

EXPERT
REVIEWS

Fish-allergic patients may be able to eat fish

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Reported fish allergy prevalence varies widely, with an estimated prevalence of 0.2% in the general population. Sensitization to fish can occur by ingestion, skin contact or inhalation. The manifestations can be IgE or non-IgE mediated. Several fish allergens have been identified, with parvalbumins being the major allergen in various species. Allergenicity varies among fish species and is affected by processing or preparation methods. Adverse reactions after eating fish are often claimed to be 'allergy' but could be a reaction to hidden food allergen, fish parasite, fish toxins or histamine in spoiled fish. Identifying such causes would allow free consumption of fish. Correct diagnosis of fish allergy, including the specific species, might provide the patient with safe alternatives. Patients have been generally advised for strict universal avoidance of fish. However, testing with various fish species or preparations might identify one or more forms that can be tolerated.

KEYWORDS: anaphylaxis • *Anisakis simplex* • fish allergy • fish poisoning • food allergy • occupational asthma • occupational dermatitis • occupational allergy • scombroid poisoning • seafood allergy

The prevalence of allergic disease has increased worldwide, especially in the industrialized countries. According to the World Allergy Organization [1], up to 30% of the world population in 2008 was affected by some type of allergy, with a prominent increase in food allergy [2]. It has been estimated that up to 4% of adults and 8% of children have food allergy, with approximately 30,000 cases of food-induced anaphylaxis reported annually in the USA [3], with seafood being the most common among adults [3].

Seafood has become increasingly popular, with China being the largest consumer followed by Japan and the USA [4]. The per capita consumption of seafood in the USA was 15.8 pounds in 2009 [5] versus 15.5 pounds in 2002 and 12.5 pounds in 1970 [6]. Because of its palatability and nutritional value, consumption of seafood is constantly increasing, which has led to more frequent adverse reactions. In some countries, such as Scandinavia, Portugal, and Spain, it is one of the most common food allergens [7].

Seafood classification

Seafood is generally classified into two main groups: shellfish and finfish (FIGURE 1). This review will be limited to finfish. There are at least 32,400 different species of fish [7]. The

class of bony fish comprises 45 orders with diverse families in each. The most commonly consumed bony fish belong to the orders Clupeiformes, Salmoniformes, Cypriniformes, Gadiformes, Siluriformes and Perciformes [8]. The top consumed fish species worldwide in descending order are anchoveta, Alaska pollock, Atlantic herring, skipjack tuna, chub mackerel, largehead hairtail, blue whiting, Chilean jack mackerel, Japanese anchovy and yellowfin tuna [9].

Epidemiology

Seafood allergy in general is estimated to affect 1–2% of adults and <1% of children [10,11]. Allergy to finfish seems to occur in approximately 0.2% of the general population [12,13]. The reported figures, however, varied markedly according to the geographic region, the studied population and the study methodology (TABLE 1).

In a random telephone survey of 5529 households (14,948 total individuals) in the USA, the rate of fish allergy by self-report was 0.8% compared to 0.4% diagnosed by physicians, and only 0.1% diagnosed by physician and had positive allergy testing. The figures were significantly lower in children than in adults, in male adults than in female adults (0.2 vs 0.6%), and in Caucasians than in black (0.3 vs 1.1%). The most common

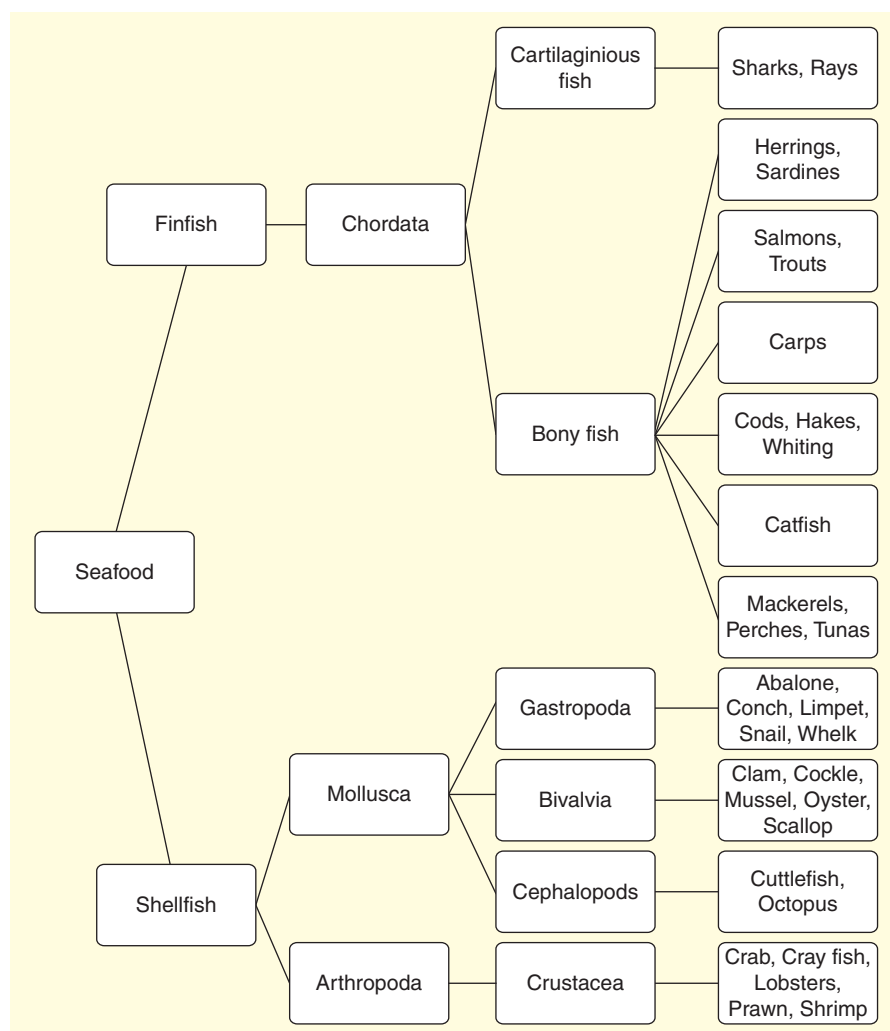


Figure 1. Seafood classification.

reported causative species, in order of decreasing frequency, were salmon, tuna, catfish, cod, flounder, halibut, trout and bass, with 67% of subjects having allergy to multiple species [10].

Exposure to high concentrations of fish allergen in various work environments is a high-risk factor. The Food and Agriculture Organization reports that >45 million people are directly involved in fishery and aquaculture production worldwide [9]. The first case of occupational fish allergy was reported in 1937 in a fisherman when handling codfish [14]. Other fish species reported to cause occupational fish allergy are trout, salmon, pilchard, anchovy, plaice, hake, tuna, haddock, cod and Pollock [15]. Several studies have been published on occupational fish allergy. In one study, workers in fish canning and fishmeal processing were found to have occupational rhinitis in 26% and asthma in 16% [16]. The reported rate of fish-induced occupational asthma was 2% in Poland [17], 7% in South Africa [15] and 8% in the UK. [18]. Fish-induced occupational dermatitis was reported as 3–11% [15].

Clinical manifestations

In addition to ingestion, fish sensitization and provocation can occur by skin contact or by inhalation. The latter two routes are more common in occupational settings [19] and are frequently encountered sporadically [20]. Risk factors are concomitant asthma and eczema. Regardless of the exposure route, the manifestations can be IgE or non-IgE mediated: generalized or localized.

IgE-mediated fish reactions are the most common. They usually appear within minutes to an hour after exposure (TABLE 2), as gastrointestinal (nausea, vomiting, colic and diarrhea), cutaneous (urticaria or angioedema), respiratory (rhinitis, conjunctivitis, cough and wheezing) or systemic anaphylaxis. Approximately two-thirds of patients with fish allergy experienced urticaria/angioedema, and around one-half reported upper or lower respiratory symptoms. In food-dependent, exercise-induced anaphylaxis, eating fish followed (or sometimes preceded) by physical exercise within 2–4 h may cause anaphylaxis or other symptoms. Fish seems to be the next most common implicated food after wheat [21]. Fish is among the foods that commonly exacerbate atopic dermatitis [22], usually within minutes to a few hours, but sometimes up to several hours.

Food protein-induced enterocolitis syndrome (FPIES), a non-IgE-mediated reaction mainly in young children, is characterized by explosive symptoms that occur within a few hours of food protein ingestion [23]. Fish-induced FPIES accounts for 5–10% of all cases of fish allergy [24]. In a series of 14 children (9–12 months) with FPIES, skin prick testing (SPT) was negative in all patients, and fish-specific serum IgE was positive in only one patient. Four of these children eventually became tolerant to the causative fish [24].

Exposure to fish by inhalation, occupational or sporadic at home or in restaurants, may cause upper and/or lower respiratory symptoms and occasionally urticaria or anaphylaxis [15,25]. The onset of occupational rhinoconjunctivitis symptoms may precede or coincide with the onset of occupational fish-induced asthma and vice versa. A large proportion of individuals with occupational asthma also report occupational rhinoconjunctivitis symptoms [26]. Interestingly, 7% of workers with ingestion-related fish allergy have asthma symptoms on fish exposure by inhalation [16]. Conversely, there are few case reports of fish workers with occupational asthma who subsequently developed ingestion-related allergic symptoms to fish [15]. Environmental exposure to fish antigen

Table 1. Reported prevalence of fish allergy in different countries.

Geographic region	Country	Number of subjects	Setting	Age	Rate (%)	Remarks	Ref.
Multinational 15 countries	Europe, US, Australia	17,280	Interview survey	20–44 years	2.2	Self-report	[100]
North America	USA	14,948	Phone survey	All	0.4	Self-report	[10]
	Canada	9667	Phone survey	All	0.5	Self-report	[101]
Europe	Turkey	2739	Students survey	6–9 years	0.3	Self-report	[1]
					0.2	Fish slgE [†]	
	France	2716	Community survey	2–14 years	0.7	Self-report	[1]
	Norway	2803	Birth cohort	0–2 years	3	Self-report	[1]
	Denmark	1834	Birth cohort	All	0.6	Fish slgE	[1]
	Sweden	2614	Birth cohort	0–4 years	0.7	Fish slgE	[1]
	Poland	51	Fish meal workers		2	Occupational asthma	[17]
	UK	291	Salmon processing workers		8	Occupational asthma	[18]
Asia	Norway	102	Fish stick		8	Occupational dermatitis	[102]
		122	Fish fillet		3		
	Philippines	11,434	Students survey	14–16 years	2.3	Self-report	[103]
	Singapore	6498	Students survey	14–16 years	0.3	Self-report	[103]
		227	Food allergy	Children	13	Self-report	[104]
		67	Food-induced anaphylaxis	Adults	3.3	Self-report	[105]
Africa	Thailand	2034	Students survey	14–16 years	0.3	Self-report	[103]
	Korea	40,429	Food-induced AD	6–15 years	12.5–15	Self-report	[106]
	South Africa	594	Pilchard canning and fishmeal processing workers	25–46 years	26	Occupational rhinitis	[16]
Australia					16	Occupational asthma	
	Australia	2999	Allergy clinic	Children	5.6	Self-report	[107]

[†]Fish specific IgE.

levels of $>30 \text{ ng/m}^3$ has shown significant correlation with sensitization and work-related asthma symptoms [16].

Similar to inhalation, exposure by skin contact may cause localized urticaria or allergic contact dermatitis [15,20]. Skin contact with fish may even result in generalized urticaria, angioedema or wheezing [27]. Allergic contact dermatitis initially manifests as itchy, erythematous and vesicular lesions and may evolve into chronic eczema with episodic acute exacerbations with repeated contact with the offending allergen [28]. The volar aspect of the forearm and dorsum of the hands are predominantly affected [29].

Other potential routes for food allergen include transplacental, transmammary [30,31] and bone marrow [32,33] or liver transplantation [34,35].

Fish allergens

Several allergenic fish proteins have been identified, including parvalbumin, enolases, aldolases, gelatin, vitellogenin and others (TABLE 3).

Parvalbumin, the major fish allergen, is responsible for IgE-mediated reactions in 95% of cases [36,37]. It is highly stable, can withstand cooking and remains airborne in steam. It has two distinct main isoforms: α and β . Cartilaginous fish muscle contains mainly α -parvalbumin, whereas bony fish muscle expresses mainly the β -homolog. Despite the structural similarity between the two isoforms, fish α -parvalbumin is generally considered nonallergenic [38]. On the other hand, α -parvalbumins in frog and chicken have been responsible for some allergic reactions [39,40]. Most fish express two or more different types of β -parvalbumin, ranging from $\beta 1$ to $\beta 11$. Recently, two novel parvalbumin isoforms of the β -type were identified as the only allergens in barramundi and subsequently designated as Lat c 1.0101 and Lat c 1.0201 by the International Union of Immunological Societies. These two isoallergens do not differ in their ability to bind IgE antibodies, but are differentially expressed in barramundi tissue [41]. Also the quantity of parvalbumin differs considerably among fish species, which can explain their varying degree of allergenicity [42].

Table 2. Clinical manifestations and mechanisms of fish allergy according to route of exposure.

Route of exposure	Clinical manifestations	Underlying mechanism	Diagnostic tests	Ref.
Ingestion	Immediate allergic reaction: gastrointestinal, skin, respiratory, anaphylaxis	IgE	SPT [†] , sIgE [‡] , challenge	[1,10]
	Food-dependent, exercise-induced anaphylaxis	IgE	SPT, sIgE, challenge	[21]
	Food protein-induced enterocolitis syndrome	Non-IgE	SPT, sIgE, challenge	[23]
Inhalation	Rhinitis, conjunctivitis, cough, asthma, urticaria, anaphylaxis	IgE	SPT, sIgE, challenge	[15,26]
Skin contact	Localized or generalized urticaria, respiratory symptoms	IgE	SPT, sIgE, challenge	[15,20]
	Allergic contact dermatitis	T cell	Patch test	[15,20]

[†]Skin prick test; [‡]Specific IgE.

Van Do *et al.* reported that cod, salmon, Pollack, herrings and wolffish contain the most potent and cross-reacting allergens, whereas halibut, flounder, tuna and mackerel were the least allergenic [43]. Parvalbumin is considerably more in light color

than in dark parts of fish muscle. It is also more in the ventral and rostral regions than in the dorsal and caudal regions [44].

Parvalbumin is responsible for >50% of clinical cross-reactivity among various species of fish, especially the closely

Table 3. Main fish allergens identified in various fish species.

Allergen class	Fish species	Allergen name	Biochemical function	Clinical importance	Ref.
Parvalbumin	Most species	α and β homolog	11.5–12.3 kD,	Pan-allergen, 95% of fish-allergy	[36,37]
	Herring	Clu h,	113 amino acids + glucose,		
	Pilchard	Sar sa	Regulates calcium switching in		
	Carp	Cyp c	muscle		
	Cod (Baltic)	Gad c			
	Cod (Atlantic)	Gad m			
	Barramundi	Lat c			
	Tuna	Thu a 1.0101			
	Swordfish	Xip g			
	Whiff	Lep w			
	Trout	Onc k			
	Salmon	Sal s			
	Redfish	Seb m			
	Pollock	The c			
	Chub	Sco j			
	Mackerel	Sco a			
	Atlantic	Sco s			
Vitellogenin	Salmon	Onc k	Yolk protein	Roe allergy	[48]
Enolase β	Cod (Atlantic)	Gad m	Enzyme in metabolic glycolysis	Subjects also have parvalbumin IgE antibody	[45]
	Tuna	Thu a 2.0101			
	Salmon	Sal s			
Aldolase	Cod (Atlantic)	Gad m	Enzyme in metabolic glycolysis	Subjects also have parvalbumin IgE antibody	[45]
	Tuna	Thu a 3.0101			
	Salmon	Sal s			
Tropomyosin	Tilapia	Ore m	32–49 kD Filamentous muscle protein	Possible role in inflammatory bowel disease	[45]
Glyceraldehyde-3-P dehydrogenase	Platyfish Silversides		36 kD Enzyme in metabolic glycolysis	Ingestion and Inhalation allergy	[49]
Collagen	Bigeye tuna			No cross-reactivity with other animals' collagen	[50]
Gelatin	Cod		Irreversibly hydrolyzed collagen	Food and pharmaceutical Contamination with parvalbumin	[45]

related ones [43]. Yet, even highly fish-allergic subjects can tolerate one or more fish species with less parvalbumin, such as tuna. Sensitivity has been reported to a single species (e.g., sole, swordfish or salmon), or limited to two species such as pangasius/tilapia, tuna/marlin [45]. Of note, parvalbumins of different fish species can have different homology and allergenicity, particularly between the common bony fish versus cartilaginous fish such as shark and ray [7]. Although no immunologic cross-reactivity has been identified between fish and other seafood, co-sensitization can occur and could be attributed to the general atopic constitution [45]. Recently, *tropomyosin*, a major filamentous muscle protein in crustacea, was identified as an allergen in tilapia-sensitized patients [46].

Vitellogenin, a fish yolk protein, has been identified as an allergen in caviar (fish roe) of different fish species as well as from chicken egg [47]. To the best of our knowledge, there is no reported cross-reactivity between caviar and chicken egg. Makinen-Kiljunen *et al.* [48] reported two patients who had severe reactions after meals that included roe (one of rainbow trout and the other of whitefish). Both patients ate fish without any reactions and had positive SPT and specific IgE (sIgE) to roe but negative tests to six types of fish, including rainbow trout, whitefish, shrimp and oyster. Therefore, it is possible to be allergic to caviar but not to fish.

Additional fish allergens are *enolase* and *aldolase* that have been demonstrated in cod, salmon and tuna [45]. Their clinical relevance is not clear because most of the enolase-/aldolase-positive patients also had IgE antibodies to parvalbumin. Other potential allergens were found in cod (*aldehyde phosphate isomerase*), salmon (*triosephosphate isomerase*, *fructose-bis-phosphatase isomerase*, *serum albumin*) and tuna (*creatine kinase*, *beta-enolase*) [45]. Furthermore, fish-derived *glyceraldehyde-3-phosphate dehydrogenase* has also been identified through experimental murine model exposed to fish allergens by inhalation [49]. The collagen, isolated from the bigeye tuna, can cause allergy regardless of fish species. There is no antigenic cross-reactivity observed between collagens from fish and other animals [50].

Fish gelatin is commonly incorporated into many food and pharmaceutical products. In one study, SPT with fish gelatin was positive in 3 out of 30 cod-allergic patients, although oral challenge testing was positive in only one of the three [45]. Severe anaphylaxis in a patient was attributed to eating sweets that contained several grams of fish gelatin [45]. We did not encounter any report of cross-reactivity between mammalian and fish gelatins. Isinglass is derived from fish swim bladder, often used for filtering beer or wine; it seemingly contains harmless quantities of gelatin. However, its small quantity of parvalbumins (0.4147 mg/g) may be of potential risk for exquisitely fish-sensitive patients [51]. On the other hand, the potential contamination with parvalbumin in gelatin derived from fish skin is trivial and, to the best of our knowledge, did not cause allergic reactions.

Effect of processing on fish allergenicity

In addition to the quantitative and qualitative variability of parvalbumin in various fish species, the muscle type (dark vs light-

Table 4. Effect of processing on fish allergenicity.

Processing method	Effect on allergenicity	Ref.
Heating	Increase	[53]
Storage	Increase	[57]
Canning	Decrease	[54]
Enzymatic digestion	Decrease	[58,59]
Gastric acidity	Decrease	[58,59]

color), and the anatomic part of the fish, allergenicity can be markedly affected by the method of processing or preparation (TABLE 4). Processing may decrease or increase food protein allergenicity depending on the effect on the linear and conformational IgE epitopes [52]. Similar to some other foods, heat tends to increase the allergenicity of parvalbumin [53], whereas canning tends to decrease it [54]. According to one study [55], more than 20% of children allergic to salmon or tuna were able to tolerate that fish in a canned form, and over time was associated with a reduction in the initial SPT positivity. This finding suggests that consumption of the canned form may have induced tolerance. However, monoallergy to canned tuna has been reported [56]. Furthermore, storage has been found to increase parvalbumin capacity for IgE-binding in immunoblotting assays [57]. Studies in experimental animals and in humans demonstrated that enzymatic digestion of fish protein reduces allergenicity, whereas the concomitant intake of antacids enhances allergenicity [58,59]. In the mouse model [58], the concomitant administration of antacids predisposed to allergic reactions. In the human study, the allergic individual reacted to codfish at a lower dose or after a shorter time when the codfish was predigested at pH 3 versus pH 2, with obvious correlation with the duration of predigestion [59].

Mechanisms of fish allergy

Fish protein hypersensitivity can be mediated by different immunologic mechanisms that result in different clinical manifestations. Most reactions are IgE mediated and manifested as urticaria, angioedema, rhinoconjunctivitis, bronchospasm, gastrointestinal symptoms or anaphylaxis. In addition, the findings of an *in vitro* study suggest that fish digestive enzymes such as trypsin from salmon and pilchard can activate specific receptors called protease activation receptors-2 on epithelial cells of the airways, with resultant airway inflammation through the expression of IL-8 and other cytokines [60].

Cell-mediated allergic contact dermatitis is mediated by the cytokines of Th1 cells and macrophage. In cases of fish-induced FPIES, the mechanism is not well defined; perhaps cytokines from both Th2 and Th1 are involved [61].

Diagnosis of fish allergy

Like any other food allergy, the diagnosis of fish allergy is usually suspected by the medical history, which in some cases may be convincing enough by itself to settle the diagnosis. In many

cases, the diagnosis is suspected by a positive allergy skin testing or blood testing; both of which merely indicate sensitization. Confirmation of the diagnosis would require an appropriately designed oral food challenge test.

The medical history can provide very valuable information regarding the manifestation, time of onset, provoking quantity, frequency, type(s) of fish, method of preparation, incorporation of other ingredients and possible associated co-factors. It is worth noting that the frequency of self-claimed food allergy far exceeds reality. Occasionally, the history by itself can be very convincing in patients who report rapid onset of objective manifestations after eating fish on multiple occasions, particularly when witnessed by medical professionals. Differential diagnosis of the symptoms must be considered, including Munchausen stridor in subjects who repeatedly pretend to be sick or get sick on purpose to gain attention [62].

SPT is the most commonly used procedure in allergy practice. However, a positive test merely indicates sensitization that may or may not have clinical relevance. It can also be falsely negative if the test extract is of a low potency or from a different fish species. Intradermal testing with food extracts is not favored because of the high sensitivity and potential risk of anaphylaxis. The SPT negative predictive value is high, whereas the positive predictive value is low [63]. In general, the larger the size of SPT reactivity, the more likely it is to be clinically relevant, although it may not reflect the severity [64]. Because of processing effects, SPT may need to be done using the same preparation that provoked symptoms (prick-by-prick technique). Testing with multiple fish species can be valuable in designing a management plan.

sIgE testing is also commonly used and also reflects sensitization. The reliability would depend on the assay used and on the fish species tested. Again, the higher the level, the more likely to have clinical relevance, although not necessarily the severity. Some studies reported sIgE levels predictive of clinical allergy. However, such levels were derived from certain populations and cannot be extrapolated to patients with different characteristics. They also reflect probabilities that cannot be applied with certainty on individual patients. One study [65] reported a 95% positive predictive value of sIgE to cod fish as 20 kU/l. However, some patients with anaphylaxis to pilchard or anchovy had sIgE levels as low as 1 kU/l [53].

sIgE testing or SPT with a fish mixture may be of value for screening so that a negative result together with a weak suspicion by history would obviate the need for testing with multiple individual species. A more differentiating procedure can be sIgE measurement to Atlantic cod, Atlantic salmon, Pacific pilchard and European hake to cover the spectrum of the pan-fish allergen parvalbumin [1].

sIgE molecular allergen component testing has been recently introduced and suggests that positivity to certain allergen components may have higher predictive value of clinical reactivity, whereas others predict tolerance. At present, the test is available for a limited number of foods, including two fish allergens, rCyp c 1 (carp) and rGad c 1 (cod), which represent the most

cross-reacting fish allergens [66]. In addition to the limited availability and high cost, this test provides probabilities and is not a substitute for the above-mentioned diagnostic procedures. The definitive diagnostic proof remains the challenge test.

For non-IgE-mediated reactions, such as delayed gastrointestinal symptoms, eosinophilic gastroenteropathies or FPIES, sIgE and SPT are generally not useful. In rare cases of FPIES, IgE mechanism is involved and sIgE or SPT would be positive. Allergy patch testing, though not standardized, is generally positive in cases of allergic contact dermatitis and in some cases of eosinophilic gastroenteropathies or FPIES [61].

Oral challenge testing is usually necessary to confirm the diagnosis of food allergy and possibly to identify one or more fish species that can be tolerated by the patient [67–69]. In patients with frequent or persistent symptoms, the test should start with an elimination phase of the suspected food(s) to document improvement, particularly after discontinuation of symptomatic medications. Blind placebo-controlled challenge method would be preferred, although open-challenge would be reliable in young children with objective manifestations. The starting dose should be individualized to be a safe quantity for the patient being tested, being guided by the anticipated reaction and the inciting quantity by history. The test fish should be prepared in a similar manner as the initial provoking one as long as it can be disguised in an appropriate placebo. The latter can be a beef or chicken burger. Although using fish powder in capsules is easy, it can give a falsely negative test due to allergenicity difference [54]. If food-dependent, exercise-induced reaction is suspected, oral challenge should be followed by physical exercise at 1–2 h and may be repeated at 3–4 h.

In patients who react through inhalation, it would be difficult to perform blind challenge. Open challenge would be acceptable, particularly because the manifestations are objective and should be supplemented with monitoring the vital signs and spirometry.

Management of fish allergy

Management of any food allergy is basically avoidance, combined with an action plan for treatment of acute reactions. At present, immunotherapy protocols for certain foods are being developed, but not for routine clinical practice yet.

Treatment of acute reactions

Pharmacologic therapy for acute reactions is primarily symptomatic according to the type and severity of the reaction. In addition to wearing a Medic-Alert identification, patients with a history of severe reactions should be provided with an action plan, including the use of epinephrine autoinjector. For FPIES episodes, rapid administration of iv. fluid is the principal therapy.

Avoidance

Traditionally, fish-allergic patients have been advised to strictly avoid fish in general. As mentioned above, recent studies indicate that fish allergy is not universal. Most patients can tolerate

at least one type of fish or even the same species processed/prepared in a certain way. To explore that, the patient may be subjected to SPT (or sIgE test) to multiple fish species or different preparations of fish and then challenged by those that show negative result.

Patients should be advised to carefully read food labels and to be cautious of possible contamination, particularly in restaurants. Fish is one of the eight allergenic foods required by the US FDA to be listed on food packages [70].

Those who are highly allergic may need to avoid even touching or being in the vicinity of fish. Control of concomitant eczema would reduce the risk of reactions by skin contact, and control of concomitant asthma would reduce the risk of reactions by inhalation. Severe reactions have occurred after kissing a person who just ate fish [71,72]. Such patients should alert their family members and close friends of their severe allergy. Tooth brushing and mouth rinsing can be helpful, although the allergen can be excreted in the saliva after ingestion and absorption.

The fish protein quantity in certain products, such as fish oil, omega-3 fatty acid supplements, wine, medications and cosmetics are generally minute and safe in the vast majority of subjects [73]. In a case report, anaphylaxis occurred after eating marshmallows containing fish gelatin [74]. The misconception about cross-reactivity between seafood and radiocontrast media, commonly claimed as 'iodine allergy', is unfounded and fish-allergic subjects are not at an increased risk of reaction to radiocontrast media [75].

Immunotherapy

The first case of fish immunotherapy was through the subcutaneous route in 1930 [76]. Another case report was on desensitization to codfish using rush immunotherapy [77]. However, subcutaneous immunotherapy with food extracts is risky, and different methods have not been developed yet. Novel methods through the sublingual or oral routes are being investigated for both efficacy and safety but are not at the stage of application in routine clinical practice yet [78,79]. The use of a recombinant parvalbumin could have a great potential; its testing in mice demonstrated a maintained immunogenicity without allergenicity [80].

Prognosis

Fish is one of the most allergenic foods, and its allergy usually persists for many years, depending on the severity of manifestation and the provoking quantity. In general, the stricter the avoidance, the earlier tolerance develops, although sensitization without symptoms may persist for long periods. It has been suggested that IgE antibodies from patients with persistent allergy may be directed against epitopes different from those in patients with transient allergy [57]. Recurrence after tolerance has also been reported [81].

Testing for tolerance would require the performance of a carefully conducted titrated challenge testing under supervision. The timing would vary according to the degree of sensitivity

and the compliance with avoidance. In cases of anaphylaxis, intentional challenge may not be prudent, and tolerance may be discovered by accidental exposure. A decrease in SPT reactivity or drop in sIgE level can be a guide. For fish-induced FPIES, tolerance has occurred in 25% of 14 patients after 4 years of avoidance [24]. It has been recently reported that milk-induced FPIES in children who had positive sIgE can have a protracted course and eventual transition to IgE-mediated reactions [82]. It is unknown whether the same applies to fish-induced FPIES.

Not every 'fish allergy' is fish allergy

Allergy is often claimed for any adverse reaction following eating a food. However, the reaction may be an allergy to an ingredient other than the main food or may not be an allergy at all (TABLE 5). Allergic reactions to non-fish protein can be to another food ingredient added to the fish, to a hidden contamination (common in restaurants or in packaged foods) or to the fish parasite *Anisakis*.

Anisakis simplex allergy

Anisakis simplex (AS) is a parasite that can infest fish, with high infestation in herring, hake, black plaice and cod and in certain regions, particularly Japan and Spain [83]. Marine mammals are hosts of anisakids whose eggs are excreted via feces into the sea. Then the developing larvae are ingested by tiny crustaceans that are subsequently ingested by larger crustaceans, cephalopods and fish. When live larvae (~2 cm long) in infested fish are ingested by humans, they do not develop into adult parasites and become attached to the gastric mucosa unless they become digested or ejected by vomiting and diarrhea [3]. Affected subjects usually present 2–24 h after ingestion, but can be as short as few minutes [84] or as long as over 24 h [85], with gastrointestinal symptoms (abdominal pain, nausea, vomiting and/or diarrhea). Subjects who become sensitized to the parasite protein may exhibit urticaria, angioedema, bronchospasm and even anaphylaxis [3]. Exposure to live larvae is not required for allergic reactions to occur. Sensitization and provocation can occur in fish processing workers by inhalation or skin contact, resulting in airway hypersensitivity or contact dermatitis [86].

More than 13 AS allergens have been identified [87], and the major allergens (recognized in over 50% of patients) are Ani s 1, Ani s 2, Ani s 7 and Ani s 12 [3,88]. Cross-reactivity has been demonstrated *in vitro* between Ani s 3 (a tropomyosin) and crustaceans and dust mites, but the clinical implication is not clear [89]. The parasite is killed at temperatures above 60°C for 10–20 min or below –20°C for 24 h [57]. However, its allergenicity is resistant to heat, cooking or digestion [1,90]. Allergy to AS should be suspected in subjects who report reactions to a fish species on some occasions (particularly in endemically infested regions) but not on others, or when SPT (or sIgE) is negative to multiple fish extracts. Positive SPT or sIgE to AS, if available supports the diagnosis while oral challenge with noninfested fish would be negative [36]. Albendazole is effective

Table 5. Adverse reactions to fish caused by non-fish protein.

Disorder	Underlying cause	Source examples	Onset	Clinical manifestations	Treatment	Ref.
Anisakis parasite	Allergic reaction to the parasite larvae	Herring, hake, black plaice, cod	Min – >24 h	Gastrointestinal symptoms, allergic reactions symptoms	Avoidance Epinephrine Antihistamines	[83]
Scombroid poisoning	Histamine produced in the fish by bacterial action	Spoiled fish; mainly mackerel, salmon, tuna	Min – 4 h	Oral tingling or burning, flushing, urticaria, headache, dizziness	Antihistamines Proper storage	[94]
Puffer fish poisoning	Tetrodotoxin produced out of fish bodies by bacteria and accumulate in fish bodies	Fugu, globefish, blowfish	Min	Nausea, weakness, dizziness, paresthesias, loss of reflexes, hypotension, generalized paralysis, respiratory failure	Supportive care	[96]
Ciguatera toxin	Ciguatoxins, maitotoxin and scaritoxin produced out of fish bodies by <i>Gambierdiscus toxicus</i> and accumulate in fish bodies	Reef fish: barracuda, amberjack, moray eel, and certain types of grouper, snapper, or parrotfish	Min – 4 h	Gastrointestinal, neurologic, cardiovascular	Supportive care	[97]

for killing the parasite, but in some cases endoscopic removal may be needed [91].

Fish poisoning

Fish offered for human consumption is generally safe but may cause poisoning through multiple ways.

Fish botulism is rare but can be serious. It is caused mainly by *Clostridium botulinum* Type E toxin that causes neurologic symptoms. The toxin can withstand freezing, but is destroyed by high heat (boiling for 10 min). To kill the bacterium, higher and longer heating is required. It can occur from home-canned fish. The consumption of whale meat 'mukluk' has also been associated with outbreaks of botulism in Alaska and the Canadian Arctic. 'Rakish' in Norway, salted gray mullet 'faseikh' in Egypt, salted uneviscerated whitefish 'kapchunka' in Israel and New York, uncooked salmon 'ashbal' in Iran, and fermented fish preserved in rice 'izushi' in Japan have been associated with fish botulism. Sporadic cases of botulism Type E in Europe also have been linked to imported vacuum-packed whitefish [92].

Scombroid poisoning occurs following eating fish that has been spoiled by bacteria. Dark-muscle fish (e.g., tuna, bluefish, and mackerel) is rich in histidine that can be decarboxylated into histamine by certain bacteria such as *Morganella morganii*, *Enterobacter aerogenes*, *Raoultella platicola* and *Hafnia alvei* [93]. Eating such fish, even cooked, may cause symptoms that mimic IgE-mediated allergy. Depending on the histamine content, within an hour the subject may develop perioral sensations of tingling or burning, flushing, urticaria, headache and dizziness. The treatment of the acute reaction is mainly antihistamines; corticosteroids are ineffective [94]. The diagnosis is suspected when symptoms develop in multiple subjects who ate the same

meal. Allergy testing would reveal negative SPT, sIgE, and oral challenge with the same type of fish. For prevention, the fish industry regulations require proper handling and storage conditions. In addition, histamine detection techniques are used for screening of fish; at a threshold of 50 mg/kg in the USA and 100–200 mg/kg in Europe [95].

Pufferfish poisoning is caused by the fish fugu (also called globefish or blowfish), a popular delicacy in Japan, but sporadic cases have been reported in the USA [95]. Certain bacteria (*Pseudomonas* or *Vibrio*) act on the fish body and induce the production of tetrodotoxin. Tetrodotoxin is a neurotoxin not affected by washing, cooking or processing the fish. Symptoms occur rapidly after ingestion and include weakness, dizziness, paresthesias of the face and extremities, nausea and loss of reflexes. High doses can cause severe hypotension, generalized paralysis and even respiratory failure [96]. Treatment is mainly supportive care.

Ciguatera fish poisoning can be caused by large reef fish (e.g., barracuda, amberjack, moray eel, and certain types of grouper, snapper, or parrotfish) prevalent in the tropical and subtropical waters of the Pacific and the Caribbean [36]. Under the influence of *Gambierdiscus toxicus* bacteria, ciguatoxin, maitotoxin and scaritoxin are produced out of fish bodies and accumulate in fish. These neurotoxins are lipid-soluble, heat-stable and acid-resistant [97]. Affected fish have no untoward appearance or taste, making identification difficult. Soon after eating the affected fish, patients typically experience cutaneous tingling or burning sensation, gastrointestinal upset and less commonly cardiovascular symptoms [98]. Treatment is primarily supportive. Studies are underway for developing monoclonal antibodies for detection and neutralization of ciguatoxins [99].

Apart from the above-mentioned toxins, fish may be contaminated with sea organisms that may cause adverse reactions in certain individuals, such as *Hoya* (sea squirt) and algae (seaweed). Also, the processing of fish may include the addition of various additives (e.g., sulfiting agents, monosodium glutamate or spices) that can cause adverse reactions.

Patients diagnosed with fish allergy may eat fish

The popularity of fish has been continuously increasing, and fish-allergic subjects are generally cautioned against eating any fish. However, recent studies, referred to above, indicate that such patients may be able to tolerate a different species or tolerate the same fish processed in a way that denatures the allergenic epitopes. In other words, fish allergy, in some patients, may only manifest if certain species were consumed or the fish was consumed in certain circumstances. For instance, in cases of post-prandial exercise-induced reactions, most patients would not react if the subject allows 2–4 h between the two factors. It would be prudent to confirm the safe fish species or form by appropriately designed oral challenge. Acquired tolerance may be discovered by accidental exposure or by challenge testing after a prolonged elimination period that depends on the initial severity of the reaction and the provocative dose.

Expert commentary & five-year view

Recent studies have increased our knowledge regarding variation in fish allergenicity according to species, different parts of fish muscle and method of processing. In addition to parvalbumin, a few other allergens have been identified (enolases, aldolases, vitellogenin and others). The reports of spontaneous

tolerance developing after elimination periods confirm that fish allergy is not forever.

During the next several years, advances are expected in the areas of diagnosis and treatment. Studies on molecular diagnostic testing might lead to better test result interpretation for clinical relevance regarding the type or severity of clinical reactions, cross-reactivities and tolerance. It is very likely that studies on using recombinant allergens or modified 'hypoallergenic' parvalbumin would lead to immunotherapy protocols with high safety and efficacy.

For high-risk occupations, enforcing appropriate environmental control measures would reduce the risk. In this regard, it would be useful to conduct studies to determine critical thresholds of exposure, including duration and intensity, as well as the degree of sensitization that predicts high risk for overt clinical reactions. The importance of accurate labeling of commercial products regarding fish-derived ingredients cannot be overemphasized.

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Key issues

- Fish is one of the potent allergenic foods and comprises more than 32,000 species. Its increasing consumption has been associated with increased prevalence of fish allergy worldwide.
- The prevalence of fish allergy is estimated at 0.2% of the general population, but varies widely according to the geographic region, dietary habits, population and study methodology.
- Fish allergy sensitization and provocation can occur by ingestion, skin contact or inhalation.
- The manifestations can affect various body systems, vary in severity, and can be IgE or non-IgE mediated.
- Fish allergy is one of many causes of adverse reactions following eating fish. Differential diagnosis should include allergy to other food ingredients, allergy to the fish parasite *Anisakis simplex*, scombroid poisoning and intrinsic fish toxins.
- In addition to the major allergen – parvalbumin – several fish allergens have been identified, including enolase, aldolase and vitellogenin.
- Fish allergenicity can be markedly affected by the method of processing and tends to increase by heating and decrease by canning.
- The diagnosis of fish allergy is suspected by the medical history, supported by documenting sensitization (skin prick testing or serum sIgE) and often needs to be confirmed by oral food challenge.
- Management of fish allergy is basically avoidance and providing an action plan for treatment of acute reactions. Good control of associated asthma or eczema would reduce the reaction's severity.
- Fish allergy usually persists for many years, but rarely for life.
- The general notion of universal avoidance of fish is not valid for all fish-allergic subjects. Some patients may only react to certain species or when the fish is prepared in a certain way or consumed without associated enhancing factors.

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