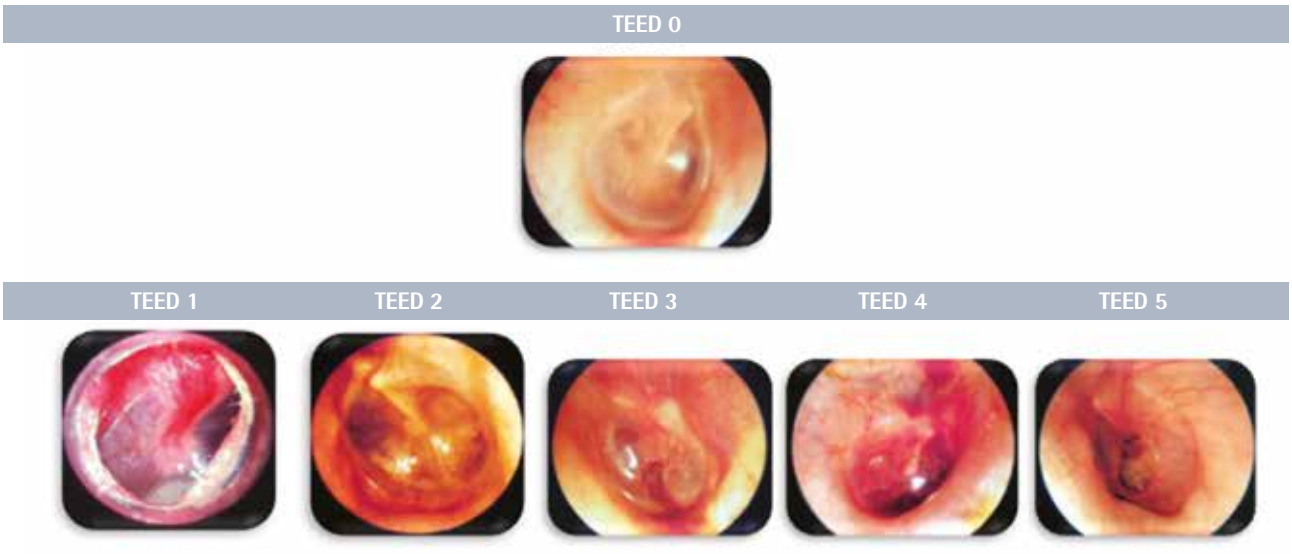


Figure 3 TEED classification of ear barotrauma



leled in other contexts of life in the air. If we observe a diver with an average pneumatised mastoid (approximately 8 cc (4)) undertaking a single dive to a depth of 10 m, where the pressure is double that at the surface, we realise that a single descent and ascent involves the passage through the Eustachian tube of as much as 16 cc of air, eight times more than the ventilation volume of an entire day. Furthermore, the movements of the eardrum resulting from equalisation manoeuvres are vastly greater than the auditory excursions of the tympanic membrane, reaching up to several hundred microns—an exaggerated dimension when compared to the few nanometres associated with the perception of sounds at the threshold limit, or even the few microns documented for sounds of exceptional intensity (140 dB) (5).

In light of the above, it is clear that every diver must be able to perform equalisation manoeuvres correctly and effectively, and be fully aware of the risks and strategies for preventing barotrauma.

5. Ear equalisation manoeuvres

Ear equalisation manoeuvres are techniques used to achieve pressure equilibrium between the middle ear and the surrounding environment. They were first described in the 1950s, when diving began to be practised in a pioneering manner by the first enthusiasts. The first structured description, as far as I can recall, is that found in Duilio Marcante's 1973 "Manuale Federale d'Immersione", where the manoeuvres are described in terms of method of execution, mechanism of action and pathophysiological impact; this description remains, to this day, valid and correct (6). Without going into the details of each individual manoeuvre for the sake of brevity, it should be noted that the Valsalva manoeuvre achieves equalisation by generating sufficient positive pressure in the nasopharynx to open the eustachian tube orifice; swallowing, certain movements of the jaw, tongue and soft palate encourage the Eustachian tube to open by activating the velar muscles; whilst the Marcante-Odaglia manoeuvre, otherwise known as the Frenzel manoeuvre, combines

the two previous methods. Whichever manoeuvre the diver uses, the prerequisites for effective and safe equalisation are normal Eustachian tube function and the correct and timely execution of the chosen manoeuvre.

6. Ear barotrauma during diving

Failure to equalise or delayed equalisation of the middle ear cavity during a change in depth whilst diving can cause ear damage known as barotrauma. Barotrauma most frequently affects the middle ear or, more rarely, the inner ear, and is classified according to otoscopic findings, following the TEED classification, into grades 1 to 5 plus a grade 0 (Figure 3).

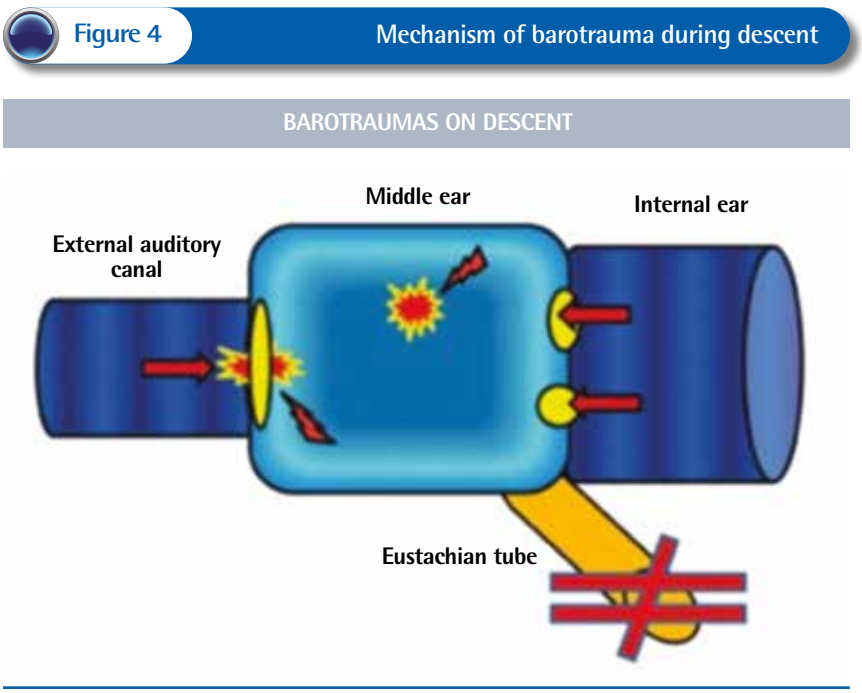
Grade 1 involves hyperaemia of the malleus handle only; grade 2 involves hyperaemia extending to the tympanic membrane; grade 3 involves haemorrhagic suffusions on the membrane itself; grade 4 involves haemotympanum with air-fluid levels; and grade 5 involves tympanic perforation. In grade 0, there is autophony, a sensation of fullness and a history of compensation problems, with a normal tympanic membrane; grade 0 is the one most frequently associated with cochlear damage resulting in sensorineural hearing loss.

Ear barotrauma occurs predominantly during the descent phase (Figure 4), following failure to perform or a delay in performing the equalisation manoeuvre. In these cases, the diver experiences pain in the affected ear, which worsens if the descent is not halted. The onset of earache is a late warning sign and is associated with the development of tympanic inflammation, which will be evident on otoscopy after surfacing, with findings of increasing severity depending on the extent of the damage. This process predominantly leads to middle ear barotrauma.

In some cases, when the Eustachian tube function is impaired, but the diver, by forcing and repeatedly performing equalisation, still manages to descend, it may happen that, during ascent (Figure 5), the expanding air in the tympanic cavity encounters unusual resistance at the level of the eustachian tube opening, causing implosive stimulation of the inner ear via the oval and round windows, resulting in labyrinthine and/or cochlear barotrauma, which may manifest during the dive as vertigo (alternobaric vertigo) (7) and, after surfacing, as autophony, fullness and sensorineural hearing loss. This mechanism predominantly leads to inner ear barotrauma (4).

In our clinical experience, gained from 1998 to the present day across more than 100 cases of divers and freedivers who came to our centre for the diagnosis and treatment of sudden sensorineural hearing loss of barotraumatic aetiology occurring during a dive, we have never been able to observe the patterns of damage development as descri-

Figure 4 Mechanism of barotrauma during descent



bed by Goodill (8) in 1972, namely as a result of the forced execution of the Valsalva manoeuvre during descent, in an implosive or explosive manner, leading to the development of a perilymphatic fistula.

7. Prevention of ear barotrauma

The rules for preventing ear barotrauma are simple and intuitive, and can be summarised in two key points:

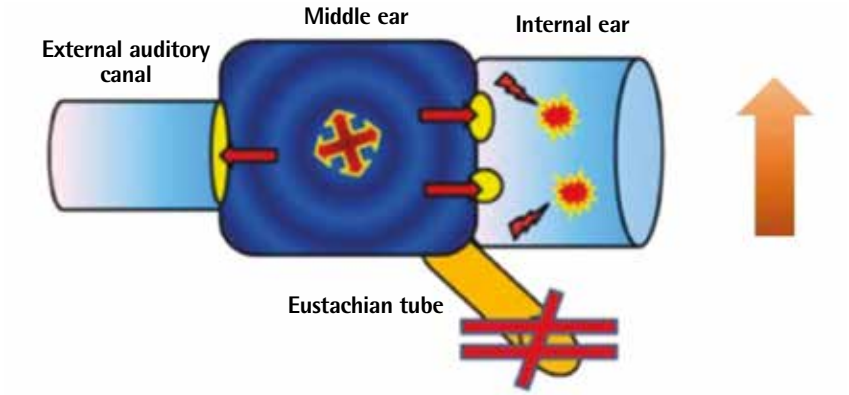
- proper and thorough awareness and technique;
- normal Eustachian tube function.

7.1 Awareness and technique

To acquire awareness and technical skill regarding equalisation, it is necessary to study and practise, even on dry land. In fact, the manoeuvres that best respect the physiological ventilation of the Eustachian tube are those that also utilise the action of the velar muscles to induce the opening of the Eustachian tube orifice. Today, to achieve this, it is possible not only to attend courses, mostly dedicated to training freedivers, but also to perform simple speech therapy exercises using a calibrated latex balloon that is inflated by blowing air through the nose (Figure 6). This medical device was originally designed to prevent catarrhal otitis in children, but is widely used to restore tubotympanic ventilation during convalescence from acute upper respiratory tract infections and for equalisation training.

It is particularly important to equalise pressure in the presence of small pressure gradients between the nasopharynx and the tympanic cavity, i.e. to do so very frequently, especially in the first few metres below the surface.

Figure 5 — Mechanism of barotrauma during ascent



7.2 Physiological Eustachian tube function

It is well known that physiological Eustachian tube function can be easily compromised by acute upper respiratory tract conditions such as colds and allergic rhinitis; divers should therefore avoid diving when these conditions are in their acute phase.

Allergic rhinitis deserves special mention, as even in its quiescent phase it can impair Eustachian tube function due to chronic changes in the nasopharyngeal mucosa. In such cases, it is common to find persistent mucosal oedema, turbinate hypertrophy, eosinophilic infiltration, glandular hyperplasia and fibrosis, with direct negative effects on the function of the Eustachian tube, affecting its pharyngeal ostium (9-10). In this regard, it is important to note that in certain circumstances, particularly in the presence of chronic inflammation of the pharyngeal mucosa, the diver may enter the water with entirely normal Eustachian tube function but see this deteriorate during the dive, due to errors in performing equalisation manoeuvres, the inhalation of seawater, or stress on the temporomandibular joint. In such cases, equalisation, which is initially straightforward, will begin to present problems during the dive, often exposing the diver to the risk of barotrauma during ascent – events that are more serious and unpredictable than those occurring during descent – and

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Figure 6
Calibrated latex balloon in use

may lead to the onset of alternobaric vertigo and barotraumatic sensorineural hearing loss. Even in situations such as these, when Eustachian tube function is partially compromised by allergic reactions or the aftermath of infections, the calibrated latex balloon (11) to be inflated through the nose proves useful, even in conjunction with appropriate medical treatment. Allergic divers should undergo regular ENT check-ups during non-critical periods and, where indicated, undergo the recommended treatments under specialist supervision, such as the use of topical inhaled steroids or systemic therapies in the most severe cases.

8. Conclusion

Nowadays, diving activities are accessible to everyone and practised by a large number of people; for this very reason, the prevention of adverse events, especially those affecting the auditory system, becomes fundamental for the safety of the individual and for preserving the health of the community. In this regard, knowledge of the pathophysiology of the ear during diving and of the medical interventions useful for improving Eustachian tube function are the only effective tools available to both specialists and general practitioners.

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Vegan diets and allergies

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1. Introduction

A diet is defined as "vegan" when it excludes all products of animal origin (e.g. meat, poultry, fish, molluscs, crustaceans, cow's milk, eggs, gelatine and honey) except human breast milk (1). In recent years, increased focus on environmental sustainability and animal welfare has boosted and popularised the adoption of this dietary style. In the United States, 3.4% of the total population report following a vegan diet, with an estimated 1% of young people aged between 8 and 18; whilst in Europe, it affects around 1% of the population (2, 3). The complete avoidance of foods of animal origin could have implications from both a nutritional and an allergological perspective that warrant attention. The role of this dietary pattern in the context of a possible increase in certain food allergies remains a subject of scientific debate (4).

2. Risks and benefits of a vegan diet

A vegan diet consists of a variety of foods: whole grains, pulses, vegetables, fruit, nuts, seeds, plant-based fats, herbs and spices (2). Reasons for adopting this dietary approach include considerations relating to environmental sustainability, animal welfare or personal well-being, and the improvement of clinical outcomes for certain conditions (5, 6). Benefits include the prevention of cardiometabolic diseases, metabolic syndrome and type 2 diabetes. However, these findings may be confounded by the fact that individuals who choose to adopt this diet are generally more aware of their health status and therefore at lower risk of developing conditions associated with metabolic syndrome (7). Furthermore, a reduction in cardiovascular risk would not be a feature exclusive to the vegan diet, as it has already been observed in the Mediterranean diet, which is rich in fish, white meat, eggs and dairy products (8). Among the risks are those

ABSTRACT

Keywords
• Vegan diet • Food allergies • Hidden allergens • Pulses • Nuts • Seeds

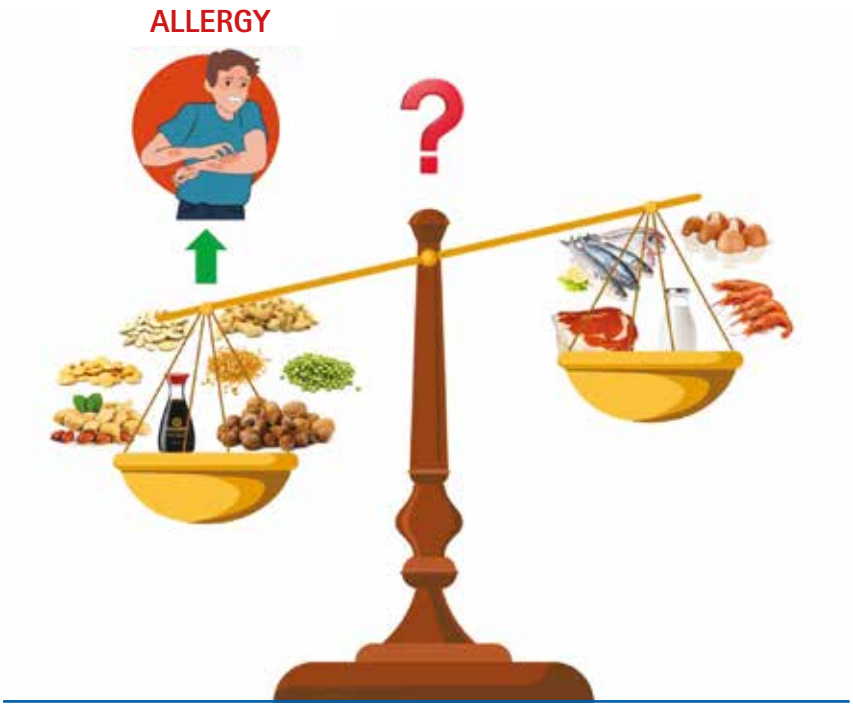
In recent years, an increasing number of people have adopted a vegan diet. Reasons for adopting this dietary style include considerations of environmental sustainability, animal welfare or personal well-being, and the improvement of clinical conditions associated with certain diseases. Among the risks are those of a possible deficiency in macro- and micronutrients resulting from a restrictive diet. The shift in the market from 'traditional' animal-based products towards plant-based substitutes (e.g. pulses, nuts, seeds) could lead to an increase in allergic sensitisation to such products. Many of these foods are not subject to mandatory labelling and may therefore potentially act as "hidden allergens". The role that this dietary pattern might play in the context of a possible increase in certain food allergies remains a subject of scientific debate (Figure 1).

of a possible deficiency in macro- and micronutrients resulting from a restrictive diet. Protein intake comes exclusively from plant-based foods, for which a varied daily intake, in the right quantities, is recommended in order to achieve sufficient levels of essential amino acids and prevent potential malnutrition (9). Groups at risk include children and adolescents, who require higher levels of energy and nutrients than adults and for whom the evidence supporting this diet remains currently debated (1, 10). Furthermore, poor dietary planning could also lead to a deficiency in micronutrients such as iodine, iron, zinc, calcium, vitamins (B12, B2, D and A) and long-chain omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (10).

3. Plant-based foods and allergy risk

The shift in the market from 'traditional' animal-based products such as milk, eggs and meat towards plant-based alternatives has led to an increased risk of reactions in patients with plant-based food allergies. For these patients, it is often difficult to identify the potential allergens to be avoided, as many 'alternatives' contain ingredients that have not previously been classified or declared. Currently, in fact, only certain types of nuts (walnuts, hazelnuts and almonds), pulses (peanuts, soya and lupin) and seeds (sesame and mustard) are subject to mandatory labelling in Europe. Another issue concerns the risk of contamination, as products labelled as "vegan" do not account for any unintentional animal-derived contamination linked to industrial production processes. Plant-based foods (e.g. wheat, hazelnut, soya and celery) are a common cause of anaphylaxis, particularly among adults (11), and the food groups most frequently implicated are pulses, nuts and seeds (Figure 2). These foods contain a high number of potential allergens such as storage proteins (e.g. 2S albumin, 7/11S globulin), non-specific lipid transfer protein (ns-LTP), pathogenesis-related (PR)-10 proteins, profilin, defensins and oleosins.

Figure 1 The uncertain role of the vegan diet in the context of new forms of food allergies



Legumes

Pulses are an important source of protein in a vegan diet and can cause IgE-mediated allergic reactions. Peanuts and soya (known as priority pulses) are among the nine foods most commonly responsible for anaphylaxis worldwide. The remaining pulses (peas, lentils, chickpeas, lupins, etc.) are classified as 'non-priority' due to their low incidence of allergic reactions, and the frequency of sensitisation varies depending on geographical distribution and consumption patterns. In accordance with current European Regulation No. 1169/2011, only peanuts, soya and lupin are subject to mandatory labelling.

Peanuts

Peanuts (*Arachis hypogaea*) are the most well-characterised legumes from an allergological perspective, with 20 allergens currently recorded in the World Health Organization/International Union of Immunological Societies (WHO/IUIS) database. They are not discussed in this article for reasons of space; for a more comprehensive treatment, please consult other texts (12).

Soya

Soya (*Glycine maxima*) is a highly versatile legume with significant nutritional value, used in a wide variety of dishes and foods. It is native to East Asia and is widely cultivated in the United States, South America and Asia. Allergic reactions to soya have been reported following exposure to whole seeds, protein products and unprocessed soya (13). As a low-cost source of protein, soya-based ingredients can be found in many food products such as meat and meat substitutes, baked goods and cereals. Eight allergens are currently listed in the WHO/IUIS database (Table 1).

The allergens Gly m 5, Gly m 6 and Gly m 8 are associated with severe allergic reactions. However, even individuals sensitised to Gly m 4 and allergic to birch pollen may experience allergic reactions after ingesting food products containing soya powder or beverages made from unprocessed soya. Cooking processes generally reduce the Gly m 4 content and symptoms are usually limited to oral allergy syndrome; however, as these processes are highly variable, the risk of systemic allergic reactions must be taken into account. In some cases, systemic reactions have been documented following the ingestion of soya milk (14). Food products in which the protein fraction has been separated (e.g. refined soya oil or soya lecithin) or fermented products containing hydrolysed proteins such as tempeh, soya sauce or miso are thought to pose a lower risk to allergic individuals (15). In patients allergic to soya, cross-reactivity with peanuts has been documented in 6.5–15% of cases, often mediated by storage proteins such as cupins and prolamins (16).

Figure 2 Whole seeds, pulses and nuts

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Lupin

The lupin is a legume that grows most commonly in Mediterranean countries, of which four species are of particular agricultural interest: *Lupinus albus, Lupinus angustifolius, Lupinus luteus and Lupinus mutabilis.* Its seeds are commonly eaten as appetisers or snacks, whilst lupin flour is routinely added to certain food products such as baked goods, diet foods (e.g. milk and soya substitutes), coeliac foods, stock cubes and dehydrated soups (17). Currently, only three allergens are listed in the WHO/IUIS database: Lup an 1 (beta-conglutin) and Lup an 3 (ns-LTP) from *Lupinus angustifolius*, and Lup a 5 (profilin) from Lupinus albus. The prevalence of sensitisation is higher in the Mediterranean region and may be primary (via food or inhalation for those working in close contact with lupin flour) or secondary due to cross-reactivity with other

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legumes (particularly peanuts, with a prevalence ranging from 4 to 37%) (17).

Pea

The pea (*Pisum sativum*) is widely used in the food industry and promoted as a vegan and hypoallergenic source of protein. Three allergens are currently listed in the WHO/IUIS database (Table 1). Pis s 1 (vicilin) and Pis s 2 (convicilin) are storage proteins proposed as major allergens (18). Pis s 3 (ns-LTP) has been documented as being responsible for food-dependent exercise-induced anaphylaxis (FDEIA) (19). Two other allergens that have been identified but not yet officially registered are the homologues of profilin (Pis s 5) and Bet-v 1 (Pis s 6). The latter allergen, similarly to Gly m 4 in soya, has sometimes been associated with systemic reactions when consumed in protein drinks (14).

Lentils

The lentil (*Lens culinaris*) is a rich source of protein with antioxidant and anti-inflammatory properties. It is a legume frequently consumed in the Mediterranean, the Middle East, Asia and North America. Several commercial varieties are available, varying in shape, colour and size. There are currently three allergens recognised by the WHO/IUIS (Table 1). Around 80% of patients allergic to lentils are sensitised to Len c 1 (20). Allergic reactions have also occasionally been reported following exposure to the cooking vapours of this legume alone (21).

Chickpeas

Chickpeas (*Cicer arietinum*) are among the most widely consumed pulses in the world and one of the oldest to be cultivated in Asia and Europe. They are widely used in various vegan recipes such as falafel and hummus. Chickpea allergy remains relatively rare and almost never occurs in isolation, but rather in association with allergies to other pulses (e.g. lentils or peas). Currently, only one allergen is included in the WHO/IUIS database: Cic a 1 (late-embryogenesis protein 4), which shows cross-reactivity with other storage proteins in lentils, peas, soya and hazelnuts (22). A few cases of FDEIA to chickpeas have also been reported in the literature (23). Cross-reactivity between lentils, chickpeas and peas is very common and is often clinically significant (16).

Fenugreek

Fenugreek (*Trigonella foenum-graecum*) is a legume that grows in Iran, India, Ethiopia, Canada, Oman and Turkey. It has been known since ancient times in traditional medicine for its antioxidant, anti-inflammatory, cholesterol-lowering, anti-diabetic, anti-hypertensive and liver-protective properties due to its high fibre and micronutrient content (24). It is used in various food products in the form of herbs or spices (e.g. curry), cheeses, baked goods, and coffee and tea substitutes. Cases of allergy have been reported in the literature, including anaphylaxis and occupational asthma following ingestion, inhalation and contact (25). Allergic reactions to this legume are often secondary to a primary peanut allergy, suggesting cross-reactivity between homologous proteins present in the two legumes. Some cases have also been described in individuals allergic to lentils and broad beans (26). Four allergens have been identified: Tri f 1 (7S vicilin), Tri f 2 (2S albumin), Tri f 3 (11S legumin), Tri f 4 (PR-10 protein), but none of these has yet been officially registered in the WHO/IUIS database.

Nuts and seeds

Nuts and seeds are major causes of food-induced anaphylaxis (11) and contain a wide range of potential allergens. In recent years, a progressive increase in the incidence of anaphylaxis to these foods has been documented in both Europe and the United States (27). Among nuts, walnuts, hazelnuts and cashews are the foods most commonly involved, whilst among seeds, sesame is the most common cause. All of the aforementioned foods are subject to mandatory labelling in Europe.

- ***Cashew nuts***

Cashew nuts (*Anacardium occidentale*) are nuts belonging to the *Anacardiaceae* family, the production and consumption of which have increased in recent years. They are mainly eaten roasted but are also used as ingredients in many processed foods such as pesto, desserts and other baked goods. As their consumption has risen, so too has the incidence of anaphylaxis triggered by these nuts (28). The WHO/IUIS database currently lists three storage proteins: Ana o 1 (vicilin-like protein), Ana

o 2 (legumin-like protein) and Ana o 3 (2S albumin). The actual prevalence of cashew nut allergy is not currently known, although in Europe it accounts for approximately 28% of food-induced anaphylaxis among nuts (11). The most common cross-reactivity is with pistachios, accounting for approximately 65% of cases according to a recent study (29). Other described cross-reactivities include those with citrus seeds and pectin (30).

- ***Walnuts and Hazelnuts***

Walnuts (*Juglans regia*) and hazelnuts (*Corylus avellana*) are nuts, both belonging to the order *Fagales*, and are among the most common food allergens causing anaphylaxis in Europe, accounting for 16% and 30% of anaphylaxis cases among nuts respectively (11). They are often consumed both as individual food products and as ingredients in a wide variety of dishes, salads, baked goods and desserts. The pattern of sensitisation to these foods has increased in recent years due to their rising consumption

Table 1 Allergens from the main foods used in vegan diets currently registered in the WHO/IUIS database and available in in vitro diagnostics

Foods	Registered allergens (WHO/IUIS database)	In vitro tests	
		Molecules available in the singleplex system	Molecules available in multiplex systems
Legumes			
Soya (*Glycine max*)	Hydrophobic protein: Gly m 1 2S albumin: Gly m 8 7S globulin: Gly m 5 11S globulin: Gly m 6 PR-10 protein: Gly m 4 Profilin: Gly m 3 Defensin: Gly m 2 Seed biotinylated protein: Gly m 7	Gly m 4: PR-10 protein Gly m 5: 7S globulin Gly m 6: 11S globulin	Gly m 4: PR-10 protein Gly m 5: 7S globulin Gly m 6: 11S globulin Gly m 8: 2S albumin
Lupin (*L. angustifolius*)	Conglutin beta (7S globulin): Lup an 1 ns-LTP: Lup an 3	//	//
Lupin (*L. albus*)	Profilin: Lup a 5	//	//
Pea (*Pisum sativum*)	Vicilin: Pis s 1 Convicilin: Pis s 2 ns-LTP: Pis s 3	//	Pis s 1: 7/8S globulin Pis s 2: 7/8S globulin Pis s 3: ns-LTP
Lentil (*Lens culinaris*)	Vicilin: Len c 1 Seed byotinilated protein: Len c 2 ns-LTP: Len c 3	//	Len c 1: vicilin Len c 3: ns-LTP
Chickpeas (*Cicer arietinum*)	Late embryogenesis protein family 4: Cic a 1	//	//
Fenugreek (*Trigonella foenum-graecum*)	//	//	//

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and is also influenced by geographical differences. In Central Europe and Northern Italy, hazelnut allergy is primarily associated with birch pollen allergy due to cross-reactivity between the allergen Bet v 1 and the homologous hazelnut protein Cor a 1. This sensitisation is generally associated with mild symptoms (12). Sensitisation to storage proteins such as Cor a 14 (2S albumin), Cor a 9 (11S globulin), and Cor a 11/Cor a 16 (7S globulin), on the other hand, is often associated with severe allergic reactions (31). Similarly to hazelnuts, sensitisation to Jug r 5 (PR- 10 protein) in walnuts is also associated with birch pollen and is found mainly in Central and Northern Europe, whilst sensitisa-

Table 1 Allergens from the main foods used in vegan diets currently registered in the WHO/IUIS database and available in in vitro diagnostics

Foods	Registered allergens (WHO/IUIS database)	In vitro tests	
		Molecules available in the singleplex system	Molecules available in multiplex systems
Nuts			
Cashew (*Anacardium occidentale*)	Vicilin-like: Ana o 1 Legumin-like: Ana o 2 2S albumin: Ana o 3	//	Ana o 1: 7/8S globulin Ana o 2: 11S globulin Ana o 3: 2S albumin
Hazelnut (*Corylus avellana*)	PR-10 protein: Cor a 1 Profilin: Cor a 2 Isoflavone reductase: Cor a 6 ns-LTP: Cor a 8 7S globulin: Cor a 11 and Cor a 16 11S globulin: Cor a 9 2S albumin: Cor a 14 Oleosins: Cor a 12, Cor a 13 and Cor a 15 Luminal binding protein: Cor a 10	Cor a 1: PR-10 protein Cor a 8: ns-LTP Cor a 9: 11S globulin Cor a 14: 2S albumin	Cor a 1: PR-10 protein Cor a 8: ns-LTP Cor a 9: 11S globulin Cor a 14: 2S albumin Cor a 11: 7/8S globulin
Walnut (*Juglans regia*)	2S albumin: Jug r 1 7S globulin: Jug r 2 and Jug r 6 11 S globulin: Jug r 4 ns-LTP: Jug r 3 and Jug r 8 PR-10 protein: Jug r 5 Profilin: Jug r 7 Phospholipase D alpha 1: Jug r 9	Jug r 1: 2S albumin Jug r 3: ns-LTP	Jug r 1: 2S albumin Jug r 3: ns-LTP Jug r 2: 7/8S globulin Jug r 6: 7/8S globulin Jug r 4: 11S globulin
Seeds			
Sesame (*Sesamum indicum*)	2S albumin: Ses i 1 and Ses i 2 7S globulin: Ses i 3 11S globulin: Ses i 6 and Ses i 7 Oleosins: Ses i 4 and Ses i 5	Ses i 1: 2S albumin	Ses i 1: 2S albumin

Table 1 Allergens from the main foods used in vegan diets currently registered in the WHO/IUIS database and available in in vitro diagnostics

Foods	Registered allergens (WHO/IUIS database)	In vitro tests	
		Molecules available in the singleplex system	Molecules available in multiplex systems
Others			
Common buckwheat (*Fagopyrum esculentum*)	2S albumin: Fag e 2 Alpha-hairpinin: Fag e 3 Vicilin-like: Fag e 5 Hevein-like antimicrobial peptide: Fag e 4	Fag e 2: 2S albumin	Fag e 2: 2S albumin
Tartary buckwheat (*Fagopyrum tataricum*)	2S albumin: Fag t 2 Oleosin: Fag t 6	//	//
Oats (*Avena sativa*)	//	//	//
Quinoa (*Chenopodium quinoa*)	//	//	//
Chia seeds (*Salvia hispanica*)	//	//	//

Abbreviations: PR-10: pathogenesis-related protein 10; ns-LTP (non-specific lipid transfer protein).

tion to Jug r 3 (ns-LTP) is more common in Southern Europe. Sensitisation to the storage proteins Jug r 1 (2S albumin), Jug r 2/Jug r 6 (7S globulin) and Jug r 4 (11S globulin) are markers of primary walnut allergy and are associated with severe allergic reactions (32).

- ***Sesame***

Sesame (*Sesamum indicum*) is the oldest known edible seed, cultivated since 3,500 BC, primarily in India and Africa. Its seeds are used to produce oil or tahini paste, which is used in dishes such as halva, hummus and other sauces. Whole seeds, on the other hand, are used as ingredients in confectionery and baked goods. Since 2014, it has been included on the list of allergens subject to mandatory labelling in Europe. The overall prevalence of sesame allergy is estimated to be around 0.1–0.2% (33). In Israel, however, it is the third most common cause of IgE-mediated food reactions and the second leading cause of food-induced anaphylaxis (34). There are currently seven allergens registered in the WHO/IUIS database (Table 1). Cross-sensitisation with peanuts, walnuts and hazelnuts is common.

Other vegan food products

Buckwheat is a pseudocereal belonging to the *Polygonacea*e family, with properties and characteristics similar to those of other cereals. It is used in various types of food such as noodles, pancakes, porridge, kasha, polenta, pasta, bread and bread substitutes. Two species are cultivated: *Fagopyrum esculentum* (or common buckwheat) and *Fagopyrum tataricum* (or Tatar buckwheat). Originally used in Asian countries, it has more recently become popular both in Europe and in Italy, where some cases of anaphylaxis have been reported (35).

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Four allergens from Fagopyrum esculentum and two from *Fagopyrum tataricum* are currently listed in the WHO/IUIS database (Table 1). Cross-reactivity with latex, peanuts, poppy seeds and quinoa has also been demonstrated (35).

Oats (*Avena sativa*) are a cereal belonging to the Poaceae family, often used as a substitute for wheat, and for which cases of anaphylaxis have been documented following the consumption of beverages made from this food (36).

Quinoa (*Chenopodium quinoa*), which is also used as a wheat substitute, has seeds that are commonly used to produce flour; there have been some reported cases of anaphylaxis following its ingestion or inhalation (37).

Chia seeds (*Salvia hispanica*), recently introduced to Europe, are instead considered a 'superfood' due to their high nutritional and energy content; they are consumed in dishes such as muesli or with drinks or plant-based puddings, and rare cases of anaphylaxis following their ingestion have recently been reported (38).

Other plant-based food products have long been recognised as significant from an allergological perspective, such as wheat and its derivatives, fruit (e.g. those belonging to the Rosaceae family), vegetables (e.g. celery, turnip, mustard, asparagus); but also other seeds besides those mentioned above (e.g. flax seeds (39), poppy, sunflower, hemp) and spices (e.g. cumin, pepper, mustard) (11).

4. Vegan foods and their immunological role

The market for vegan and vegetarian products has expanded significantly in recent years, leading to a wider choice for consumers. However, the difficulties of following a diet based on fresh and minimally processed foods—which require time in terms of planning, shopping and preparation—have led both the market and consumers to turn towards ready-to-eat foods such as processed and ultra-processed foods (UPFs) (40). The latter are characterised by high energy content (e.g. salt, sugar, starch) but low nutritional value (e.g. protein, fibre and micronutrients), which in the long term can lead to malnutrition and other health risks; furthermore, the consumption of UPFs may have adverse effects on the gut microbiota, the intestinal barrier and the immune response (41). For the prevention of allergies, it is recommended to follow a varied diet that includes preferably fresh or minimally processed foods, and animal-based foods (e.g. yoghurt, milk, eggs and fish) appear to play a protective role in this regard (42). Conversely, a diet based on fresh plant-based foods such as fruit and vegetables is associated with better lung function and a lower prevalence of asthma and atopic dermatitis (43, 44). However, there is currently no clear evidence that a vegan diet is superior to other balanced dietary patterns, such as the Mediterranean or vegetarian diet.

5. Conclusions

Given the growing number of people who have adopted a vegan diet in recent years, it is likely that we will see an increase in allergic sensitisation to plant-based products and foods (e.g. pulses, nuts, seeds), even though we do not yet have clear evidence of this. Many of these foods (e.g. lentils, peas, chickpeas, buckwheat and various seeds) are not subject to mandatory labelling and may potentially act as 'hidden allergens' (45). The decision to follow a vegan diet, both in terms of nutrition and allergy prevention, remains a subject of considerable debate and is not recommended for children and adolescents. For those intending to follow this dietary approach, it is advisable that they are monitored by expert nutritionists to prevent any nutritional deficiencies and that they are aware of potential allergic reactions, including severe ones, associated with the consumption of certain plant-based foods.

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Food allergy to peach: a guide for the allergist

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1. Introduction

Peaches (*Prunus persica spp.*) are one of the most popular fruits globally and are grown across large areas of the Northern Hemisphere, mainly in China, Europe (particularly Italy, Spain, and Greece), Turkey and the United States of America (mainly in California), and to a lesser extent in the Southern Hemisphere, where the main producer is Chile. Other production centres include Mexico, Iran, Egypt and Morocco. In addition to fresh consumption, a significant portion of production is destined for the processing industry (jams, juices, peaches in syrup, confectionery). The peach belongs to the *Rosaceae family,* along with the apple, pear, apricot, plum, cherry, almond, medlar, service tree and quince, and is a drupe characterised by a velvety or smooth skin (nectarine) and juicy, white or yellow flesh, or firm flesh (percoca). It consists of a thin skin (epicarp), flesh (mesocarp) and a woody inner stone (endocarp) containing the seed.

2. Peaches in allergology

Although it shares most of its genetic characteristics with other members of the Rosaceae family, in the field of allergology the peach represents a truly unique case, a singular phenomenon, in a sense comparable to a crossroads of potential primary and secondary allergenic sensitisation that may occur individually or in various combinations, giving rise to clinical presentations ranging from complete tolerance to anaphylactic shock. This variability depends essentially on the chemical and physical characteristics of the individual allergenic proteins, together with the influence of external factors—both environmental and non-environmental—which we define as co-factors.

ABSTRACT

Keywords
• Peaches • Plant-based foods • Food allergy
• LTP • PR-10 • profilin • GRP

Over the years, it has gradually become clear that, within the field of food allergies, peaches represent a highly complex allergenic source containing allergens homologous to pollen proteins (PR-10, profilin, Gibberellin-Regulated protein and others not yet well characterised), natural rubber latex, as well as a panallergen (lipid transfer protein) that causes primary sensitisation in patients living mainly in the Mediterranean region, subsequently leading to secondary cross-reactivity in a wide range of plant-based foods and pollens. This article reviews the currently known allergens in peaches and analyses their clinical relevance as well as the main diagnostic aspects in vivo and in vitro

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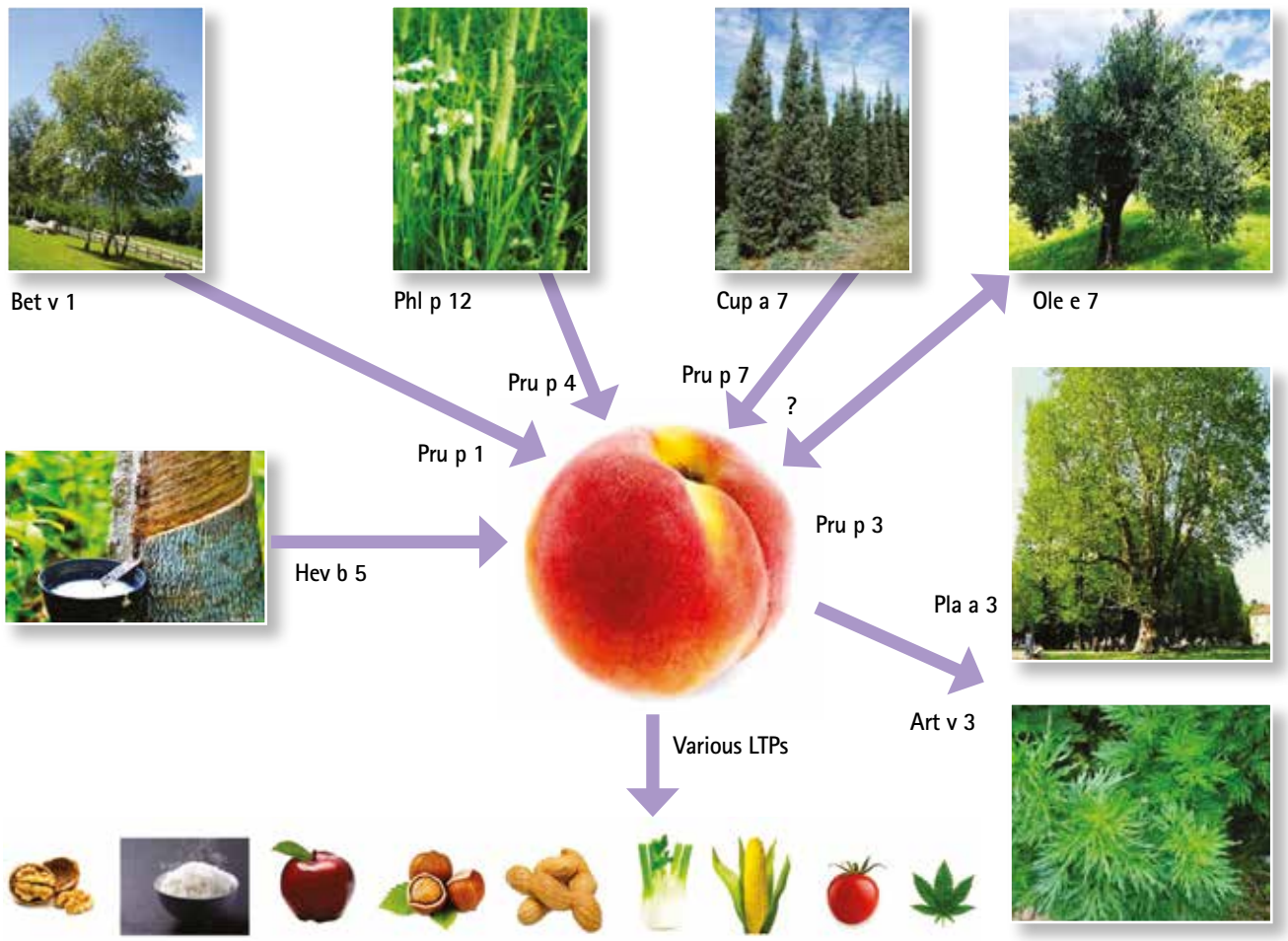
Figure 1 The central role of the peach in allergic cross-reactions to various plant species



This article aims to summarise current knowledge on food allergy to peaches, providing diagnostic and interpretative guidelines useful in clinical practice. To this end, the sections will be divided according to the different allergenic proteins. It is important to note that foods of plant origin, specifically the Rosaceae family, represent the main cause of food allergy and systemic food reactions in Italy (1, 2).

2.1 PR-10 (Pru p 1)

The high prevalence of plant food allergy in patients hypersensitive to *Betulaceae* pollen has been known for around 50 years (3), and early in vitro studies had already demonstrated a very high sequence identity between the major allergen in birch pollen, Bet v 1, a PR-10 (Pathogenesis-related protein group 10), and homologous food allergens, thereby providing a scientific basis for cross-reactivity

between these proteins (4). The demonstration of the presence of PR-10 in a large number of plant foods has made these proteins the paradigm of the so-called 'pollen-food syndrome'. Clinically, allergic reactions to peaches due to sensitisation to PR-10 almost always present with local symptoms (oral allergy syndrome, an immediate-type allergic reaction resulting from direct contact with the allergen affecting the oral and pharyngeal mucosa, presenting as itching and occasionally oedema) following ingestion of the fresh fruit. Due to the heat- and heat- and gastro-sensitivity of most PR-10 proteins, patients sensitised to Pru p 1 are able to tolerate commercial fruit juices, fruit in syrup, or jams perfectly. Under specific conditions characterised by inhibition of gastric secretion, such as those occurring during antacid therapy with proton pump inhibitors (PPIs), or reduced retention of food in the stomach, such as following the ingestion of large quantities of the fresh allergen in liquid form (e.g. smoothies), systemic reactions, including severe ones, are possible (5). A useful tip for patients who are hypersensitive to Pru p 1 and who experience oral food allergy syndrome from fresh food is to carry out a sort of 'pasteurisation' using a microwave oven, heating the food to 70–80°C for a few seconds and then consuming it once cooled. This procedure, which should be adapted to the individual case, is often effective and avoids altering the organoleptic characteristics of the food.

In vivo diagnostic tests (SPT) using commercial extracts will show marked reactivity to Betulaceae pollens (birch, hazel, alder, oak, etc.), but the skin test with peach extract will most likely be negative, as the allergen Pru p 1, due to its chemical and physical characteristics, is degraded during the preparation of the diagnostic test. Conversely, the skin test with fresh food (using the prick-by-prick method) will be clearly positive. In vitro, the assay for specific IgE to peach extract will generally be positive (as the Pru p 1 allergen is still present, unlike in SPT extracts), and markers of sensitisation to PR-10 in component-resolved diagnostics (CRD) such as Bet v 1 (birch), Cor a 1 (hazelnut), Que a 1 (oak), and/or Fag s 1 (beech) for pollens, and Pru p 1 for the fruit, available both in singleplex and on commercial multiplex platforms.

2.2 Profilin (Pru p 4)

Profilin is an allergenic protein expressed ubiquitously in all eukaryotic cells, and is the plant panallergen par excellence, causing extensive cross-reactivity between pollen, natural rubber latex and numerous foods (6). Traditionally considered a minor allergen, often clinically irrelevant (7), profilin has recently been re-evaluated as a possible cause of significant local allergic reactions in approximately 50% of sensitised patients. Although, due to its heat- and heat- and gastro-sensitivity, profilin generally induces only SOA following the ingestion of raw plant foods, similar to what occurs with PR-10, systemic reactions may occur in specific circumstances (5). In in vivo diagnostic testing, a patient sensitised to peach profilin, Pru p 4, will test positive for all pollens (with the possible exception of pellitory and cypress) and negative in SPTs with peach extract, whilst testing positive in SPTs with fresh food. A commercial extract of date palm pollen enriched with profilin (Pho d 2) for SPTs, which allowed immediate identification of the panallergen during the initial allergy consultation, is no longer available. In vitro, in addition to pollen-specific IgE, the test will demonstrate the presence of IgE specific to peach extract (albeit often at low titres) and to the pollen markers of sensitisation to profilin (Phl p 12 and Bet v 2), as well as, of course, to Pru p 4, the peach profilin, available both in singleplex and on a multiplex platform.

2.3 Non-specific lipid transfer protein (Pru p 3)

Non-specific lipid transfer proteins (nsLTPs) are small, non-glycosylated and highly stable allergens that are widely distributed throughout the plant kingdom, particularly in fruit, vegetables and certain pollens (8, 9). LTP was initially recognised as the cause of systemic allergic reactions induced by peaches (10), and it was only later that its presence was also recognised in plant foods botanically distant from *the Rosaceae family* (11, 12), as well as in certain pollens (olive, Artemisia, plane tree, Parietaria). The peach LTP, Pru p 3, remains, however, the

prototype of such allergens. Its alpha-helix structure, strongly stabilised by disulphide bonds, is responsible for its marked resistance to heat treatment and peptic digestion (11). The route of sensitisation to nsLTP remains a subject of debate. In some regions of China, allergy to nsLTP appears to result from primary sensitisation to Artemisia pollen, presenting as a clear case of pollen-food syndrome (13), whereas in our latitudes, sensitisation to LTP seems to represent a classic example of primary food allergy in which peaches play a major role (14). However, in areas of Spain characterised by a very high concentration of Oleaceae pollen, a possible cross-reactivity to Pru p 3 has been suggested, arising from sensitisation to the pollen LTPs Ole and 7 (15).

Clinically, although there are sensitised patients who are completely asymptomatic, sensitisation to Pru p 3 manifests itself in a very wide range of allergic reactions, ranging from oral allergy syndrome to contact urticaria, gastrointestinal disorders, generalised urticaria, rhinitis/asthma and anaphylaxis. In fact, allergy to LTPs is the leading cause of anaphylaxis in Mediterranean countries (2); sometimes systemic food allergy symptoms are preceded by local manifestations such as respiratory symptoms, contact urticaria or oral allergy syndrome (16–18). It is interesting to note that clinical reactivity to LTP exhibits a dynamic pattern over time in sensitised patients (19) and that the severity of allergic reactions is greater in mono-sensitised patients (i.e., those who are not simultaneously sensitised to PR-10 and/or profilin) (20). An interesting observation is that sensitisation and allergy to lipid transfer proteins very often follow a very specific hierarchical sequence, starting almost invariably with peaches, at least in the Mediterranean region (21). Another interesting aspect of this food allergy is that the clinical manifestation of sensitisation to nsLTPs and to Pru p 3 in particular is among those most affected by the presence of co-factors such as physical exertion, or the consumption of alcohol or anti-inflammatory drugs (NSAIDs) in conjunction with the ingestion of the food (22). Another factor capable of determining the severity of symptoms is the level of Pru p 3-specific IgE; the higher it is, the greater the likelihood of severe reactions and of exhibiting a wide range of cross-reactivity with other plant-based foods botanically distant from the Rosaceae family (23). The very superficial distribution of this allergenic protein means that patients sometimes tolerate peeled peaches or even nectarines (which have smooth skin!), and react only to peaches with 'fuzzy' skin (24). The skin of the peach is also the main cause of contact urticaria in sensitised individuals (16, 17).

According to in vivo diagnostic tests, patients hypersensitive to LTP test clearly positive to commercially available peach extract, as the allergenic protein is stable during industrial processing. In a commercially available peach extract for skin prick testing (SPT), the Pru p 3 protein is labelled as having a concentration of 30 mcg/ml. The skin test with fresh food will yield a clearly positive result for the skin, and a weaker positive or even negative result for the pure flesh. In vitro, the determination of specific IgE reactivity to peach extract, and more specifically to the Pru p 3 protein, allows for an accurate diagnosis of the patient's allergic status. The determination of Pru p 3-specific IgE remains the best marker of LTP sensitisation, at least in Mediterranean countries. A series of excellent review articles on LTP allergy sponsored by the EAACI and the AAIITO have recently appeared in the literature (8, 9, 25).

2.4 Gibberellin-regulated protein (Pru p 7)

Gibberellin-regulated proteins (GRP) are small, cysteine-rich and highly stable peptides, widely distributed throughout the plant kingdom (26). They are present in both the skin and flesh of many fruits, including peaches, citrus fruits, apricots, cherries, pomegranates, and likely other sources, as well as in the pollen of Cupressaceae (27). GRP molecules are highly resistant to heat and peptic digestion due to the presence of six disulphide bridges, which enables them to pass through the gastric filter unscathed and trigger systemic allergic reactions (28). The peach GRP, Pru p 7, was the first to be identified as an allergen within this family of highly cross-reactive proteins. Allergy to GRP is in all likelihood another example of

Table 1 Clinical and diagnostic characteristics of the main peach allergens

Allergen	Inhalant SPT	Clinical (peach)	Fresh peach SPT	SPT peach extract	Peach extract IgE	In vitro markers
PR-10 (Pru p 1)	Birch	From absent to SOA (rarely systemic)	+++	-	+++	Bet v 1 Pru p 1
Profilin (Pru p 4)	Various pollens (except cypress e/o Pellitory)	From absent to SOA	+++	-	+	Phl p 12 Pru p 4
Lipid transfer protein (Pru p 3)	Negative or positive	from absent to anaphylaxis	+++ peel +/- fresh	+++	+++	Pru p 3
Gibberellin regulated protein (Pru p 7)	Cypress	From SOA to anaphylaxis	++	+	+	Pru p 7 Cup a 7

pollen-food syndrome triggered by Cupressaceae pollen, as demonstrated by its geographical distribution in the Mediterranean region and in Japan (29). In vivo diagnosis is characterised by skin test positivity (sometimes variable) to commercial peach extract associated with intense reactivity to cypress pollen. Measurement of specific IgE for peach extract may prove negative due to the low concentration of Pru p 7 in the substrate. To date, pending the availability of Cup a 7, Pru p 7 is the only allergen available for the in vitro diagnosis of sensitisation to this allergenic family (30, 31).

2.5 Other allergens

Thaumatin-like protein (Pru p 2)

Thaumatin-like proteins (TLPs), which belong to the PR-5 family, are defence molecules with antifungal activity that are relatively stable under heat and acidic conditions due to their compact structure containing eight disulphide bonds. These are cross-reactive allergens found in various pollens and fruits (32). Allergic reactions ranging from oral allergy syndrome to anaphylaxis have been described (33, 34), although their true clinical significance is difficult to define, as IgE-mediated hypersensitivity to TLPs is almost always associated with sensitisation to other allergens (35). The presence of specific IgE against peach TLP (Pru p 2) cannot currently be determined directly but can be inferred indirectly by measuring specific IgE for apple TLP, Mal d 2 (35).

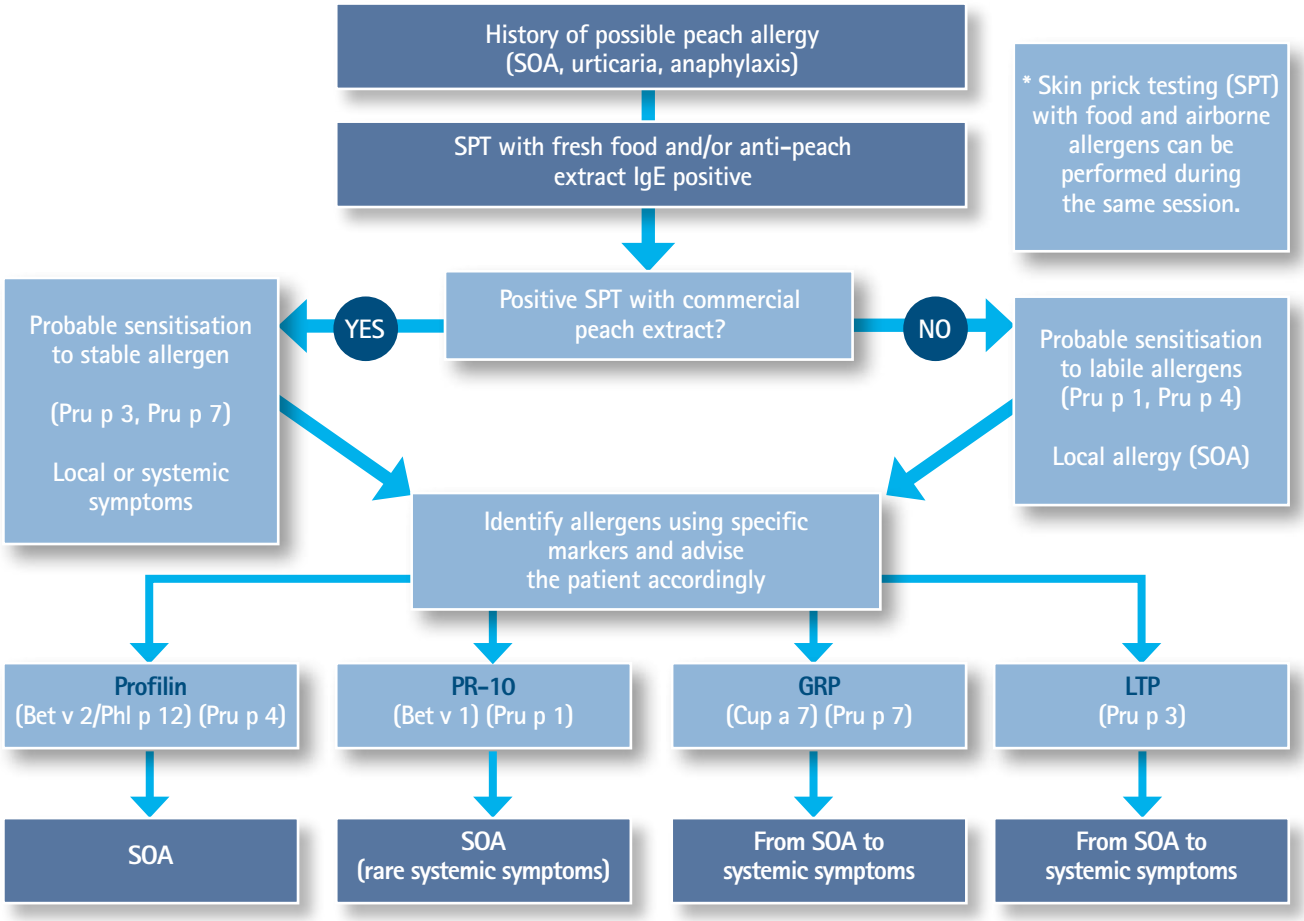
PR-1 family (Pru p 9)

PR-1s are small, fairly compact glycoproteins that are resistant to heat and digestion, found in various pollens including that of the peach (Pru p 9). This allergen appears to cause occupational respiratory symptoms during the peach blossom season (36). No symptoms related to food ingestion have been reported, nor are specific diagnostic tests available for PR-1.

Hev b 5-like protein (Pru p 5)

A protein homologous to Hev b 5 present in natural rubber latex, it is a potential cause of cross-reactive food allergy in patients sensitised to rubber (latex-fruit allergy syndrome). Clinical data on this allergenic protein are very limited, although it appears to be of potential clinical significance (37).

Figure 2 Diagnostic algorithm for peach allergy



Polygalacturonase

During a preliminary Italian multicentre study on GRPs (34), immunoblot analysis revealed several patients hypersensitive to cypress pollen and with a history of peach allergy who exhibited marked IgE reactivity at a molecular weight of 50–60 kDa, entirely incompatible with the molecular weight of GRPs or LTPs. Treatment with periodate ruled out reactivity to carbohydrate determinants. Based on the molecular weight, hypersensitivity to polygalacturonase was hypothesised; this enzyme is involved in pectin degradation and is expressed during the fruit ripening phase, with a molecular weight of around 50–60 kDa. Polygalacturonase is also present in the pollen of various Cupressaceae (Cup a 2/Cup s 2) (38–40) as well as in foods such as tomato (38) and papaya (41).

3. Conclusions

Over the years, the significance of fish as a source of allergens has only increased. The variety of the chemical and physical characteristics of the allergens contained in this fruit, together with the wide range of clinical manifestations that may result from its ingestion by a sensitised patient, presents a challenge for the clinical allergist, particularly when practising in the Mediterranean region, where exposure to a variety of respiratory allergens not found elsewhere occurs. The concept of the peach as a 'crossroads' of allergic cross-reactions is illustrated in Figure 1.

Current diagnostic techniques allow for the precise identification of the allergens responsible for allergic reactions or sensitisation. However, as molecular diagnostics is a second-line investigation, and one that is often prohibitively expensive for many patients, it is useful to precede it with a routine procedure (including immediate-read skin tests) to provide a general guide. In vivo and in vitro diagnostic investigations with their respective results by allergen are summarised in Table 1, and a diagnostic algorithm is suggested in Figure 2.

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The silent memory of allergy

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1. Introduction: when memory outlasts exposure

In the allergist's daily practice, a seemingly simple yet immunologically counterintuitive fact is observed with remarkable regularity: levels of specific IgE can remain stable for years, sometimes for decades, even when exposure to the responsible allergen has long since ceased. A patient who no longer lives with a cat continues to have substantially unchanged anti-Fel d 1 IgE levels. Those who have eliminated an allergenic food from their diet often do not show a significant reduction in specific IgE. Similarly, many sensitivities documented in childhood persist into adulthood despite profound changes in the living environment.

This is not merely a laboratory curiosity, but a significant immunological paradox. IgE is, in fact, the antibody isotype with the lowest serum concentration and the shortest half-life among immunoglobulins — on the order of a few days in plasma (1, 2). Despite this, allergic sensitisation shows surprising stability over time. The traditional model attributes this phenomenon to the periodic reactivation of memory B cells by the allergen, within a context characterised by alterations in the Treg/Tfr regulatory circuits, well documented in the literature on immunotherapy (3, 4).

This is a robust model, but it is not entirely satisfactory in explaining certain recurring clinical observations: the persistence of sensitisation in individuals who scrupulously avoid the allergen for years, the tendency for IgE levels to re-

ABSTRACT

Keywords
• IgE • long-lived plasma cells • immunological memory • allergy • allergen-specific immunotherapy • biologics • type 2 memory B cells

Immunoglobulin E (IgE) is the antibody isotype with the lowest serum concentration and the shortest plasma half-life, yet allergic sensitisation can persist for years or decades even in the absence of obvious allergen exposure. This apparent paradox has traditionally been attributed to the periodic reactivation of memory B cells, within a context of altered immunological regulation and an imbalance in the Treg/Tfr (*T regulatory cells/T follicular regulatory cells*) circuits. Recent immunological findings, however, suggest a more complex model. Type 2 memory B cells constitute a dynamic reservoir capable of rapidly regenerating high-affinity IgE-secreting plasma cells. In parallel, recent experimental data indicate that a minority of IgE+ plasma cells may acquire long-survival characteristics, contributing to a relatively continuous antibody production that is partially independent of antigenic stimulation. These findings offer the clinical allergist a more coherent interpretative framework for allergic memory and future therapeutic strategies.

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turn to near-baseline values following the discontinuation of biologics, and the relative rarity of stable spontaneous remission in the natural history of allergic diseases.

In recent years, immunological research has begun to provide more precise interpretative tools, outlining a further dimension of allergic memory. Two recent findings have helped to redefine the perspective. The first concerns the identification of type 2 memory B cells, high-affinity allergen-specific cells, described almost simultaneously by independent groups and published in 2024 in *Science Translational Medicine* (7, 8). These cells do not express the IgE receptor on their surface, but are programmed to rapidly differentiate into IgE-producing plasma cells when they encounter the allergen again in a type 2-polarised immunological context. The second finding concerns the emergence — primarily in mouse models, but with consistent observa-

Figure 1 From plasmablast to long-lived plasma cell: a biological continuum

Characteristic	SHORT-LIVED PLASMA CELLS	LONG-LIVED PLASMA CELLS (LLPCS)
Origin	Mainly follicular	Germinal centres (mainly)
Antibody affinity	Low-moderate	High; extensive somatic hypermutation
Lifespan	Days-weeks	Months-decades
Metabolism	Mainly glycolytic	Mitochondrial oxidative phosphorylation
Survival niche	Absent or unstable	Specialized (bone marrow, spleen, mucosae)
Anti-CD20 sensitivity	Higher (sensitive)	Minimum (resistant)
Primary function	Rapid and transient antibody response	Stable and sustained antibody production
In the IgE context	Newly formed IgE plasma cells, early apoptosis	IgE$^+$ LLPCs in the spleen and bone marrow

Immediate, intense but transient response → Deep, silent, persistent memory

Short-lived plasma cells and long-lived plasma cells (LLPCs) do not represent rigidly distinct categories, but rather the opposite poles of a biological continuum modulated by the microenvironment and the cell's intrinsic transcriptional programme. IgE$^+$ LLPCs, although numerically rare, occupy the long-lived end of this spectrum

tions in humans as well — of long-lived IgE+ plasma cells (LLPCs), capable of producing antibodies continuously and relatively independently of antigenic stimulation. Two papers published in Immunity in November 2025 provided the first systematic evidence of this phenomenon (9–11). These observations do not replace the classical model, but complement it, outlining an allergic memory system organised into multiple compartments, each characterised by specific maintenance mechanisms and potential biological vulnerabilities. For the clinical allergist, this framework offers a more coherent interpretative key to phenomena that until recently remained only partially explained.

2. Long-lived plasma cells: silent architects of antibody memory

To understand what makes IgE+ LLPCs unique, it is useful to start with what we know about *long-lived plasma cells* in general. Their biology represents one of the most significant advances in modern immunology, with implications extending far beyond allergology.

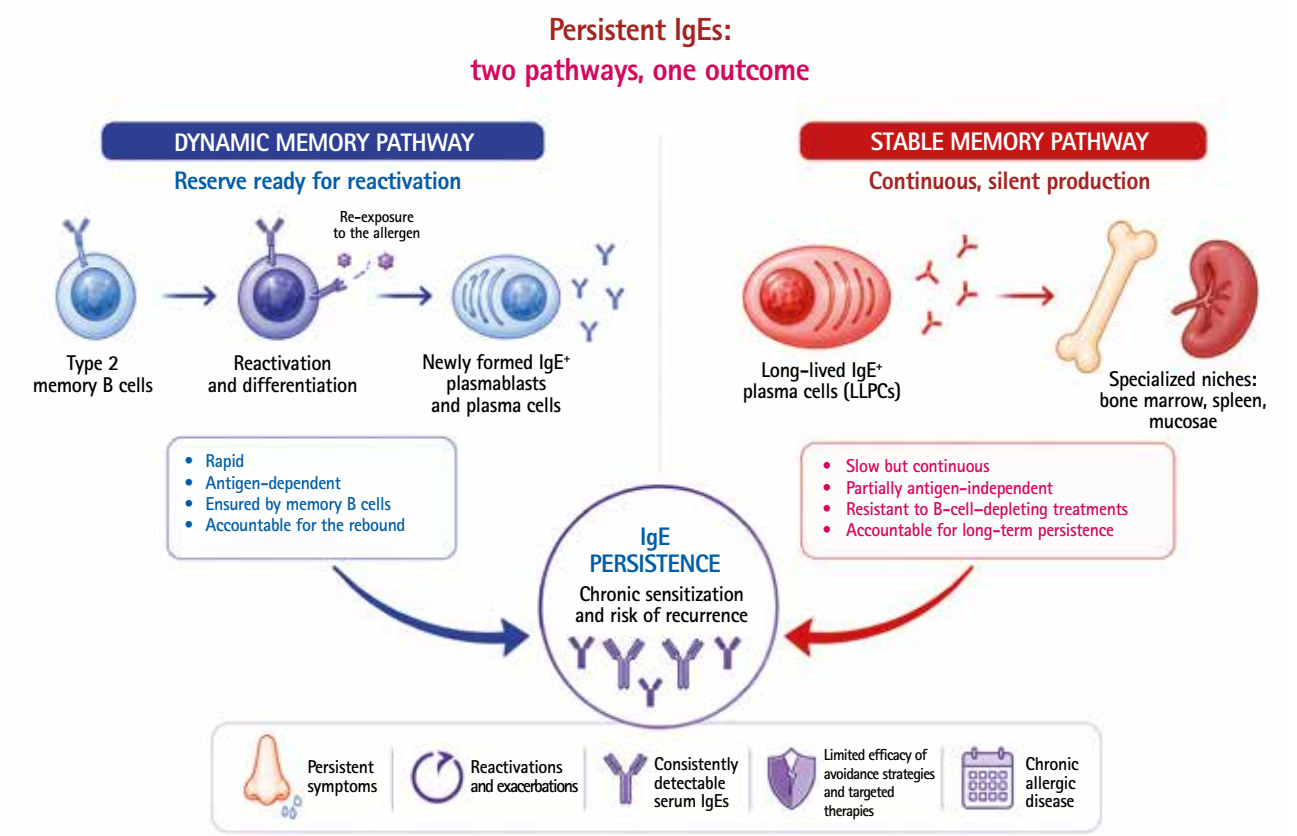
Plasma cells are the end product of B-cell differentiation and represent the main source of circulating antibodies. For many years, a seemingly simple classification was adopted: short-lived plasma cells, which play a key role in acute immune responses and are active in the first few weeks following antigen exposure; and long-lived plasma cells, responsible for maintaining antibody memory over time (12). Today we know that this distinction is more nuanced and, above all, more complex. LLPCs — Long-Lived Plasma Cells — are not simply plasma cells that 'live longer', but a highly specialised population, characterised by a specific transcriptional, metabolic and phenotypic programme, qualitatively different from that of short-lived plasma cells (13, 14). From a physiological perspective, the role of LLPCs is crucial for long-term immune protection. It is these cells that maintain protective levels of antibodies against pathogens encountered in childhood or following vaccination for years, sometimes for decades, without the need for further antigenic exposure. In other words, a significant part of the body's serological memory depends on their persistence. The long- -term stability of immunity against numerous childhood infections or against vaccines administered decades earlier represents the most evident clinical manifestation of this phenomenon.

The most elegant and direct demonstration of the longevity of LLPCs comes from *bomb pulse dating* studies. The atmospheric increase in carbon-14 produced by nuclear tests in the 1950s and 1960s left a measurable isotopic trace in cells generated during that period. By analysing the carbon-14 content of human plasma cells, it has been possible to estimate their biological age with considerable precision. Some human intestinal plasma cells were found to be over twenty years old (15). These are cells that originated when the patient was still a child and are still actively engaged in antibody production. This longevity represents a clear evolutionary advantage, as it allows for the maintenance of stable immune protection without the need for repeated exposure to the pathogen. The same mechanism can, however, take on pathological significance when plasma cells produce unwanted antibodies, as in autoimmune diseases and, likely, in certain forms of persistent allergy.

LLPCs originate predominantly in germinal centres, transient lymphoid structures that develop in secondary lymphoid organs in response to antigenic stimulation. In these sites, B lymphocytes are selected based on their ability to recognise the antigen with progressively increasing affinity, through the processes of somatic hypermutation and clonal selection that lead to the maturation of antibody affinity. Once differentiated, LLPCs migrate to specialised tissue niches, located mainly — but not exclusively — in the bone marrow (14, 16). These niches provide essential survival signals: cytokines such as IL-6, chemokines such as CXCL12, and other more specific factors that promote cell recruitment and retention, as well as the metabolic and structural support of the surrounding stromal cells. In the absence of such signals, LLPCs also undergo apoptosis (17). Their longevity is therefore not an automatic or intrinsically inherent property in the absolute sense, but the result of a dynamic and continuous interaction between the cellular programme and the tissue microenvironment (Figure 1).

This concept is also particularly important from an allergological perspective. When discussing the persistence of sen-

Figure 2 — Dual model of IgE persistence in allergic memory



Two complementary immunological compartments may contribute to the persistence of allergic sensitisation. On the left, the 'dynamic memory pathway', supported by type 2 memory B cells, allows for rapid reactivation and the generation of new IgE-secreting plasma cells following allergen re-exposure. On the right, the "stable memory pathway", supported by long-lived IgE+ plasma cells (LLPCs), can ensure continuous IgE production that is relatively independent of antigenic stimulation. The interaction between these two compartments contributes to the stability of serum IgE, the chronicity of sensitisation and the risk of recurrence.

sitisation, one should not merely envisage cells 'programmed to last', but cells that are able to find and maintain biological conditions favourable to long-term survival. Antibody persistence therefore depends not only on the cell itself, but also on its ability to occupy and maintain a suitable survival niche.

A further element that is emerging with increasing clarity concerns the role of the gut microbiota. Signals derived from the microbiota contribute to the early programming of plasma cell differentiation pathways, influencing the likelihood that a plasma cell will acquire long-lived characteristics (18, 19). In allergology, this link is particularly striking, given the now well-established

role of the microbiota in the maturation of the immune system and in susceptibility to atopic diseases. It is therefore plausible that early microbial exposures influence not only the likelihood of developing an allergy, but also its persistence over time.

From a metabolic perspective, LLPCs differ markedly from short-lived plasma cells. The latter rely predominantly on glycolysis to sustain rapid antibody production: a strategy that is effective in the short term but inefficient for prolonged secretion. LLPCs, on the other hand, adopt a more sustainable metabolic programme, based predominantly on mitochondrial oxidative phosphorylation (13, 16). This mechanism allows for continuous antibody production over very prolonged periods, potentially for years or decades, even in the absence of persistent antigenic stimulation. Essentially, this is an energetic adaptation consistent with their biological function.

From a phenotypic perspective, too, LLPCs exhibit distinctive characteristics. Long-lived plasma cells residing in human bone marrow are generally characterised by expression of the CD138 marker with low or absent expression of the CD20 marker (13, 14). This aspect has concrete clinical relevance. The reduced expression of CD20 makes these cells resistant to B-cell depletion therapies based on anti-CD20 antibodies, such as rituximab. In autoimmune diseases driven by the persistent production of autoantibodies, this resistance represents one of the main therapeutic limitations. In principle, the same concept could also apply to IgE+ LLPCs.

It is important to remember, however, that LLPCs do not constitute a homogeneous population. Single-cell transcriptomics studies have identified distinct subpopulations based on ontogenetic origin, transcriptional programme, antibody isotype produced and tissue localisation (13, 16, 19). Plasma cell longevity therefore emerges not as a binary property — long life or not — but as a biological continuum modulated by the interaction between the intrinsic cellular programme and the microenvironment.

This concept will be particularly relevant when considering IgE-producing plasma cells. The question, in fact, is not merely whether an IgE plasma cell can survive for a long time, but which biological conditions enable it to do so and whether there is a sub e capable of acquiring, at least in part, the typical characteristics of long-lived plasma cells of other isotypes (Figure 2).

3. The dynamic reservoir of IgE memory: type 2 memory B cells

The picture of allergic persistence now appears to be underpinned by complementary immunological compartments. On the one hand, IgE+ LLPCs may contribute to a relatively continuous and antigen-exposure-independent production of anti- s. On the other hand, type 2 memory B cells ensure the ability to rapidly regenerate new IgE-secreting plasma cells when the allergen is encountered again. These two compartments are not alternatives, but cooperate in determining the robustness and persistence of IgE memory (5–8).

The identification of type 2 memory B cells has helped to clarify an immunological problem that had remained unresolved for many years: how high-affinity allergenic memory is maintained in the absence of a stable population of IgE+ memory B cells, which are notoriously rare or almost absent. IgE+ memory cells are in fact extremely underrepresented, likely due to the same molecular mechanisms that limit the survival of IgE-producing plasma cells. IgE memory therefore appears to be maintained indirectly, via IgG-class memory B cells functionally oriented towards the type 2 response.

These cells express CD23 (FcεRII), the low-affinity receptor for IgE, and IL-4R, the receptor for interleukin-4; they also show transcription of the germinal gene for IgE, indicative of a predisposition to isotype switching (5, 7). These are cells already selected in the germinal centres for their high affinity towards the allergen and capable of rapidly differentiating into IgE-secreting plasma cells in the presence of IL-4 and appropriate costimulatory signals.

The absence of expression of the membrane IgE receptor allows them to evade the apoptotic mechanisms that limit the survival of mature IgE+ cells, whilst retaining a highly specific allergenic memory.

Two independent research groups described these cells almost simultaneously, publishing their findings in 2024 in *Science Translational Medicine* (7, 8). The data obtained in humans

Table 1 Take-home message

- The persistence of IgE reflects a complex and multi-layered immunological memory, not exclusively dependent on allergen re-exposure.
- Type 2 memory B cells represent a dynamic reservoir capable of rapidly regenerating IgE-secreting plasma cells.
- Long-lived IgE+ plasma cells (LLPCs) may contribute to continuous and relatively antigen-independent production.
- This model helps to explain the stability of IgE, the rebound following discontinuation of biologics, and the limitations of allergen avoidance.
- Allergen-specific immunotherapy remains the only approach capable of modifying the natural course of allergic disease.
- Future therapeutic approaches could target not only the effects but also the cellular sources of the IgE response.

are convincing. The frequency of type 2 memory B cells in peripheral blood correlates with circulating levels of specific IgE. In patients with persistent and clinically relevant sensitisation, allergen-specific B cells are predominantly concentrated in this functionally type 2-polarised compartment (5–8). In the most difficult-to-treat patients, a significant proportion of high-affinity allergenic memory may therefore depend on this cell population.

The clinical relevance of these observations also emerges in relation to allergen-specific immunotherapy. Preliminary data and biological considerations suggest that allergen-specific immunotherapy may modulate this compartment, favouring a shift towards non-pathogenic isotypes such as IgG4 and reducing the ability to recruit an IgE response (25). This could help to explain, at least in part, the persistent effects of immunotherapy observed in clinical practice.

This is a rapidly evolving field of research. The possibility of using type 2 memory B cells as predictive biomarkers of response to immunotherapy, or as potential therapeutic targets, represents an area of growing interest. Together with IgE+ LLPCs, these cells complete the biological picture of allergic persistence and pave the way for a better understanding of the role of long-lived IgE+ plasma cells.

4. Long-lived IgE+ plasma cells: an evolving paradigm

For a long time, IgE+ plasma cells were considered short-lived by definition, predominantly located in secondary lymphoid organs and characterised by limited survival (20, 21). This interpretation was based on robust and biologically coherent experimental observations. IgE+ cells exhibit particularly intense antigen receptor signalling, which promotes plasma cell differentiation but, at the same time, limits their survival. Their migration to survival niches in the bone marrow appears less efficient than that of IgG plasma cells, and their frequency in the bone marrow remains extremely low even in highly sensitised individuals.

Added to these factors is a particularly compelling intrinsic molecular mechanism. The expression of the membrane IgE receptor generates a tonic signal capable of promoting apoptosis through a specific intracellular cascade. In other words, IgE+ cells appear to incorporate a biological limit on survival into their differentiation programme (20). Newly formed IgE plasma cells are also particularly susceptible to cell death induced by receptor stimulation, a vulnerability that further reduces their persistence compared to other isotypes (22). Migration towards survival niches also appears less efficient. The response to the chemokine CXCL12, the primary signal for recruitment to the bone marrow, is attenuated, at least in part due to increased expression of RGS1 (*Regulator of G-Protein Signalling 1*), which is a negative regulator of chemokinergic signalling, and to reduced expression of the CXCR4 receptor in the early stages of maturation (10, 11). Overall, most newly formed IgE plasma cells tend to remain in secondary lymphoid organs, where they undergo cell death relatively quickly.

For years, this picture supported the idea that IgE production depended almost exclusively on repeated cycles of memory B-cell reactivation, with the continuous generation of short-lived plasma cells. From this perspective, the persistence of IgE over time was interpreted as the result of recurrent antigenic stimulation, even when this could not be clearly documented clinically. This model explained many observations, but not all. The persistence of relatively stable levels of specific IgE after years of allergen avoidance, the stability of the IgE profile during treatments that neutralise circulating IgE without eliminating plasma cells, and the rapid rebound in antibody levels following the discontinuation of omalizumab are difficult to explain solely through the cyclic reactivation of memory B cells.

In recent years, this picture has gradually been enriched with new elements. Studies conducted in both mice and humans indicate that a minority fraction of IgE+ plasma cells can acquire characteristics compatible with prolonged survival (11, 22). The process appears gradual and biologically plausible. Over time, these cells reduce the expression of the membrane IgE receptor, attenuating the apoptotic signal associated with its activation. Concurrently, the expression of anti-apoptotic factors increases, leading to progressively greater resistance to both spontaneous and antigen-stimulation-induced cell death. A small proportion of IgE-positive plasma cells therefore appears to acquire a more stable survival programme, functionally resembling the behaviour of long-lived plasma cells described for other isotypes. The most systematic evidence has been published in *Immunity*, where two independent studies documented the presence of long-lived IgE plasma cells in mouse models (10, 11). Miranda-Waldetario and colleagues used a genetic *timestamping* model that allows plasma cells present at a given time to be stably labelled and those generated subsequently to be selectively tracked. This approach showed that a fraction of IgE plasma cells persists for over 150 days, a duration incompatible with classification as short-lived cells. These cells exhibit a stable phenotype characterised by reduced expression of MHCII (Major Histocompatibility Complex II) and the membrane IgE receptor, and are predominantly localised in the spleen as well as in the bone marrow (11). The preferential localisation in a secondary lymphoid organ is an interesting finding, as it suggests that the maturation pathway of IgE+ LLPCs may not fully coincide with that of LLPCs of other isotypes.

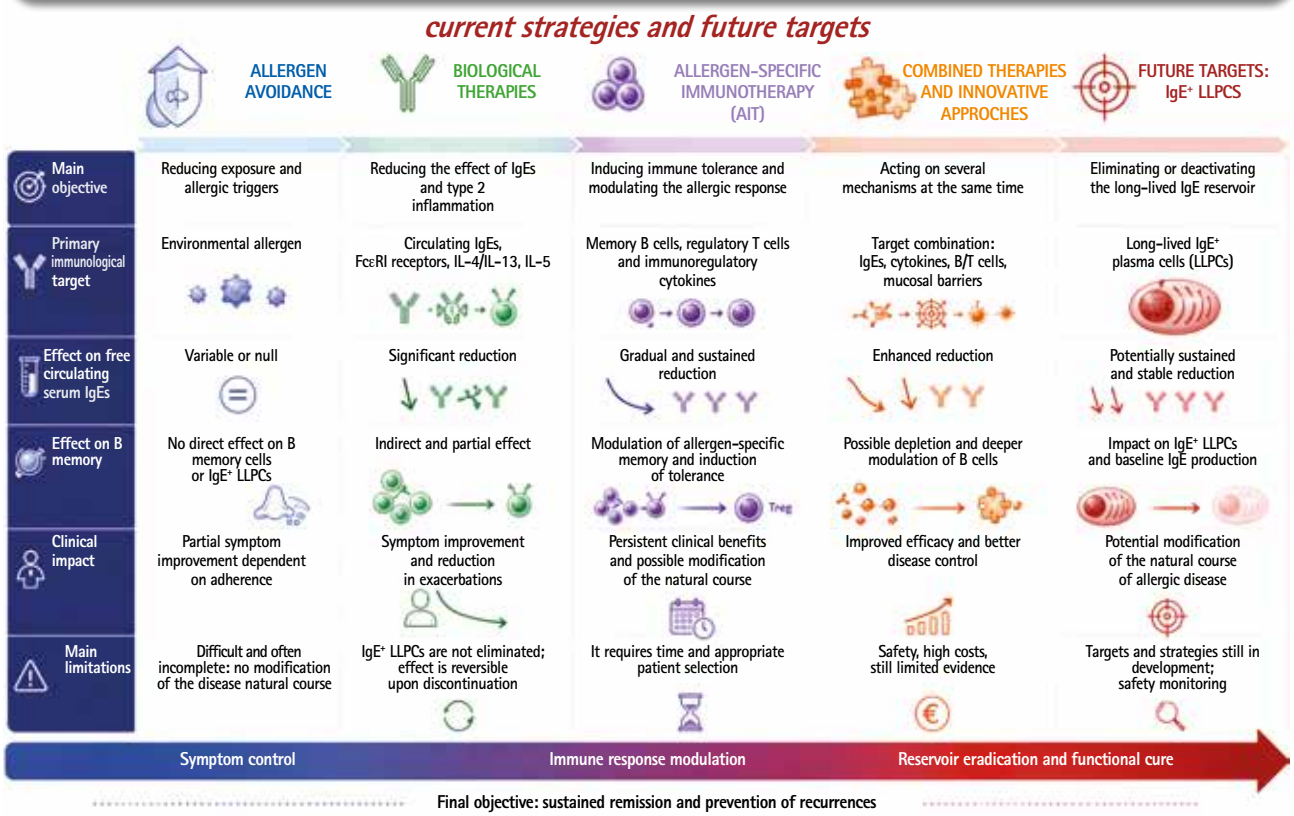
A complementary approach was adopted by Ding and colleagues, who applied mathematical models of cell dynamics to estimate the survival kinetics of IgE-producing plasma cells (10). The analysis identified two distinct populations: a short-lived one, with a half-life of approximately three days, consistent with historical observations, and a longer-lived population with a half-life of approximately 88 days, located predominantly in secondary lymphoid organs. This finding suggests that the persistence of IgE does not depend exclusively on the continuous generation of new short-lived plasma cells, but may also be sustained by a proportion of cells with significantly longer survival.

A further significant aspect concerns their specific anti-apoptotic programme, which differs from that observed in other isotypes. This finding suggests the existence of an isotype-specific biological vulnerability, which is conceptually relevant even if its clinical applicability remains, for the time being, purely exploratory (9).

It is important to clearly emphasise the limitations of the available evidence. The most robust data derive from mouse models, and the direct and systematic demonstration of IgE+ LLPCs in humans remains a necessary step. However, some observations in humans are consistent with this scenario. In the nasal mucosa of patients with allergic rhinitis and in chronic rhinosinusitis with nasal polyps, local IgE-positive plasma cells have been described with characteristics consistent with a relatively mature phenotype, including high expression of survival and anti-apoptotic genes, within a microenvironment reminiscent of plasma cell survival niches (23, 24). Although not constituting definitive proof, these data suggest that conditions favourable to the prolonged survival of IgE-producing plasma cells may also be present in human tissues.

Many clinical observations are now better understood in the light of this model. The persistence of relatively stable levels of specific IgE even after years of allergen avoidance, the stability of the IgE profile during treatments that

Figure 3 From understanding immunological mechanisms to therapeutic strategies



Current therapeutic options for allergic disease act on different compartments of the immunological memory. Allergen avoidance reduces exposure and symptoms but does not permanently alter sensitisation. Biologics reduce the effects of IgE and type 2 inflammation without necessarily eliminating persistent cellular compartments. Allergen-specific immunotherapy (AIT) can modulate immunological memory and alter the natural course of the disease. Combined strategies and future approaches targeting long-lived IgE+ plasma cells could allow for deeper and more lasting control of the allergic response.

neutralise circulating IgE without eliminating plasma cells, and the rise in antibody levels following discontinuation of omalizumab can be interpreted, at least in part, as the expression of a relatively autonomous source of antibody production that is largely independent of antigenic exposure. These phenomena are difficult to explain solely through the cyclic reactivation of memory B cells and appear more consistent with the presence of plasma cells capable of producing IgE continuously (11, 21).

Overall, the picture that emerges is one of a possible biological continuity between short-lived IgE-producing plasma cells and a minority of cells capable of acquiring characteristics compatible with prolonged survival. Although numerically rare, IgE+ LLPCs could contribute significantly to the persistence of

antibody production, providing a plausible biological basis for the stability of IgE levels observed in clinical practice even in the absence of obvious allergen exposure. This interpretation does not replace the role of type 2 memory B cells, but introduces a further dimension to the problem, suggesting that IgE memory may be sustained by distinct yet complementary compartments.

5. What this means for the allergist: new clinical insights

The biology of IgE+ LLPCs and type 2 memory B cells not only represents an advance in basic immunological knowledge but also offers the clinical allergist more coherent interpretative tools to explain phenomena observed daily in practice, which are often difficult to account for satisfactorily using traditional models.

A first point concerns the persistence of sensitisation in the absence of clearly documented allergen exposure. The classical model often required hypothesising continuous residual exposure to the allergen or cross-reactivity with structurally related allergens to explain the stability of IgE over time. IgE+ LLPCs, by producing antibodies in a relatively autonomous manner and with little dependence on antigenic stimulation, offer a biologically plausible explanation without having to rely exclusively on these hypotheses. The stability of specific IgE therefore does not merely reflect a memory ready to be reactivated, but may also depend on relatively continuous antibody production. This also alters the realistic expectations to be shared with patients adopting strict avoidance strategies: avoidance remains fundamental for reducing symptomatic triggers, but does not necessarily lead to the disappearance of sensitisation (26).

A second aspect concerns the dynamics of IgE during and after biologic treatments. Omalizumab neutralises circulating IgE by binding to the constant region of the molecule and preventing its interaction with high- and low-affinity receptors. However, this mechanism does not eliminate IgE-secreting plasma cells nor, in all likelihood, the LLPCs that sustain their production. It is therefore not surprising that, following treatment discontinuation, IgE levels tend to return to values close to baseline in a significant proportion of patients. Data from the Italian IRSA registry confirm this observation in real-world clinical practice (27). In light of the most recent biological evidence, this dynamic can be interpreted as the resumption of antibody production sustained by persistent cellular compartments.

Similar considerations apply to biologics that act further upstream of IgE production. Dupilumab, by blocking IL-4 and IL-13 signalling via the common receptor subunit, reduces type 2 immune polarisation and the isotype switch towards IgE. Tezepelumab, by neutralising TSLP (*Thymic Stromal Lymphopoietin*), interferes with earlier epithelial signals in the inflammatory cascade. Both mechanisms are effective in reducing the production of new IgE and the generation of new IgE+ plasma cells, but they do not lead to the elimination of already differentiated plasma cells, and even less so of IgE+ LLPCs that have acquired relative independence from external cytokine signals. In this context, type 2 memory B cells — which express IL-4R and are sensitive to the signals blocked by dupilumab — could represent a more direct target than already stabilised LLPCs. This distinction could have future implications for treatment selection and sequencing.

Allergen-specific immunotherapy remains, based on the available evidence, the only strategy capable of modifying the natural course of allergic disease, with benefits that may persist over time even after treatment is discontinued and with possible preventive effects on the development of new sensitisation and asthma (3). In light of the most recent findings, it is plausible that part of these effects also stems from the modulation of type 2 memory B cells and the reduction in their ability to trigger an IgE response. This mechanism could contribute to the persistent effects observed in clinical practice, as demonstrated in both sublingual immunotherapy for respiratory allergens and for hymenoptera venom, a field in which Italian research has made significant contributions (28, 29) (Figure 3).

The question of whether immunotherapy can also directly influence IgE+ LLPCs, however, remains open. From a biological perspective, these cells are at a more advanced stage of maturation, characterised by reduced expression of the membrane receptor and greater autonomy from external signals. It is therefore plausible that they are only partially

sensitive to the effects of immunotherapy. This could help explain why some patients show a resumption of IgE production after treatment discontinuation despite a good clinical response during therapy (10, 11). It should be noted that systematic direct evidence comes from mouse models. Studies specifically designed to monitor IgE+ LLPCs before, during and after immunotherapy will be necessary to clarify this aspect.

An area of growing interest concerns the sequential combination of biologics and allergen-specific immunotherapy, particularly in severe allergic asthma. The biological hypothesis is that biologics may create immunological conditions more conducive to the efficacy of immunotherapy by reducing underlying inflammation and allergen reactivity, whilst AIT may have a more lasting effect on allergen-specific immunological memory. Preliminary data suggest that, in a selected group of patients, it may be possible to reduce or discontinue the biologic after an appropriate course of AIT, with potential clinical and economic benefits (30).

It should also be noted that no immunotherapy can fully demonstrate its efficacy in the presence of unrecognised or untreated comorbidities. Obesity, gastro-oesophageal reflux, obstructive sleep apnoea and persistent exposure to environmental irritants such as tobacco smoke or domestic pollution contribute to maintaining underlying inflammation and influence the therapeutic response. The management of the complex allergic patient therefore remains an exercise in integrated, non-algorithmic medicine, in which an understanding of the biology of LLPCs and type 2 memory B cells represents an additional, but not exclusive, tool.

From a translational perspective, the observation that IgE+ LLPCs appear to depend on autonomous families for survival identifies a potentially significant biological vulnerability (9). At present, this finding remains primarily of conceptual and experimental interest, but it opens up the prospect of future therapeutic strategies targeting not only the effects of the IgE response but also its cellular sources (Table 1).

6. Conclusions: an integrated view of allergic persistence

Allergic persistence does not appear to be a random phenomenon nor one exclusively dependent on continuous allergen exposure. Rather, it reflects a structured and layered immunological memory, supported by cellular mechanisms capable of operating over very prolonged time scales. Understanding this architecture represents an important step towards interpreting the natural history of allergic disease more coherently and guiding the development of more effective therapeutic strategies.

The most recent evidence suggests the existence of a robust and redundant system, supported by at least two complementary immunological memory compartments. Type 2 memory B cells ensure a rapid and highly specific response in the event of new allergen exposure, generating new high-affinity IgE-secreting plasma cells. IgE+ LLPCs introduce a further dimension, characterised by relatively continuous antibody production that is at least partly independent of antigenic stimulation. The interaction between these compartments helps to explain the persistence of sensitisation and the difficulty in achieving complete and stable remission in the most complex cases.

Allergen-specific immunotherapy, when indicated and conducted for an adequate duration, remains the only intervention capable of modifying the natural course of allergic disease, with documented benefits that may persist after treatment discontinuation and with possible preventive effects on the development of new sensitisation and asthma. New biological insights do not diminish this role, but rather clarify its cellular mechanisms and current limitations.

For the clinical allergist, this knowledge offers a more coherent interpretative framework for understanding the stability of specific IgE despite avoidance, the resumption of antibody production following the discontinuation of biologics, and the variability of the response to immunotherapy. It is likely that further mechanisms contribute to this complexity and that new evidence will further modify the current model.

Direct and systematic demonstration of IgE+ LLPCs in humans remains a necessary step to consolidate this paradigm. The development of reliable methods to identify and characterise these cells in human tissues will pave the way for clinical studies aimed at clarifying their quantitative contribution to IgE production and their potential for the-

rapeutic modulation.
In the meantime, the growing understanding of IgE memory mechanisms is already steering research towards new therapeutic targets, with the prospect of intervening not only on the effects of allergic sensitisation, but also on its deeper immunological foundations. A perspective that does not replace current strategies, but places them within a broader and more coherent biological framework.

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Overview of aeroallergens in Asia

Landscape of Aeroallergen Sensitization in Asia

Xiaoling Y et al. Clin Exp Allergy, 2025, 55: 901-915.
https://doi.org/10.1111/cea.70137

In this comprehensive review, the authors address the broad topic of the role of aeroallergens and their impact on the health of populations in various Asian countries.
The discussion focuses on allergic asthma (AA) and allergic rhinitis (AR): the prevalence rates of these conditions are rising and have reached significant levels, with a third of the populations of South Korea and the United Arab Emirates affected by AR and nearly 40 million Asian citizens affected by AA.
The main triggers are sensitisation to airborne allergens from house dust mites (HDMs) in indoor environments and seasonal pollens in more temperate areas, such as *Cryptomeria japonica* in Japan and *Artemisia vulgaris* in northern China.

Aeroallergens: mites

Great emphasis is placed on the central role of HDMs across much of Asia. Mites are the primary source of allergens in indoor environments, ahead of pet dander and cockroach allergens. Generally, more temperate regions (e.g. eastern China) provide fertile ground for the proliferation of *Dermatophagoides pteronyssinus* (DP) and *Dermatophagoides farinae* (DF), whilst more tropical regions in the south-east (e.g. Guangdong, Taiwan, Malaysia) see an abundance of *Blomia tropicalis* (BT), though this does not rule out cases of significant presence of multiple mite species (e.g. Singapore). In general, HDM sensitisation rates exceed the average of 75% in Southeast Asia.
Even in desert regions, such as the Middle East, mites can proliferate in certain microenvironments near humid coastal areas; one need only consider the extremely high sensitisation rates among Israeli AR patients in such areas (92%), although the rates in the central mountainous regions (62%) and the arid southern regions (46%) are also noteworthy.

Aeroallergens: pollen

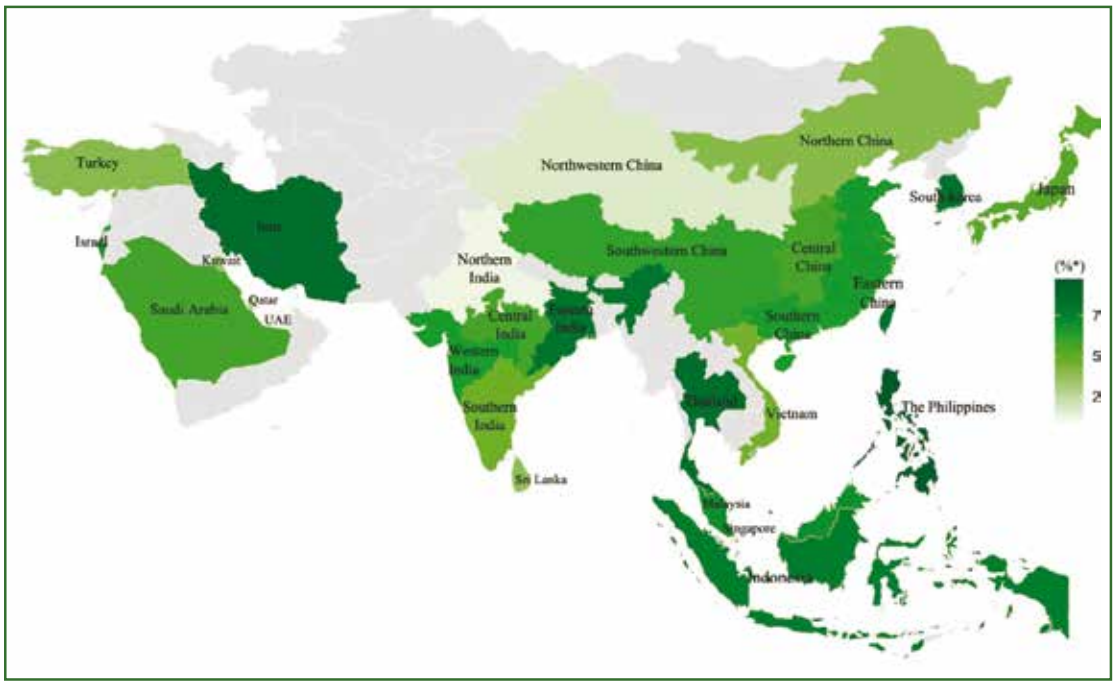
In outdoor environments, pollen is a significant source of sensitisation to airborne allergens across much of Asia. In northern China, there is an abundance of cases of allergy to mugwort and ragweed; in Korea, birch and alder; in Japan, Japanese cedar; and then again *Parthenium hysterophorus* in India, olive, *Salsola tragus* and *Chenopodium album* in the Middle East, and mulberry in China, Taiwan and Pakistan.
Noteworthy is the role of the paper mulberry (*Broussonetia papyrifera*), which has recently emerged as a significant allergen in numerous Asian countries; sensitisation rates in atopic individuals stand at 38.4% in Taiwan and China and 41.9% in Pakistan, with peak concentrations of pollen particles in the air exceeding 30,000 $^{grains/m^3}$. The paper mulberry is also widespread in numerous other countries, such as Cambodia, Japan, South Korea, Laos, Malaysia, Myanmar, Thailand and Vietnam: it is fair to say that it should be included in the routine allergen panels of these countries, although further investigations into its clinical relevance are required*.
In Japan, the role of the Japanese cedar is well known. Its widespread presence across much of the country is the result of massive post-war afforestation campaigns in urban and suburban areas; today, sensitisation rates to Japanese cedar reach peaks of 60% among young adults in metropolitan areas. Sensitisation is primarily to the Cry j 1 and Cry j 2 allergens, which are now consistently present in both diagnostic kits and dedicated immunotherapy products.
For Japanese hop (*Humulus japonicus*), notable sensitisation rates are evident particularly in north-north-western China (15–36.2%), as well as to a lesser extent in South Korea (2.4–16.4%); its main allergen is Hum j 6, a defensin-like protein.

Effects of factors that may influence the properties of airborne allergens

Unfortunately, airborne allergens do not remain inert in the air they circulate in; there are various factors with which they interact, complicating their effects on susceptible individuals. Air pollution (PM2.5, PM10, NO2) has been shown to alter

Figure 1

Geographical map of the prevalence of sensitisation to house dust mites (*D. pteronyssinus, D. farinae, B. tropicalis*) based on SPT or sIgE results from Asian studies



the structure of pollen and enhance its allergenic effect, thereby exacerbating its effects. Pollutants interact with airborne allergens, stabilising them and increasing their persistence in the environment; chemical processes induced by pollutants (nitration, oxidation, oligomerisation) can increase the binding capacity of specific IgE antibodies, as well as causing stress to the plants involved, resulting in the overproduction of allergenic molecules.

Several biological factors influence the prevalence of sensitisation in Asia. Males are more likely to develop allergic symptoms in childhood, with a positive association with testosterone levels. For HDMs, for example, sensitisation rates in the Singaporean population show a sharp rise among children aged 3–5 years (84.5%), reaching 97.3% in those over 14 years of age, plausibly due to repeated environmental exposure and the possible implications of age on the development of the immune system.

Finally, numerous gene variants specific to allergic susceptibility have been documented in Asia. For example, GWAS have revealed the existence of loci contributing to mono- and poly-sensitisation, such as variants of CD28, IL7R, STAT6 and HLA.

Remedies

Given the complex situation across the Asian continent, the authors emphasise the importance of understanding sensitisation patterns at a regional level, so as to develop countermeasures that are as specific as possible to the contexts under

consideration.
Whilst environmental control and prevention are essential and indispensable measures, it is a sad reality that the total avoidance of allergenic molecules is virtually impossible. Pharmacotherapy therefore remains the primary method for symptom control; many Asian countries already follow the ARIA and GINA guidelines, and in recent times the use of biologics has established itself as an essential tool.
Although the soothing effect of pharmacotherapy offers rapid and reliable relief, it must be emphasised that the only approach capable of 'tackling the root of the problem' is specific immunotherapy (AIT) administered parenterally (SCIT) or sublingually (SLIT). To date, the uptake of AIT in Asia remains relatively low, with usage rates below 10% in certain regions; the reasons for this lie in the scarcity of sufficiently standardised products for many allergenic sources, treatment costs, regulatory constraints, and the still limited understanding of allergic conditions among both patients and the medical profession.

Challenges and limitations

Despite the extensive evidence used in compiling this comprehensive 'allergenic report' on the Asian continent, it is worth mentioning the challenges that still need to be overcome.
Among these, as the authors later mention, the heterogeneity of diagnostic products (skin prick tests, SPTs) across the various Asian countries considered could make the results difficult to compare; it is plausible that the SPTs used vary in terms of the allergen panels investigated, diagnostic cut-offs and standardisation of extracts.
Whilst urbanisation may be associated with higher rates of awareness, it is important to take certain confounding factors into account: people living in these environments tend to undergo diagnostic and therapeutic procedures more readily, due to the greater availability of adequate healthcare services. In general, wealthier countries may be over-represented compared to poorer ones. The review also draws on relatively older articles (prior to 2015) to compensate for the scarcity of recent studies specific to certain Asian regions.
It is therefore certainly necessary to strive to identify a comparative analysis of the various published studies in order to clarify the causal relationships between risk factors and the conditions under examination, thereby enabling useful conclusions to be drawn to improve both the diagnostic and therapeutic approaches. From this perspective, the review serves as a 'pioneer' in highlighting this principle; the path to prevention must involve harmonised diagnostic protocols and well-coordinated regional surveillance services.

**Some cases of allergy to this pollen have also been reported in Italy (1, 2).*

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Interaction between the gut microbiome and metabolomics in allergic rhinitis

Integrated gut microbiome and metabolomics analysis reveals microbial-metabolic cross-talk in allergic rhinitis.

Sun G et al. Frontiers in Microbiology (2025); doi: 10.3389/fmicb.2025.1652915

As is well known, allergic rhinitis (AR) is one of the most common allergic diseases; it is characterised by chronic inflammation of the nasal mucosa and represents a significant public health problem given the risk of its chronicity and association with other comorbidities such as

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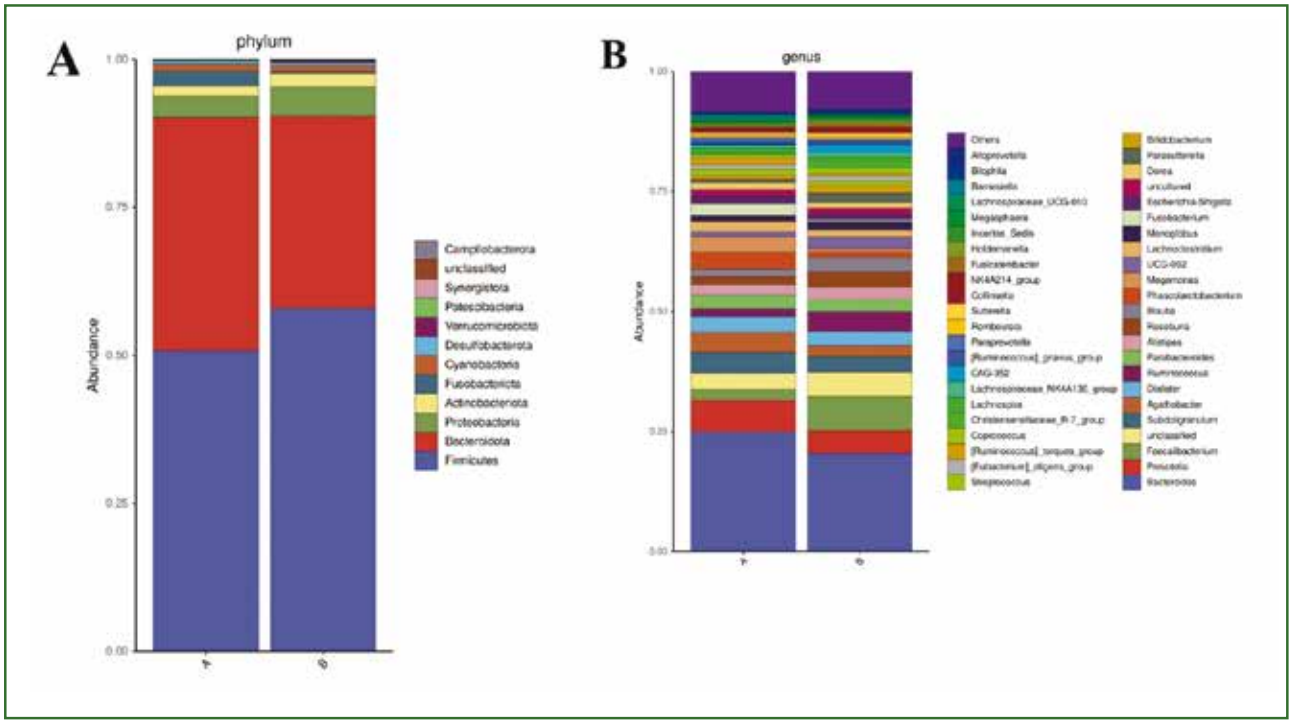
Figure 1

Gut microbial composition and taxonomic differences between RA patients and healthy controls



A) Relative abundance of bacterial phyla **B)** Relative abundance of bacterial genera

conjunctivitis and asthma. Although there has been an improvement in our understanding of its pathophysiology in recent years (including eosinophilic infiltration, IgE-mediated mast cell activation and the release of pro-inflammatory cytokines such as IL-4, IL-5 and IL-13), the exact mechanism underlying the development of AR is not yet fully understood. Several research groups are aiming to discover new pathogenic mechanisms of the disease in the hope that these may then represent potential therapeutic targets. In this article, the authors, having reviewed the literature on the importance of the gut microbiota in modulating systemic immunological homeostasis, go on to emphasise that other scientific evidence appears to demonstrate how disturbances in microbial richness, taxonomic and structural diversity, and the metabolites they produce, could influence the development and progression of RA. With the aim of contributing to a further characterisation of this possible influence, the authors present data from their own study, which aimed to investigate the possible role of gut dysbiosis* in the development of allergic rhinitis.

To this end, stool samples from 23 subjects with allergic rhinitis and 15 healthy subjects were collected and subjected to an integrated multi-omic analysis** (as described in detail by the authors) with the aim of: 1) identifying

AR-specific alterations in gut microbial composition and metabolic pathways; 2) characterise any correlations between gut dysbiotic bacteria and the production of immunomodulatory metabolites.

The multi-omic analysis of the gut microbiota revealed that patients with allergic rhinitis exhibited a different microbial community, at both phylum and genus levels, compared to the control population. For example, at the phylum level (Fig. 1A), whilst Firmicutes and Bacteroidetes were dominant in both groups, a marked increase in the pro-inflammatory phylum Fusobacteriota was observed in AR patients, whereas this phylum was almost absent in healthy subjects. An analysis at the genus level (Fig. 1B) revealed that Faecalibacterium, a key genus in the production of immunoregulatory metabolites such as short-chain fatty acids (SCFAs), was particularly abundant in healthy subjects and, conversely, was significantly reduced in patients with RA. In addition, other SCFA-producing genera, including Ruminococcus, were not particularly abundant in the group of patients with RA.

Taken together, these data suggest that the presence, on the one hand, of a microbiota characterised by reduced immunoregulatory capacity and, on the other, of a microbiota potentially associated with inflammation, may lead to the development of a state of intestinal microbial dysbiosis in RA patients, and this alteration could provide a microbial basis for the systemic immune dysregulation observed in allergic rhinitis.

Metabolomic analysis*** also revealed significant differences; in particular, it was observed that in patients with allergic rhinitis, the vitamin synthesis pathways involving the biosynthesis of pantothenate and coenzyme A (CoA) were disrupted and the energy storage pathways were altered. Furthermore, this analytical approach revealed significant correlations between specific bacterial genera and metabolites. For example, the positive correlation between phenolic compounds such as 2-methoxy-4-vinylphenol and SCFC-producing genera (Ruminococcus, Faecalibacterium) suggests a link between these beneficial bacteria and the production of immunomodulatory metabolites, i.e. those capable of protecting the intestinal barrier. Conversely, the negative correlation between 2-methoxy-4-vinylphenol and species sometimes associated with intestinal inflammation reinforces the concept of functional antagonism within the microbial community. These microbiome-metabolite interactions provide mechanistic insights into how intestinal dysbiosis may contribute to the pathophysiology of allergic rhinitis, highlighting the role of metabolites of microbial origin in immune regulation via the gut-nose axis.

The authors conclude their paper by emphasising that the integration of data from microbial taxonomy and functional metabolomics via a multi-omic approach may be useful for identifying potential targets and thus new strategies in the clinical management of patients with AR. At the same time, however, they acknowledge the study's limitations; these include the relatively small sample size, the fact that they examined only: 1) the bacterial community and its metabolites, and no other microorganisms potentially present in the gut ecosystem such as viruses and fungi; 2) the gut microbiome and not that present in the upper airways, since alterations in the composition of the nasal microbiome could negatively affect local immunological homeostasis and the integrity of the mucosal barrier, thereby facilitating a Th2-type inflammatory response as a consequence of exposure to allergens.

**Intestinal dysbiosis is a quantitative and qualitative imbalance of the gut microbiota (bacterial flora), which loses its normal biodiversity and beneficial functions*

*** Multi-omic analysis is an advanced biological approach that simultaneously integrates data from various 'omic' disciplines (genomics, transcriptomics, metabolomics, etc.) on the same biological sample.*

**** Metabolomics is the systematic study of metabolites (small molecules) detectable in biological fluids as a result of specific cellular processes.*

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Effects of house dust mite sensitisation on the clinical presentation of shellfish allergy

House dust mite sensitization shapes the clinical expression of shellfish allergy

Scala E et al. European Annals of Allergy and Clinical Immunology. 2026. 10.23822/EurAnnACI.1764-1489.434

When discussing food allergies, there is often a certain 'overlap' between house dust mite allergy and shellfish allergy, to the extent that they manifest simultaneously in affected individuals. The reason for this lies in the presence, in both species of invertebrates, of allergens which, despite their phylogenetic distance, exhibit significant sequence homology (hence the name 'panallergens'); these include tropomyosin, arginine kinase, troponin C, the myosin light chain and the sarcoplasmic calcium-binding protein, components that reflect evolutionary links related to muscle motility and contraction.
Knowledge regarding the actual clinical relevance of this phenomenon of IgE cross-reactivity is, however, still incomplete. In particular, does allergy to decapod crustaceans and molluscs develop as a result of primary sensitisation via the diet, or is it due to a cross-reactivity phenomenon following initial sensitisation to house dust mites? These are the foundations of the multicentre observational study, conducted between January 2020 and December 2024, by Dr Scala E. and colleagues. The authors considered data from a large cohort collected at various specialist allergy centres operating in three Italian geographical

Figure 1 Sensitisation patterns to *Sarcoptiformes, Mollusca* and *Decapoda*

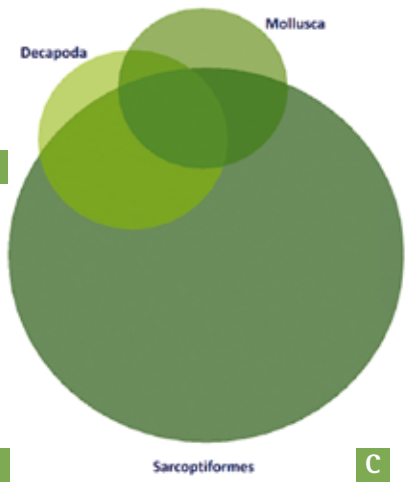
A

N (%)	Sarcoptiformes	Decapoda	Mollusca
195 (6,0%)	(-)	(-)	(+)
122 (3,7%)	(-)	(+)	(-)
18 (0,6%)	(-)	(+)	(+)
2261 (69,2%)	(+)	(-)	(-)
139 (4,3%)	(+)	(-)	(+)
345 (10,6%)	(+)	(+)	(-)
185 (5,7%)	(+)	(+)	(+)

B

N= 3265		Sarcoptiformes (-)	Sarcoptiformes (+)	Decapoda (-)	Decapoda (+)	Mollusca (-)	Mollusca (+)
Sarcoptiformes	(-)	335 (10,3%)					
	(+)		2930 (89,7%)				
Decapoda	(-)	195 (6,0%)	2400 (73,5%)	2595 (79,5%)			
	(+)	140 (4,3%)	530 (16,2%)		670 (20,5%)		
Mollusca	(-)	122 (3,7%)	2606 (79,8%)	2261 (69,2%)	467 (14,3%)	2728 (83,6%)	
	(+)	213 (6,5%)	324 (9,9%)	334 (10,2%)	203 (6,2%)		537 (16,4%)

C



A: Numbers and percentages of patients sensitised to each allergen group
B: Patterns of co-reactivity at the molecular level and indication of the number of patients showing IgE reactivity to specific analytes within and between the three allergen groups.
C: Intersection of sensitisation patterns among the three taxa.

regions (north, central and south). All participants (3,777) underwent an allergy test using a standardised proteomic platform that allows the simultaneous measurement of the *IgE-binding* profile against several hundred allergenic molecules or extracts in a single serum sample.

Participants were recruited into the study on a strictly laboratory-based basis, having to demonstrate allergic sensitisation to at least one of the individual components or extracts derived from a range of invertebrates; 3,265 participants tested positive for molluscs, decapods and mites. Of these, 2,261 (69.2%) were positive for mites without showing any cross-sensitisation to molluscs or decapods. Conversely, among patients allergic to decapods, 530 out of 670 were also positive for mites, whilst among those positive for molluscs, 324 out of 537 showed co-sensitisation to mites, suggesting the hypothesis of cross-reactivity linked to the presence of homologous IgE-binding epitopes. It should be noted that 335 patients (10.3% of the total cohort and 33.3% of those sensitised to molluscs and decapods) were monosensitive, showing no cross-reactivity to house dust mites, suggesting the existence of alternative sources of sensitisation. Furthermore, when considering clinically relevant symptoms, those related to shellfish are predominantly found in patients allergic to house dust mites, whereas they are rather rare in patients who test negative for house dust mites, despite detectable serum IgE, suggesting that exposure to house dust mites represents the primary factor in the development of allergic symptoms. Another interesting observation is that 85% of patients sensitised to both house dust mites and molluscs/decapods exhibit IgE reactivity to various mite-specific molecules (Group 1, Group 2, Der p 10, Der p 23), reinforcing the hypothesis that house dust mites are the dominant source of sensitisation. Particular emphasis was then placed on panallergens known to mediate IgE cross-reactivity, and in 95% of the aforementioned patients, specific IgE was detected against tropomyosin, which is associated with a high risk of severe allergic reactions in the event of seafood ingestion. Conversely, an inverse relationship generally results in only 'mild reactions', as does sensitisation to the arginine kinase component, whilst systemic reactions were observed in cases of sensitisation to other components such as sarcoplasmic calcium-binding protein and troponin C.

The evidence emerging from this study supports the role of mites, particularly *Sarcoptiformes*, in inducing IgE cross-reactivity with homologous allergens from molluscs and decapods. Contrary to what one might expect, sensitisation induced by seafood via the diet remains a secondary occurrence.

The study does, however, have limitations, as highlighted by the authors: clinical data were mostly reported directly by the patients themselves, with possible omissions of all relevant details and consequent errors. Furthermore, the study population consisted exclusively of Italians, with consequent limitations on the generalisability of the data. Finally, the assay used for the characterisation of IgE profiles (ALEX²®) may not have included all allergens clinically relevant to this case.

The results of this study suggest that the detection of IgE to dust mite allergens in allergic individuals is a powerful biomarker for identifying patients at significant risk of systemic reactions; conversely, sensitisation to molluscs and decapods in the absence of specific IgE to dust mites is associated with a low probability of triggering allergic symptoms. Consolidating these findings would enable more personalised monitoring and risk management strategies for individual patients, allowing for more accurate diagnosis and the avoidance of unnecessary dietary restrictions for patients at risk of seafood allergy.

Potential pollen-food syndrome between nsLTPs from olive and peach pollen

Pollen-Food Allergy Syndrome: From Food Avoidance to Deciphering the Potential Cross-Reactivity between Pru p 3 and Ole e 7.

Álvarez P et al. Nutrients, 2024 Aug 27;16(17):2869. doi: 10.3390/nu16172869

In this fascinating and original study, the authors initially focus their attention on the 'non-specific lipid transfer protein' (nsLTP) molecule, noting that, particularly the one belonging to the Rosaceae family and more specifically the one found in peaches known as Pru p 3, is becoming one of

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the leading causes of *food allergy*, especially in Mediterranean countries. In Northern and Central European countries, many cases of sensitisation to this allergen are clinically insignificant and centred on other nsLTP species, which may also be present in pollen. This has prompted, as the authors subsequently emphasise, an investigation into these seasonal nsLTPs as potential primary sensitising agents capable of triggering a *pollen-food allergy syndrome* (PFAS) through a phenomenon of cross-reactivity. The aim of this study was to verify whether the form of nsLTP (known as Ole e 7) identified in *Olea europea* pollen as a minor allergen, but actually recognised as responsible for the most severe asthmatic symptoms in regions characterised by a high presence of olive pollen in the ambient air (for example, Andalusia in Spain), could cause PFAS in association with certain foods. In these regions, it has in fact been observed that patients positive for Ole e 7 often exhibit allergic symptoms to peaches or a co-sensitisation to the peach allergen Pru p 3, suggesting a potential link between these forms of nsLTP, albeit phylogenetically distant. Since no data had previously demonstrated the presence of potential *allergy-relevant* cross-reactive *epitopes* between them, the authors first identified, through complex molecular and immunological analytical approaches, the *IgE-binding epitope* regions of both Ole 7 (2 peptide sequences) and Pru p 3 (3 peptide sequences), using serum pools from patients monosensitive to Ole e 7 (MON-OLE), or to Pru p 3 (MON-PRU), or to both (BI). In particular, the epitopes recognised by the different pools are shown in Table 1, from which it can be seen that the peptide sequence "KSALALVGNKV" of Ole e 7 is recognised by all pools of serum from MON-OLE, MON-PRU and BI patients; conversely, all patient serum pools recognise the peptide sequence "ISASTNCATVK" of Pru p 3. Although sequence alignment tests between Ole e 7 and Pru p 3 show only partial identity, apparently insufficient to justify cross-reactivity, the presence in both molecules of certain key amino acids—even if not sequentially aligned—as well as the existence of significant structural homology, significantly increases their identity to values exceeding 50%, and this may underlie their potential cross-reactivity. An interesting observation from this study is that the pool of sera from BI patients shows a particularly high level of specific IgE to Ole e 7, when compared with that to Ole e 1 (the major allergen in olive pollen), and this appears to support the idea of its possible role as *a primary sensitiser*, particularly in areas with extremely high levels of '*olive pollen pressure*', and to cause a potential *pollen-food syndrome* due to cross-reactivity with Pru p 3. The authors therefore emphasise the importance of not limiting oneself to sequence identity to demonstrate potential cross-reactivity phenomena among the various nsLTP species, but of also taking into account other factors such as, for example, their structural characteristics. They conclude by acknowledging a number of limitations of the study, including the small number of patient sera analysed and the use of pools rather than individual sera, and express the hope that further studies with a larger cohort of patients will be conducted to validate or refute their initial observations.

Table 1 *IgE-binding epitopes* of Ole e 7 and Pru p 3

	Ole e 7-bound epitopes	Pru p 3-binding epitopes
MON-OLE pool	O1: KLTSCVSYLDDKS O2: KSALALVGNKV	P3: ISASTNCATVK
MON-PRU pool	O2: KSALALVGNKV	P3: ISASTNCATVK
BI pool	O2: KSALALVGNKV	P1: NVNNLAR P2: QLSASVPGVNPNNAAALPGK P3: ISASTNCATVK

MON-OLE: pool of sera from patients monosensitive to Ole e 7; MON-PRU: pool of sera from patients monosensitive to Pru p 3; BI: pool of sera from patients IgE-positive to Ole e 7 and Pru p 3.

Provide information, create a profession

Edited by **Franco Frati**
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New developments in the determination of LTP in clinical practice: the example of Can s 3

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With the recent and increasingly widespread use of hemp in the food industry, a gradual rise in hypersensitivity reactions is being observed.
Hemp derivatives, particularly the seeds, are now considered superfoods as they are rich in high-quality proteins, essential fatty acids, fibre and minerals, and are therefore widely consumed.
From a botanical perspective, hemp and cannabis belong to the Cannabaceae family; specifically, both belong to the species C. sativa and differ primarily in their tetrahydrocannabinol (THC) content.

Cannabis-related allergies can manifest clinically in a variety of ways:

- Respiratory exposure to pollen or cannabis smoke typically causes respiratory symptoms, but may also sensitise the patient and predispose them to food allergy reactions;
- The ingestion of novel foods derived from hemp, such as seeds, flours, oil and supplements, can cause mild symptoms, such as oral allergy syndrome, or more severe and systemic reactions, such as urticaria, angioedema and anaphylaxis; It is interesting to note that immediate hypersensitivity reactions to hemp may also arise following the first known exposure to hemp itself, as a result of prior exposure to and sensitisation by cannabis;
- Contact, often in the workplace, with the leaves or flowers of Cannabis can cause skin reactions such as contact urticaria, erythema multiforme or allergic contact dermatitis.

The major allergen in Cannabis is Can s 3, an nsLTP whose sensitisation can lead to allergic reactions even following the ingestion of fruit (e.g. hazelnuts, peaches, grapes), vegetables (e.g. tomatoes), cereals (e.g. wheat) or exposure to tobacco and latex.
The diagnosis of IgE-mediated cannabis allergy begins with a thorough medical history, whilst confirmation of sensitisation – in the absence of a commercially available extract – is carried out using non-standardised prick-by-prick testing or through the measurement of IgE levels for Can s 3.
The clinical management of hemp allergy is based, where possible, on avoiding hemp and cross-reactive foods, as well as on symptom control.

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New findings on the usefulness of LTP assessment in paediatrics

Dr. Chiara Trincianti, Dr. Matteo Naso
Gaslini Children's Hospital, Genoa

In recent years, the determination of Lipid Transfer Proteins (LTPs) has become increasingly important in the diagnosis of food allergies in children. LTPs are widely distributed plant proteins, particularly resistant to heat and digestion, and represent one of the main food allergens in the Mediterranean region.

Molecular diagnostics (*component-resolved diagnostics*) is now an increasingly important tool for defining the risk profile of children with suspected food allergies. Sensitisation to LTPs is, in fact, associated with an increased risk of systemic reactions, including anaphylaxis. Consequently, the personalised action plan must include, where indicated, the prescription of self-injectable adrenaline and adequate education of carers regarding the role of possible co-factors — such as physical activity, infections, medication or alcohol (in adolescents) — which may increase the risk of severe reactions.

In risk assessment, it is also essential to distinguish between primary sensitisation and cross-reactivity. For example, positivity to Par j 1 and Par j 2 indicates sensitisation to Parietaria pollen, which can sometimes be associated with cross-reactivity to foods containing LTPs; however, these forms are generally less clinically significant and more often associated with mild symptoms compared to primary sensitisation to dietary LTPs, which carries a higher risk of severe systemic reactions.

Finally, in children, the homology between proteins of the same family can be useful for predicting possible reactions to foods not yet introduced, as may occur particularly during weaning.

In conclusion, the determination of LTPs is now a fundamental tool for more accurate diagnosis, better risk stratification and a personalised therapeutic approach in paediatric food allergies.

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