

# Fish Allergy and Related Conditions in Children: A Review

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**Abstract:** Fish allergy is the important food allergies in childhood, often persisting into adulthood. It can cause severe hypersensitivity reactions, including fatal anaphylaxis; furthermore, avoiding-fish diet has negative nutritional and psychological effects. Recent research studies focus on epitope structures and aim to develop sensitive and specific diagnostic tools, which have a better correlation with clinical reactions. Protocols with hypoallergenic parvalbumin or other recombinant antigens are also under study and will likely lead to new immunotherapy protocols.

IgE-mediated fish allergy differs substantially from other forms of immunological adverse reactions to fish, such as Food Protein-Induced Enterocolitis Syndrome and eosinophilic esophagitis. In addition, fish ingestion can cause non-immunological adverse reactions, such as in the case of scombroid poisoning, anisakiasis and toxic poisoning.

This review aims to summarize the characteristics of the main immunological and non-immunological fish reactions, analyzing the epidemiology, clinical manifestations, diagnosis and therapy, with a particular focus on clinical management.

**Keywords:** Fish, allergy, children, IgE, FPIES, scombroid, poisoning, anisakis.

## 1. INTRODUCTION

Fish allergy is common in children worldwide and often persists into adulthood. Hypersensitivity reactions to fish can be severe and include fatal anaphylaxis. Furthermore, avoiding-fish diets have negative psychological effects and exclude an important source of vitamins and omega-3 long chain fatty acids. We report the characteristics of IgE and non IgE-mediated fish reactions, analyzing the epidemiology, clinical manifestations, diagnosis and therapy, with a particular focus on clinical management.

Adverse reactions to fish are divided into immunological and non-immunological reactions as summarized in Table 1 [1-4].

## 2. IgE-Mediated Fish Allergy

### 2.1. Epidemiology

Fish allergy is the frequent food allergies in children and adults globally [1-5].

Table 2 shows the prevalence of IgE-mediated fish allergy in different countries. Fish allergy is more common in

countries where fish consumption is higher, such as Scandinavia and Asia. Self/parent-assessed incidence is higher than that based on objective tests such as oral food challenge (OFC) [6]. In fact, the overall prevalence of self/parent-reported fish allergy in Europe is around 5% while in the case of OFC-confirmed allergy the prevalence is around 0.06% [7]. Since fish allergy can persist with growth and can also develop in adulthood, the prevalence in childhood is lower than in adulthood (0.2 versus 0.5%) [8].

### 2.2. Clinical Features and Natural History

IgE-mediated fish allergy occurs after either ingestion, inhalation or skin contact and causes a wide variety of clinical manifestations ranging from mild oral allergy syndrome to anaphylaxis (Table 3) [1, 8]. In some children, an anaphylactic reaction only develops when fish intake is followed by physical exertion [28].

The most common route of exposure to fish is oral intake. The use of antacid medications can impair gastric digestion and cause increased absorption of antigenic peptides leading to sensitization [29, 30].

Exposure through inhalation is also described and can occur in children during the cooking processes, although it is mostly described as a form of occupational asthma [31-35].

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**Table 1. Adverse reactions to fish ingestion.**

| Name                                                 | Cause                                                                                 | Onset            | Clinical Manifestations                                                                                    |
|------------------------------------------------------|---------------------------------------------------------------------------------------|------------------|------------------------------------------------------------------------------------------------------------|
| <b>Immunological</b>                                 |                                                                                       |                  |                                                                                                            |
| IgE-mediated fish allergy                            | IgE-mediated adverse reaction to fish                                                 | 30 min - 4 h     | Urticaria, angioedema, nausea and vomiting, rhinitis, oral allergy syndrome, anaphylaxis                   |
| Food Protein-Induced Enterocolitis Syndrome (F-PIES) | T cell-mediated intestinal inflammation (pathogenesis not clearly understood)         | 1-4 h            | Profuse vomiting, diarrhea, sepsis-like clinical picture                                                   |
| Eosinophilic esophagitis                             | Chronic immune-mediated esophageal disease                                            | Days             | GERD-like symptoms, Abdominal pain, vomiting, Dysphagia, Food impaction                                    |
| Anisakis allergy                                     | IgE-mediated adverse reaction to anisakis-infested fish                               | 2-24 h           | Urticaria, angioedema, abdominal pain, anaphylaxis                                                         |
| <b>Non-immunological</b>                             |                                                                                       |                  |                                                                                                            |
| Scombroid poisoning                                  | Ingestion of poorly preserved fish in which bacteria convert histidine into histamine | Minutes - 90 min | Urticaria, nausea and vomiting, diarrhea, wheezing                                                         |
| Anisakiasis                                          | Ingestion of raw, undercooked or pickled fish with live parasites (anisakis)          | 2-24 h           | Nausea and vomiting, abdominal pain                                                                        |
| Toxic algae poisoning                                | Ingestion of fish contaminated by toxic algae                                         | 1-4 h            | Urticaria, nausea, vomiting, abdominal pain, paresthesia, blurred vision, myalgia, arrhythmia, hypotension |
| Pufferfish poisoning                                 | Ingestion of pufferfish producing tetrodotoxin                                        | 1-4 h            | Weakness, paresthesia, blurred vision                                                                      |
| Bacterial contamination                              | Ingestion of raw fish harvested in contaminated waters                                | 2-24 h           | Nausea, vomiting, diarrhea, abdominal pain, fever                                                          |
| Staphylococcus aureus food poisoning                 | Ingestion of fish contaminated by hands at room temperature                           | 1-6 h            | Nausea and vomiting, abdominal pain, rarely diarrhea, fever                                                |

**Table 2. Prevalence of IgE-mediated fish allergy in children in different countries.**

| Country              | Method                                  | Age in Years | Prevalence | References |
|----------------------|-----------------------------------------|--------------|------------|------------|
| <b>EUROPE</b>        |                                         |              |            |            |
| Finland              | self/parent-assessed                    | 1-4          | 5%         | [9]        |
| Finland              | self/parent-assessed                    | 1-6          | 7%         | [10]       |
| Norway               | self/parent-assessed                    | 0-2          | 3%         | [11]       |
| Italy                | self/parent-assessed                    | 5-14         | 0          | [12]       |
| Finland              | SPT                                     | 7-16         | 0.3%       | [13]       |
| Russia               | SPT                                     | 7-16         | 0.2%       | [13]       |
| France               | SPT                                     | 9-11         | 0.7%       | [14]       |
| UK                   | SPT                                     | 6            | 1%         | [15]       |
| Sweden               | sIgE                                    | 4            | 0.7%       | [16]       |
| Germany              | sIgE                                    | 6            | 0.6%       | [17]       |
| Denmark              | self/parent-assessed<br>% OFC-confirmed | 0-22         | 1%<br>0%   | [18]       |
| UK                   | sIgE<br>% OFC-confirmed                 | 6            | 1%<br>0%   | [15]       |
| <b>ASIA</b>          |                                         |              |            |            |
| Israel               | self/parent-assessed                    | 0-2          | 0%         | [19]       |
| United Arab Emirates | self/parent-assessed                    | 6-9          | 2.8%       | [20]       |

| Country        | Method               | Age in Years | Prevalence | References |
|----------------|----------------------|--------------|------------|------------|
| Philippines    | self/parent-assessed | 14-16        | 2.29%      | [21]       |
| Singapore      | self/parent-assessed | 14-16        | 0.26%      | [21]       |
| Thailand       | self/parent-assessed | 14-16        | 0.29%      | [21]       |
| Vietnam        | self/parent-assessed | 2-6          | 1.62%      | [22]       |
| China          | SPT                  | 1            | 0.21%      | [23]       |
| Turkey         | SPT                  | 6-9          | 0.2%       | [24]       |
| Turkey         | OFC                  | 6-9          | 0%         | [24]       |
| Thailand       | OFC                  | 3-7          | 0.2%       | [25]       |
| <b>AMERICA</b> |                      |              |            |            |
| USA            | self/parent-assessed | 0-2          | 0.3%       | [26]       |
| USA            | self/parent-assessed | >11          | 0.6%       | [26]       |
| Canada         | self/parent-assessed | 0-14         | 0.18%      | [27]       |

**Table 3. Clinical manifestations of IgE-mediated fish allergy by route of exposure.**

| Route of Exposure | Clinical Symptoms                                                                                      |
|-------------------|--------------------------------------------------------------------------------------------------------|
| Ingestion         | Rhinitis<br>Asthma<br>Oral allergy syndrome<br>Urticaria, Angiodema<br>Nausea, Vomiting<br>Anaphylaxis |
| Inhalation        | Asthma<br>Rhinitis<br>Urticaria, Angioedema                                                            |
| Skin contact      | Urticaria, Angioedema                                                                                  |

Note: [1, 2]

Skin sensitization is generally described in fish industry workers but has also been reported in pediatric patients [36-39]. It may be promoted by a dysfunction of the skin barrier, such as a mutation in the filaggrin gene [40].

IgE-mediated fish allergy typically does not resolve with growth unlike other food allergies such as egg and milk allergy, and around 80% of patients are still allergic 10 years after the initial diagnosis [3, 41]. The reasons for the persistence of fish allergy are not clear yet. Studies on milk and egg allergies have shown that the difference between persistent and transient allergy may lie in the epitopes targeted by IgE [42, 43]. Fish allergy can develop in adulthood in up to 40% of cases [8].

## 2.3. Fish Allergens

### 2.3.1. Parvalbumin

The major fish allergen is parvalbumin, which is responsible for clinical manifestations in 90% of patients [2, 44]. Parvalbumin is a small muscle protein, extremely stable to heat and enzymatic digestion [2, 45]. Since parvalbumin is resistant to heat, its relative concentration increases in

cooked fish, while the concentration of minor thermo-sensitive allergens decreases. This explains why parvalbumin is the main fish antigen, as fish is predominantly consumed cooked [46].

There are two isoforms of the allergen,  $\alpha$ - and  $\beta$ -parvalbumin. Commonly consumed fish species belong to bony fishes (Osteichthyes) and mostly express  $\beta$ -parvalbumin [2, 47, 48]. Instead, sharks and rays are cartilaginous (Chondrichthyes) and contain almost only  $\alpha$ -parvalbumins, which is probably less allergenic [4, 49]. The main fish allergens are listed in Table 4.

The white muscle of fish contains a higher concentration of parvalbumin than the dark muscle. Thus, fish with white muscle such as cod (average parvalbumin concentration 2.5 mg/g) are more allergenic than fish with more dark muscle such as mackerel, tuna and swordfish (< 1 mg/g) [50-52]. Furthermore, even in the same species the parvalbumin content can differ between parts of the fish. The dorsal and rostral portion, which contain more white muscle, have higher concentration of parvalbumin [53].

Specific IgE-binding epitopes of parvalbumin have been characterized in five fish species (Atlantic cod, Atlantic salmon, Baltic cod, common carp and chub mackerel), defining both linear and conformational epitopes [54]. While secondary and tertiary structures are quite conserved among fish species, the amino-acidic sequence of epitopes differs substantially [2, 54-58]. The identification of IgE epitopes is one of the approaches aimed at developing specific immunotherapies for fish allergy [54].

### 2.3.2. Other Allergens

In addition to parvalbumin, minor fish allergens have been detected. Aldolase A and  $\beta$ -enolase are glycolytic enzymes and have been identified as allergens in muscle tissue of cod, salmon, and tuna. These allergens are thermo-sensitive and less resistant to food processing than parvalbumin [64, 67]. Tropomyosin is the main allergen of shellfish and has also been registered as rare allergen for fish [4, 68, 69].

Collagen has also been identified as an allergen [50, 70]. Other fish allergens have been characterized such as the hormone vitellogenin from Beluga caviar [71-73] and fish gelatin [74, 75]. Other molecules such as aldehyde phosphate isomerase, triose-phosphate isomerase, glyceraldehyde-3-phosphate dehydrogenase and creatine kinase are potential allergens. However, the clinical relevance of these allergens requires further investigation [4].

## 2.4. Diagnosis

The diagnosis of fish allergy is based on the clinical history and on the demonstration of sensitization, which is determined by *in vivo* or *in vitro* testing. However, the positivity of specific IgE may simply reflect sensitization and not necessarily clinical responsiveness. Therefore, oral food challenge remains the gold standard test for ascertaining fish allergy (Fig. 1).

**Table 4. Main fish allergens.**

| Common Name      | Scientific Name            | Allergen | Protein Type  | Molecular Weight [kDa] | References   |
|------------------|----------------------------|----------|---------------|------------------------|--------------|
| Atlantic herring | <i>Clupea harengus</i>     | Clu h 1  | β-parvalbumin | 12                     | [58, 59]     |
| Common carp      | <i>Cyprinus carpio</i>     | Cyp c 1  | β-parvalbumin | 12                     | [56, 60, 61] |
| Baltic cod       | <i>Gadus callarias</i>     | Gad c 1  | β-parvalbumin | 12                     | [62, 63]     |
| Atlantic cod     | <i>Gadus morhua</i>        | Gad m 1  | β-parvalbumin | 12                     | [47, 64]     |
|                  |                            | Gad m 2  | β-enolase     | 47                     |              |
|                  |                            | Gad m 3  | Aldolase A    | 40                     |              |
| Rainbow trout    | <i>Oncorhynchus mykiss</i> | Onc m 1  | β-parvalbumin | 12                     | [59, 65]     |
| Atlantic salmon  | <i>Salmo salar</i>         | Sal s 1  | β-parvalbumin | 11                     | [58, 64]     |
|                  |                            | Sal s 2  | β-enolase     | 50                     |              |
|                  |                            | Sal s 3  | Aldolase A    | 40                     |              |
| Pacific pilchard | <i>Sardinops sagax</i>     | Sar sa 1 | β-parvalbumin | 12                     | [66]         |
| Yellowfin tuna   | <i>Thunnus albacares</i>   | Thu a 1  | β-parvalbumin | 11                     | [55, 59, 64] |
|                  |                            | Thu a 2  | β-enolase     | 50                     |              |
|                  |                            | Thu a 3  | Aldolase A    | 40                     |              |
| Swordfish        | <i>Xiphias gladius</i>     | Xip g 1  | β-parvalbumin | 12                     | [45]         |

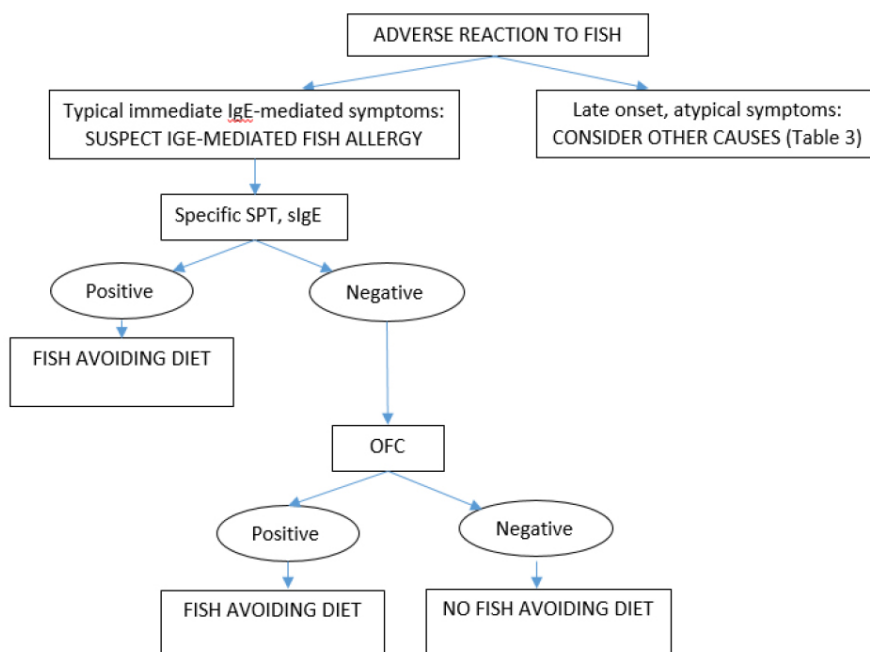


**Fig. (1).** Diagnostic algorithm for suspected fish allergy. Adapted from Sharp *et al.* (2014), Tsabouri *et al.* (2012).

### 2.4.1. SPT

Skin prick tests (SPT) are the first level test to investigate a suspected fish allergy, given the rapidity, safety and low cost of this technique. Commercial fish extracts or fresh food (prick-by-prick) are used to perform SPT. The diameter of the wheal is indicative of a positive reaction if equal to or more than 3 mm with a negative control read after 15-20 mins. SPT with multiple fish species may help to find safe alternatives [1]. Although SPTs have high sensitivity and negative predictive value, these tests are non-specific and the positive predictive value is often less than 50% [76, 77]. Furthermore, the use of SPT is complicated by the large variety of fish species and by cross-reactivity, which is reported in approximately 50% of patients [78]. Recombinant parvalbumins are available for different species such as Atlantic cod, Atlantic salmon and carp. However, recombinant parvalbumins are less sensitive than the natural extracts for SPT, probably due to the different conformation of IgE epitopes [55].

### 2.4.2. sIgE

The measurement of specific IgE antibodies can be useful. One of the most used assays is the Immuno CAP test (Phadia/Thermo Fisher Scientific, Upsala, Sweden) which contains 28 fish extracts. An IgE level of 20 kU/L to fish predicted a positive reaction with 95% certainty in children [79]. On the other hand, very low levels of sIgE can be associated with positive reactions in 10-25% of patients and IgE values as low as 1 kU/l have been determined in patients with anaphylactic reactions to fish [44, 66]. Therefore, accurate cut-off levels for sIgE are still uncertain and need to be further evaluated. Fish allergy should be excluded if specific IgE are less than 0.35 kUA/L [79].

### 2.4.3. OFC

The gold standard for diagnosing food allergy is the double-blind, placebo-controlled oral food challenge (OFC). Open OFC, which is less costly and time-consuming, is generally performed, particularly in patients with a clear history and in children younger than 3 years, who rarely report subjective symptoms. Controlled OFC is used in clinical research and when open OFC is inconclusive. In OFC, the suspect fish is given to the patient in gradually increasing doses until an age-appropriate portion is reached. The proposed starting dose for fish is 5 mg. The challenge is interrupted at the first allergic symptoms, in order to prevent more serious reactions and determine the triggering threshold dose [3, 80].

### 2.4.4. BAT

The Basophil Activation Test (BAT) measures the activation of basophils following allergen stimulation by analyzing the expression of activation markers on the surface of basophils by flow cytometry [81]. It could represent a useful tool in food allergies reducing the need of OFCs. The results are promising and the specificity of BAT in food allergies appears to be good [81, 82]. However, BAT still requires

clinical validation and standardization procedures. So far, the test is not yet used in daily practices [1, 83, 84].

## 2.5. Management

Currently, the approach to fish allergy is avoidance of food and rescue medication in case of symptoms due to accidental exposure. Manifestations of fish allergy can be life threatening and the allergy is often long lasting. Therefore, patients at risk of anaphylaxis should be prescribed an epinephrine self-injection kit and be trained in its use [1].

Since parvalbumin is highly conserved among fish species, patients are generally advised to avoid all fish, not only the original culprit [50, 85]. Cross-reactivity has been anecdotally described between fish and shellfish, frog, chicken and crocodile [69, 86-89]. On the other hand, mono- and oligo-sensitizations have been documented [90, 91]. In particular, fish with a higher content of red meat, such as tuna, are better tolerated as the concentration of parvalbumin is lower [53, 55, 92]. For this reason, testing with various fish species might identify one or more types that can be tolerated and provide the patient with safe alternatives [92].

Processing methods alter the allergenicity of the fish. Cooking increases the concentration of parvalbumin, which is heat resistant. Conversely, canning, marinating, and fermentation can lead to tolerance of previously unacceptable raw fish [1, 92]. In addition, inhaling cooking vapors containing aerosolization of fish proteins or skin contact can cause reactions [32, 93].

The fish-free diet is burdensome to follow for numerous reasons. First, it is difficult to maintain due to hidden fish allergens in the food, which often cause reactions in fish-allergic patients [94]. In addition, fish collagen and gelatin are found in many cosmetic and pharmaceutical products [67]. Second, the elimination diet has social and psychological implications for both the child and the family. In fact, it leads to worry about food and feelings of being different from peers because of the diet. This generates anxiety, stress and negative effects on social activities [95, 96]. Thirdly, eliminating fish from the diet involves the loss of an important source of vitamins, minerals and omega-3 long chain fatty acids, which are important for the growing child's diet, preventing neuropsychiatric disorders, cardiovascular diseases and asthma [97-99].

While vitamins and minerals can be included in the diet through other foods, omega-3 long chain fatty acids are found in few other foods, such as vegetable seed oils, nuts and microalgae. The fatty acids namely icosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can be integrated through food supplements, at a dose of 40-250 mg/day for children older than 6 months [100].

## 2.6. Desensitization and Oral Immunotherapy

Oral desensitization has been performed in childhood with increasing doses of boiled cod. However, allergic reactions frequently occur and it takes a long time to tolerate a typical portion of fish [101]. Similar approaches have been

recently performed using hake in pediatric populations, with promising results [102, 103].

The most studied immunotherapy for fish allergy focuses on the use of hypoallergenic recombinant parvalbumin. A recombinant parvalbumin of carp (Cyp c 1) was created, with calcium binding site mutations that can reduce the binding between parvalbumin and IgE. These mutations lead to a decreased allergenicity of the protein, confirmed by SPT *in vivo* and basophilic histamine release *in vitro*. At the same time, however, the mutations maintain the ability of parvalbumin to determine an IgG response, essential for blocking the IgE-mediated responses due to the subsequent introduction of parvalbumin [104, 105]. The application of recombinant parvalbumin has been tested on animal models and *in vitro*, confirming a reduction of the Th2 response and a protective action from allergic symptoms [46, 106, 107]. The main problem that could arise in the clinical application of these researches is that the immunological reactivity of recombinant allergens may differ from that of native allergens. For example, recombinant carp parvalbumin (Cyp c 1) is less reactive than pilchard parvalbumin [46]. Also, heated parvalbumin is more allergenic [108].

3. NON IgE-MEDIATED FISH ALLERGY

3.1. Food Protein-induced Enterocolitis Syndrome (FPIES)

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy characterized by intense gastrointestinal symptoms and dehydration following exposure to a trigger food.

3.1.1. Epidemiology and Trigger Food

The estimated incidence of FPIES, considering all trigger foods, is around 0.015-0.7% [109, 110]. The foods that most often cause FPIES globally are cow's milk, cereals and soybeans; other involved foods are fruit and vegetables, eggs, meat and fish [111]. In Mediterranean countries, fish is one of the most frequently FPIES-triggering solid food [112-115].

3.1.2. Pathogenesis

The pathogenesis of FPIES is poorly understood. A role of antigen-specific T cells in triggering intestinal inflammation has been hypothesized but remains controversial [116, 117]. Recent studies, instead, indicate a role of the innate immune system [118]. Systemic food-specific IgE antibodies are not detected in most patients with FPIES [109, 116].

3.1.3. Clinical Manifestations

Acute FPIES is characterized by profuse and repetitive vomiting, which manifests approximately 1 to 4 hours after the ingestion of a trigger food; watery diarrhea may also occur within 24 hours. Vomiting and diarrhea lead to dehydration and lethargy and, in severe cases, hypovolemia and shock. Acute FPIES typically resolves within 24 hours, and symptoms do not reoccur unless the patient ingests the trigger food again [109, 119]. Chronic FPIES occurs when the patient consumes the trigger food (usually cow's milk or soy) for days or weeks: chronic diarrheal symptoms tend to predominate and over time the patient experiences dehydration and failure to thrive [119-121]. Symptoms resolve within several days to weeks after eliminating the trigger food from the diet. Reintroduction of food after avoidance causes acute FPIES [109].

3.1.4. Natural History

The development of FPIES depends on the introduction of the food into the child's diet. For this reason, fish induced-FPIES typically occurs from 7 months of age onwards [109]. The acquisition of tolerance for fish occurs at a higher age than for milk- or soy-induced FPIES, but generally within 5 years of age [122]. However, some patients will continue to experience symptoms chronically [123]. According to recent studies, fish induced-FPIES could last beyond childhood and become a persistent allergy [124, 125].

3.1.5. Diagnosis

Diagnosis of FPIES is based on a suggestive history and on the improvement after discontinuation of the causal food. Clinical criteria are shown in Table 5. If necessary, an OFC can be used to confirm the diagnosis [109].

Table 5. Diagnostic criteria of acute FPIES. Adapted from Nowak-Wegrzyn *et al.* (2017).

|                                                                                                    |
|----------------------------------------------------------------------------------------------------|
| MAJOR CRITERIA                                                                                     |
| 1. Vomiting 1-4 hours after suspect food ingestion in the absence of classic IgE-mediated symptoms |
| MINOR CRITERIA                                                                                     |
| 1. Two or more episodes of repetitive vomiting after eating the same suspect food                  |
| 2. Repetitive vomiting episode 1-4 hours after eating a different food                             |
| 3. Extreme lethargy with any suspected reaction                                                    |
| 4. Marked pallor with any suspected reaction                                                       |
| 5. Need for emergency department visit with any suspected reaction                                 |
| 6. Need for intravenous fluid support with any suspected reaction                                  |
| 7. Diarrhea in 24 hours (usually 5 to 10 hours)                                                    |
| 8. Hypotension                                                                                     |
| 9. Hypothermia                                                                                     |
| The diagnosis of FPIES requires the major criterion and at least 3 minor criteria                  |

**Table 6. Protocol for OFC in FPIES. Adapted from Nowak-Wegrzyn *et al.* (2017).**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinician supervision, secure IV access, immediate availability of fluid resuscitation.</b>                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Baseline vital signs and complete blood count (to determine baseline neutrophil count)</b>                                                                                                                                                                                                                                                                                                                                                                       |
| Administration of food protein 0.03 to 0.6 g/kg body weight in 3 equal doses over 30 minutes not to exceed total 3 g protein or 10 g of total food (100 mL of liquid)<br>A lower dose is used in patients with a history of severe reactions.                                                                                                                                                                                                                       |
| Observe patients for at least 4 hours from the beginning of the OFC.                                                                                                                                                                                                                                                                                                                                                                                                |
| If no reaction occurs within 2 to 3 hours of administration of the final dose, propose a full age-appropriate serving of the food. Then observe patients for at least 4 hours.                                                                                                                                                                                                                                                                                      |
| Criteria for a positive challenge (major criterion + at least 2 minor criteria)<br>Major criterion:<br>1. Vomiting 1-4 hours after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms<br>Minor criteria:<br>1. Lethargy<br>2. Pallor<br>3. Diarrhea 5-10 hours after food ingestion<br>4. Hypotension<br>5. Hypothermia<br>6. Increased neutrophil count of at least 1500 neutrophils above the baseline count |

OFC is the gold standard for diagnosing FPIES. It represents a high-risk procedure in FPIES; for this reason, protocols such as the one shown in Table 6 should be followed to perform OFC safely. SPT and sIgE are not indicated to diagnose FPIES, as these tests are often negative [109]. However, SPT and sIgE are usually performed as part of the evaluation to rule out IgE-mediated sensitization to foods. Patch testing appears to have a better sensitivity, but further evaluation is needed to determine its role in diagnosing FPIES [126]. Regarding laboratory investigations, patients with acute FPIES manifest neutrophilia, thrombocytosis, metabolic acidosis and methemoglobinemia, mimicking sepsis. Methemoglobinemia in FPIES is caused by severe intestinal inflammation resulting in decreased catalase activity and increased nitrites. Patients with chronic FPIES may also have hypoalbuminemia and anemia [109, 119]. Radiological and endoscopic studies are not routinely performed but may be indicated to exclude other gastrointestinal pathologies. Radiological investigations show air fluid levels and thickening of the small intestine. Endoscopy often reveals ulceration and friability of the intestinal mucosa. Biopsies show villous atrophy, tissue edema, crypt abscesses and inflammatory infiltrate [119].

### 3.1.6. Management

Management of FPIES consists of eliminating the culprit food from the diet and treating acute emergencies. Periodic re-evaluations with OFC are indicated to monitor resolution, expected at around 5 years of age. It is not clear whether it is better to perform the reassessment OFC with the trigger food or with an alternative species [109].

The management of acute FPIES is resumed in Table 7. Treatment is based on oral or intravenous rehydration. In se-

vere cases, intravenous methylprednisolone is used in addition to circulatory supportive therapy. Ondansetron can be given to control vomiting. Patients should always carry an Emergency Treatment Plan outlining emergency treatment for acute FPIES [109].

## 3.2. Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic esophageal disease characterized by symptoms of esophageal dysfunction and eosinophil-predominant inflammation [127]. Fish is often excluded from the diet of patients with EoE due to its suspected trigger role.

### 3.2.1. Epidemiology and Risk Factors

The estimated prevalence of EoE ranges from 0.2 to around 50 cases per 100,000 and is higher for adults than for children [128]. An increase in the incidence of EoE has been observed over time, which appears to be only partially due to an increased recognition of the disorder; however data on risk factors for eosinophilic esophagitis are still limited [129-131].

There is a strong association of eosinophilic esophagitis with allergic conditions such as food and inhalant allergies, asthma and atopic dermatitis [120, 132-134]. It has been estimated that up to 90% of pediatric patients with EoE are sensitized to food or inhalants [120, 135]. Therefore, the evaluation and management of comorbid allergic disease in EoE patients is an important part of the management. Fish infrequently causes EoE, but since it is one of the main IgE food allergens it is commonly excluded in EoE empirical diets [136, 137].

**Table 7. Management of acute FPIES. Adapted from Nowak-Węgrzyn *et al.* (2017).**

| Presentation | Symptoms                                                            | Treatment                                                                                                                                                                                                                                                                                                                                                                                         |
|--------------|---------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| MILD         | 1-2 episodes of emesis, no or mild lethargy                         | 1. Oral rehydration<br>2. IM ondansetron 0.15 mg/kg/dose if > 6 months (max 4 mg)<br>Monitor for resolution about 4-6 h from the onset.                                                                                                                                                                                                                                                           |
| MODERATE     | At least 3 episodes of emesis, moderate lethargy                    | 1. IM ondansetron 0.15 mg/kg/dose if > 6 months (max 4 mg)<br>2. Oral or IV rehydration with normal saline bolus<br>Monitor for resolution at least 4-6 h from the onset of a reaction.<br>Discharge home if patient is able to tolerate clear liquids.                                                                                                                                           |
| SEVERE       | At least 3 episodes of emesis, severe lethargy, hypotonia, cyanosis | 1. IV rehydration with normal saline bolus<br>2. IV or IM ondansetron 0.15 mg/kg/dose if > 6 months (max 4 mg IM, max 16 mg IV)<br>3. Consider IV methylprednisolone 1 mg/kg (max 80 mg)<br>4. Monitor and correct acid-base and electrolyte abnormalities<br>Monitor for resolution at least 4-6 h from the onset of a reaction.<br>Discharge home if patient is able to tolerate clear liquids. |

### 3.2.2. Pathogenesis

The pathogenesis of EoE is not yet clarified but is certainly based on the interaction between genetic, immunological and environmental factors [138]. EoE is a chronic atopic disorder related to Th2 response with IgE or non-IgE-mediated reaction to allergens, in which an impaired epithelial barrier promotes the penetration of the antigen and sensitization [139-141]. In most patients, food antigens trigger EoE with non-IgE-mediated mechanism [127]. The role of food allergens is supported by the good response to diet elimination of food antigens and the recurrence with reintroduction of similar food antigens [142]. There is little evidence of EoE triggered by fish in children [136].

### 3.2.3. Clinical Manifestations

EoE is characterized by symptoms of esophageal dysfunction. In infants, the more frequent symptoms are feeding difficulties and poor growth, vomiting and sleep disturbances. School-age children and adolescents have gastroesophageal reflux-like symptoms, such as nausea, vomiting, regurgitation, abdominal pain and dysphagia. When symptoms do not respond to medical treatments for gastroesophageal reflux, EoE should be strongly considered. Food impaction may occur in adolescence and is a gastrointestinal emergency, requiring endoscopic intervention. In the case of dysphagia and alimentary impaction, the hypothesis of EoE must be taken into consideration and biopsies should always be performed during endoscopy. The major long-term consequence of chronic inflammation in EoE is esophageal remodeling with irreversible structures [127, 133, 143].

### 3.2.4. Diagnosis

The diagnosis of EoE is based on symptoms, endoscopic appearance and histological findings (Table 8). Esophageal biopsies show an eosinophil-predominant inflammation, with  $\geq 15$  eosinophils per high-power field (HPF). Radiographic and laboratory findings are not necessary to establish the diagnosis. Approximately 50% of patients with eosinophilic esophagitis have elevated serum IgE levels and

peripheral eosinophilia [127, 135, 136, 144]. Because of the strong association of EoE with allergies, patients with EoE should be evaluated by an allergist. Skin prick tests, serum IgE tests and food patch tests can be used to help identify foods associated with EoE, but are not sufficient to confirm the association between EoE and a specific food. Confirmation of the trigger role of a food occurs only by documenting the remission of the disease after elimination from the diet and the reappearance of the disease after the reintroduction of the food [120].

### 3.2.5. Management

The management of EoE is based on elimination diet, antacid drugs and topical glucocorticoids.

Dietary approaches are based upon the observation that patients with EoE have high rates of food allergies, that may contribute to the development of EoE. The main allergens in EoE are cow's milk, wheat, egg and soy. As such, these foods are included in the so-called "four-food" elimination diet. Diets with additional avoidance of nuts and fish constitute the "six-food" elimination diet. Fish is only rarely associated with EoE (probably because it is less consumed than the previously reported foods) but is included in the six-food elimination diet because it is one of the main IgE-mediated food allergens [137]. Dietary treatment is effective in children but involves important risks of nutritional deficits as well as a decrease in the quality of life. A consultation with a nutritionist is therefore important [142, 145-147].

In patients who need a pharmacologic approach, treatment with proton pump inhibitors or topical glucocorticoids is prescribed. These therapies induce clinical remission of EoE in 50-90% of patients. Esophageal dilation is reserved for management of esophageal strictures [120, 148]. Among biologic drugs, dupilumab has been successfully used in children with EoE. On the other hand, anti-IL-5 molecules, such as mepolizumab and reslizumab, have been demonstrated to improve histological patterns but without clinical improvement [120].

**Table 8. Diagnosis of EoE (adapted from Liacouras 2011).**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>HISTORY - Dysphagia and other esophageal dysfunction symptoms</b>                                                                                                                                                                                                                                                                                                                                                                                                                              |
| PHYSICAL EXAMINATION - Focus on growth and nutrition parameters; exclude other causes of esophagitis.                                                                                                                                                                                                                                                                                                                                                                                             |
| ENDOSCOPY - Endoscopic features show esophageal inflammations but cannot diagnose EoE. 2-4 biopsies from the proximal and distal esophagus should be obtained.                                                                                                                                                                                                                                                                                                                                    |
| HISTOPATHOLOGY - Esophageal biopsy is the only reliable EoE diagnostic. Histological characteristics include: mucosal eosinophilia, eosinophil micro abscesses, superficial layering of eosinophils, extracellular eosinophil granules, surface epithelial desquamation, basal zone hyperplasia, rete peg elongation, dilated intercellular spaces, subepithelial fibrosis/sclerosis/lamina propria fibrosis.<br>Gastric and duodenal biopsies should also be examined to exclude other diseases. |
| ALLERGIC EVALUATION - SPT, sIgE and food patch tests help identify foods that are associated with EoE, but are not sufficient to make the diagnosis of food driven-EoE (only identified by elimination diet). Medically supervised food reintroduction for patients with previous allergic reactions to a food.                                                                                                                                                                                   |
| GENETICS - Specific genes that pre-dispose to EoE susceptibility have been identified (thymic stromal lymphopoietin (TSLP), eotaxin-3), but are not yet ready for use in clinical settings.                                                                                                                                                                                                                                                                                                       |

## 4. NON-IMMUNOLOGICAL REACTIONS TO FISH

### 4.1. Scombroid Poisoning

Scombroid poisoning is provoked by the ingestion of a high quantity of histamine accumulated in the dark muscle of the fish. Histamine is produced from the precursor histidine, by the bacterial enzyme histidine decarboxylase contained in gram-negative bacteria that overgrew in the cutis and intestines of the fish. Scombroid poisoning is related to the ingestion of fresh, canned or smoked fish with toxic histamine levels due to improper storage at a temperature greater than 4°C. Histamine levels are higher if temperature is greater than 21°C [149]. Tuna, salmon and mackerel are considered the most frequently implicated fish. Symptoms of scombroid poisoning include flushing with warm sensation, widespread erythematous or urticarial rash, palpitations, headache, dizziness, sweating and burning of the mouth and throat; gastrointestinal symptoms such as oral tingling and metallic taste, abdominal pain, nausea, vomiting and diarrhea are usually associated. Bronchospasm, respiratory distress, hypotension and arrhythmias may also occur. Symptoms occur within 10 to 90 minutes after eating the fish. Rash lasts 2-5 hours and other symptoms usually disappear within 3-36 hours [150].

Diagnosis is based on clinical manifestations, which may also occur in people who had the same meal. A quick improvement, in about 30 minutes after antiH1-antihistamine administration, can confirm the diagnosis. In some cases, antiH2-antihistamines and intravenous fluids for dehydration due to vomiting and diarrhea may be necessary. Corticosteroids are not of benefit [92]. The appearance, taste and smell of the fish are not reliable indicators of the presence of histamine. Histamine levels in the ingested fish greater than 100 mg/100 g of fish tissue are diagnostic, but levels of 5 mg/100 g can also be dangerous [150]. The measurement of histamine levels in plasma or histamine metabolites (e.g., n-methylhistamine) in urine may help the diagnosis but it is not routinely available [151].

The diagnosis can be confirmed when SPT to the ingested fish is positive while SPT and OFC are negative with the

same type of fish that has been correctly stored. Prevention is based on prompt fish chilling after catching and quick refrigeration during processing in the supply chain and at home. However, a strain of *Morganella* can grow at 0-2 °C. Thus, temperature control may not always eliminate the risk [152].

### 4.2. Anisakiasis

Anisakiasis is a zoonotic parasitic disease caused by consumption of raw or undercooked fish or cephalopods contaminated by third stage larvae of the Anisakidae family. *Anisakis simplex* or *pegreffii* are present in European and Japanese seas, and *Pseudoterranova decipiens* in American seas. This ingested parasite does not reproduce in the human host and dies in approximately 3 weeks [153]. Anisakiasis is more common in the Mediterranean area, Japan and Norway because of the cooking habits. In Mediterranean countries it is more frequently related to the consumption of raw or marinated anchovies. In Italy the prevalence is higher in Puglia, Abruzzo, Molise, Liguria and Tirrenian regions [154].

There are three categories of parasitic infection: acute gastric (95% of cases), chronic intestinal (4%) and ectopic (0.3%). The acute gastric form occurs 2 to 8 hours after the meal. It is characterized by epigastric and/or severe diffuse abdominal pain, low-grade fever, nausea, vomiting and diarrhea when larvae are not ejected by vomiting. Hematemesis from gastric ulceration is rare. Chronic intestinal Anisakiasis occurs 5-7 days following the ingestion. It is caused by the larvae's attachment to the intestinal mucosa. It generally occurs when the primary infection causes mild abdominal pain that is tolerated by the patient. If the worm is not removed, it may cause granulomas and abscesses in the intestinal wall with chronic symptoms such as severe abdominal pain, abdominal distension, peritoneal signs, ascites, perforation, intussusception and pneumoperitoneum. After about three weeks, the larvae are surrounded by inflammatory cells, including eosinophils and multinucleate giant cells, which cause the death of the parasite. In ectopic anisakiasis, larvae pass by the intestinal wall, migrating to pleural or peritoneal cavity, lung, ovary, liver or pancreas. In anisakiasis, the first

line immune response to the larvae is the production of IgG1 antibodies [155]. Anisakis also induces the production of Th2 cytokines [156]. IL-4 stimulates IgE production, while IL-5 induces eosinophil proliferation, differentiation, activation and increases the killing ability of eosinophils. Anisakis is chemotactic for eosinophils but not for neutrophils. However, the damage of the tissue can cause neutrophil recruitment [157, 158]. Patients previously exposed to Anisakis can develop hypersensitivity to antigens with development of allergic reactions or anaphylaxis in case of re-exposure to the alive or dead larvae. The re-infection provokes not only Anisakiasis manifestations but also allergic symptoms in sensitized patients. Hypersensitivity manifestations include urticaria, angioedema, asthma, rhino-conjunctivitis and anaphylaxis. Gastrointestinal complaints occur in about 45% of anaphylactic reactions. Anaphylaxis develops in 30-120 minutes after exposure, rarely up to 6 hours [159]. Anisakis allergy should be considered particularly in countries with high prevalence of sensitization to Anisakis. In seaside Japan, 90% of anaphylactic reactions are due to anisakis allergy [160]. The suspicion should rise from a history of consumption of raw fish within 2 weeks, while other types of fish or cooked fishes were tolerated. The diagnosis is supported by increased serum tryptase levels during anaphylaxis and positive SPT and/or elevated levels of Anisakis specific IgE. IgE tests and OFC to the host fish are negative. However, positive results of IgE/SPT to Anisakis are frequently due to panallergens cross reacting with crustaceans and mites [161]. Among allergenic molecules, Ani s 1 and Ani s 7 indicate genuine sensitization as they do not cross-react with other allergens [162]. Laboratory tests can show elevated white cell counts with increased eosinophils and C-reactive protein. Serum levels of eosinophil cationic protein were found to be raised in the first 72 hours after gastrointestinal infection. Serum anisakis IgG can be detected. Definitive diagnosis can be performed through direct endoscopic visualization of the larvae with mucosal edema around the area of penetration. The larvae can be removed with forceps [163]. The management of anisakis allergy include avoidance of potential triggers, treatment of allergic reactions with antihistamine anti-H1 and steroids, anaphylaxis action plan with epinephrine devices.

### 4.3. Fish Poisoning

Ciguatera fish poisoning is caused by the ingestion of fish contaminated by ciguatoxin, which is formed by algae-like organisms that grow around coral reefs in tropical waters. Patients develop gastrointestinal symptoms (vomiting, diarrhea, abdominal pain), neurological abnormalities (dysesthesias, paresthesias) and cardiovascular signs (bradycardia, hypotension), usually lasting 3-30 hours after ingestion [164-167].

Pufferfish poisoning is due to the consumption of pufferfish, which contains the neurotoxin tetrodotoxin. This poisoning is mainly described in Japan, where pufferfish, called Fugu, is consumed. The symptoms of pufferfish poisonings, occurring rapidly after ingestion, are mainly neurological

and include weakness, dizziness, paresthesias, nausea, hypotension [168].

Fish can also be contaminated by bacteria, such as *Vibrio cholerae*, *Vibrio vulnificus*, *Listeria monocytogenes*, *Salmonella* spp, *Escherichia coli*, *Staphylococcus aureus*, causing mainly gastrointestinal manifestations such as nausea, vomiting, diarrhea and fever [169, 170].

## CONCLUSION

The diagnosis of IgE-mediated fish allergy requires more sensitive and specific tools. Recent advances in molecular diagnostics, particularly regarding epitope structures, may lead to developing diagnostic tools that better correlate with clinical reactions, tolerance and cross-reactivities. Studies on recombinant allergens or modified hypoallergenic parvalbumin will possibly lead to new immunotherapy protocols.

Many aspects of fish-induced FPIES and EoE remain under debate. Future studies should prioritize research on pathophysiology and risk factors, diagnostic testing, biomarkers and treatment approaches. Multidisciplinary teams should be established to optimize the care for these patients.

## LIST OF ABBREVIATION

|       |   |                                             |
|-------|---|---------------------------------------------|
| BAT   | = | Basophil Activation Test                    |
| DHA   | = | Docosahexaenoic Acid                        |
| EoE   | = | Eosinophilic Esophagitis                    |
| FPIES | = | Food Protein-induced Enterocolitis Syndrome |
| OFC   | = | Oral Food Challenge                         |
| SPY   | = | Skin Prick Tests                            |
| TSLP  | = | Thymic Stromal Lymphopoietin                |

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