

Fish and Shellfish Allergy

Laurianne G. Wild, MD, and Samuel B. Lehrer, PhD

Address

Tulane University Health Sciences Center, 1430 Tulane Avenue, SL-57,
New Orleans, LA 70112, USA.

E-mail: sblehrer@tulane.edu

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Fish and shellfish are important in the American diet and economy. Nearly \$27 billion are spent each year in the United States on seafood products. Fish and shellfish are also important causes of food hypersensitivity. In fact, shellfish constitute the number one cause of food allergy in the American adult. During the past decade, much has been learned about allergens in fish and shellfish. The major allergens responsible for cross-reactivity among distinct species of fish and amphibians are parvalbumins. The major shellfish allergen has been identified as tropomyosin. Many new and important potential cross-reacting allergens have been identified within the fish family and between shellfish, arachnids, and insects. Extensive research is currently underway for the development of safer and more effective methods for the diagnosis and management of fish and shellfish hypersensitivity.

Introduction

Fish and shellfish play an important role in human nutrition and in the world economy. Unfortunately, they also can be important causes of severe acute hypersensitivity reactions, including fatal anaphylaxis. Food-related anaphylaxis is a growing problem worldwide and is now estimated to be the single most frequent cause of anaphylaxis treated in emergency departments [1]. Fish and shellfish are leading causes of IgE-mediated food hypersensitivity. During the past decade, an extraordinary amount of information has been gained regarding the prevalence of food allergy in the United States. A number of major allergens and important potential cross-reacting allergens have been identified within the fish family and between shellfish, and major inhalant allergens in arachnids and insects. New methods for diagnosis and treatment of food hypersensitivity have been discovered, which may make evaluation and care of the patient easier and safer in the future. The purpose of this review is to provide an update on interesting and new findings in the area of fish and shellfish allergy.

Significance of Seafood in United States

Seafood is a very important part of the diet and economy in the United States. During the past decade, Americans have incorporated more fish into their diets to promote healthier living. The National Marine Fisheries Service reported per capita consumption of seafood at 15.6 pounds in 2002. Total seafood consumption increased 7.1% to 4.5 billion pounds, making the United States the third largest consumer of seafood products in the world.

Shrimp is a popular seafood product in the United States. In fact, in 2001, for the first time in recorded history of US seafood consumption, shrimp topped the list of the most consumed seafood products. In 2001, shrimp consumption increased 10% from the previous year to 3.4 pounds per capita and subsequently rose to 3.7 pounds in 2002. Salmon consumption increased by 26% from 2000 to 2001 to 2.02 pounds per capita. Consumer expenditure on seafood in the United States is estimated at \$26.7 billion. Table 1 is a list of the top 10 most frequently eaten types of seafood in the United States, per the National Fisheries Institute in 2001 [2].

Perception and Prevalence of Fish and Shellfish Allergy

Fish is a major source of dietary protein, especially in coastal areas. Although seafood is very popular in the diet worldwide, consumption remains a concern for many. In one survey of parents in Norway, adverse food reactions were reported in 30% of their children, nearly 3% of whom had a reaction attributable to fish by the age of 2 years [3]. Another survey reported that up to 15 million Americans suspect that they are allergic to foods [4]. Recent reports suggest that IgE-mediated food allergy affects nearly 4% of the United States population [5].

Fish and shellfish are two of the most common causes of food-allergic reactions in both children and adults. A nationwide, cross-sectional, random telephone survey performed by Sicherer *et al.* [5] found that seafood allergy is reported by 3.3% of the general population and by at least one member of 5.9% of US households. In another report by Munoz-Furlong *et al.* [6], allergy to some type of seafood was reported for 0.6% of US children younger than age 18 years and 2.8% of adults. Fish allergy accounts for an estimated 0.1% and 0.4% of food allergies in US children and adults, respectively. Shellfish are responsible for 0.1% of food allergies in children and are the number one cause of

Table 1. Top 10 most frequently eaten seafoods in the United States, per the National Fisheries Institute in 2001

Pounds per capita		
1.	Shrimp	3.4
2.	Tuna	2.9
3.	Salmon	2.02
4.	Alaska pollock	1.20
5.	Catfish	1.15
6.	Cod	0.56
7.	Clams	0.46
8.	Crab	0.44
9.	Flatfish	0.39
10.	Tilapia	0.35

IgE-mediated food allergy in US adults, affecting an estimated 2% of the adult population [7].

Manifestations of Fish and Shellfish Allergy

Hypersensitivity reactions to fish and shellfish can result from ingestion, contact, or even inhalational exposures. Many reactions have been described in allergic consumers after the ingestion of or direct contact with the offending seafood. In a double-blind, placebo-controlled oral fish challenge study, emesis was the most frequent objective sign in patients with a positive challenge. Oropharyngeal symptoms or generalized pruritus preceded emesis in all patients [8]. In another study, the most frequently reported signs/symptoms were pruritus and hives, wheezing and chest tightness, and angioedema. Although symptoms have been reported to develop more than 60 minutes after ingestion, most reactions (85%) occur within 30 minutes of ingestion of the culprit food [9].

In addition to allergy in the consumer, fish and shellfish have also been recognized as important allergens in occupational environments. In the occupational setting, reactions are most commonly associated with direct contact or inhalational exposure rather than with ingestion [10–14]. Dermatologic symptoms can result from direct handling or from inhalation of the allergen. Contact urticaria has been reported in handlers of raw fish and shellfish [15,16]. Often these workers are unable to handle the raw foods but are able to ingest the food once it is cooked, suggesting a heat-labile allergen. Occupational asthma has been associated with inhalational exposure to fish, shrimp, lobster, clam, and snow crab [14,17–19]. The prevalence of IgE-mediated occupational asthma has been reported in as many as 15.6% of snow crab-processing workers—76% have rhinoconjunctivitis, and 35% have associated urticaria [19].

Routes of Exposure and Hidden Allergens

Food allergy remains a leading cause of fatal anaphylactic reactions, often resulting from exposure to hidden aller-

gens. Although most food-allergic individuals have knowledge of their allergy and thus can make attempts at strict avoidance, many unknowingly ingest or inhale the offending food [1]. Fish- and shellfish-allergic individuals may not be aware of the various forms of potential exposure, because the seafood content of some foods is not obvious. For instance, anchovies are found in Worcestershire sauce and many Caesar salad dressings. Roe and caviar are names for fish eggs that may potentially go unrecognized as fish-derived by the consumer. Surimi is processed fish meat, derived in the United States primarily from Alaskan pollock [20]. Ingredients such as meat proteins, seafood-derived flavorings, spices, and seasonings are mixed with the raw surimi, which is shaped into analog products sold to the public. Surimi is used as an ingredient for imitation crab—often labeled “krab,” shrimp, scallops, and seafood snacks. Additionally, surimi meat-blend products are available as “meatless” hot dogs, hybrid ham and bologna, sausages, pepperoni sticks, and pizza toppings. These hidden allergens may pose a potential risk for life-threatening allergic reactions in the unsuspecting consumer.

Although most allergic reactions in food-allergic patients result from ingestion of an unrecognized allergen, any contact with such an allergen could be deadly. In one report, a young shrimp-allergic woman experienced a near-fatal anaphylactic reaction to shellfish allergens during a goodnight kiss from her boyfriend, who had eaten shrimp prior to the kiss [21].

Allergens in Fish and Shellfish

Many allergens have been analyzed in fish and shellfish. During the past several years, many new allergens and important potential cross-reacting allergens have been identified within the fish family and between shellfish, arachnids, and insects. Codfish and shrimp have been the models used to study allergy to fish and shellfish, respectively.

Fish allergens

The major allergens responsible for cross-reactivity among distinct species of fish and amphibians are parvalbumins. These proteins control calcium flow in the muscular sarcoplasm of the white meat and have a molecular weight of approximately 12 kD. Parvalbumins are resistant to thermal and enzymatic degradation.

The major fish allergen, Gad c 1, is a parvalbumin that was first identified in Baltic cod (*Gadus callarias*). Gad c 1 has been well-studied, characterized, and sequenced [22,23]. Another parvalbumin, the major allergen in the white muscle of Atlantic salmon, was identified and named Salmo salar (Sal s 1) [24]. In the Atlantic cod (*G. morhua*), an oligomeric parvalbumin encoded by a distinct gene was identified as Gad m 1 and found to have greater homology with Sal s 1 than with Gad c 1. Interestingly, Gad m 1 shares 75% homology with Sal s 1 and only 62.3% homology with Gad c 1 [25••]. Hamada *et al.* [26] have identified the major aller-

gens, Sco j 1, Sco a 1, and Sco s 1, from three species of mackerel (*Scomber japonis*, *S. australasicus*, and *S. scombrus*, respectively). Swoboda *et al.* [27••] identified the major allergen in carp (*Cyprinus carpio*) and found that it inhibited IgE binding to parvalbumins of several other fish species and, therefore, contains most of the fish-specific IgE epitopes. Because carp parvalbumin contains 70% of the IgE epitopes present in natural extracts of cod, tuna, and salmon, recombinant carp parvalbumin may be a very important tool in the diagnosis and treatment of fish-allergic subjects [28]. In addition to the well-known, major fish-allergen parvalbumin, gelatin (type I collagen) was recently identified as an important novel allergen in the muscle and skin of several species of fish [29,30].

Shellfish allergens

Shellfish are a non-taxonomic group that includes crustacea and mollusks, which are invertebrates, unlike fish. The major shellfish allergen has been identified as tropomyosin, an essential protein in muscle contraction, both in invertebrates and in vertebrates. Tropomyosins in invertebrates have a molecular weight of between 38 and 41 kD and show great homology in their amino acid sequence. They are the panallergens responsible for cross-reactivity between crustaceans (shrimp, crab, crawfish, lobster), insects (cockroaches), arachnids (house dust mites), and different classes of mollusks [31].

The major shrimp allergen has been identified as Pen a 1, and 85% of shrimp-allergic individuals show reactivity [32,33•]. A second allergen from the black tiger shrimp (*Penaeus monodon*) was recently identified and designated Pen m 2. Using Pen m 2–specific antisera and polyclonal sera from shrimp-sensitive subjects in a competitive enzyme-linked immunosorbent assay (ELISA) inhibition assay, Pen m 2, an arginine kinase, was identified as a new cross-reactive crustacean allergen [34].

Cross-reacting allergens

Cross-reactivity is the recognition of distinct antigens by the same IgE antibody, demonstrable by in vivo and in vitro tests, which clinically manifests as reactions caused by antigens that are homologous to different species. Subclinical sensitization can also occur, giving rise to patients sensitized to particular fish or shellfish but who do not manifest symptoms on consumption. Although it is estimated that 50% of individuals allergic to some type of fish are at risk for reacting to a second species, those allergic to some type of crustacean carry a risk of 75%, due to the greater similarity among tropomyosins than among parvalbumins [28].

Parvalbumins have been identified as cross-reacting allergens in several fish species and are clinically relevant in fish-allergic individuals. Most recently, the in vitro cross-reactivity between parvalbumin in fish and frog was shown to be clinically relevant. An individual experienced severe IgE-mediated anaphylaxis following consumption of fried frog legs. Inhibition studies revealed that the frog-allergic

patient was primarily sensitized to parvalbumin identified in fish and frog [35,36].

Tropomyosin is the major allergen responsible for cross-reactions in shrimp, crab (Cha f 1) [37], lobster (Pan s I or Hom a I) [38], insects such as cockroach (Per a 7) [39], arachnids such as house dust mites (Der p 10/Der f 10) [40], and mollusks such as squid (Tod p 1) [41], oyster [42], snail [43], mussels, clams, and scallops [44]. This cross-reactivity has been described clinically as well as in vitro. In one study, Daul *et al.* [45] found that more than 80% of individuals with shrimp allergy had positive skin prick test responses to crab, crawfish, and lobster. They also noted that individuals with immediate reactions to shrimp ingestion had reaction rates to lobster, crab, and crawfish between 50% to 100% per species [46].

Ayuso *et al.* [47] identified eight major Pen a 1 (major shrimp allergen) IgE antibody binding epitopes. Sera from shrimp-allergic individuals recognized 6 of 8 Pen a 1 homologous peptides in Per a 7 (cockroach), 7 of 8 in Der p 10/Der f 10 (dust mite), and 7 of 8 in Hom a 1 (lobster). Although these cross-reactivities can theoretically create the potential for severe reactions, they also may complicate diagnosis and treatment of food allergies. For example, in an interesting study by Fernandes *et al.* [48••], a population of shrimp-naïve Orthodox Jews with perennial allergic rhinitis and dust mite/cockroach hypersensitivity were found to be prick skin test positive to shrimp. The clinical relevance of this finding is not clear, because this population of patients obeys strict kosher dietary laws prohibiting the ingestion of shellfish. True clinical cross-reactivity is suggested by the work of Azofra and Lombardero [49•], which reported house dust mite–sensitized individuals with asthma showed prick skin test positivity to limpet, a mollusk. All individuals experienced respiratory symptoms with limpet ingestion. Although the clinical relevance of these cross-reacting allergens is not completely clear, it appears that the potential for severe hypersensitivity reactions exists. See Table 2 for potential cross-reacting allergens.

Diagnosis and Management

Diagnosis

The medical history continues to be the mainstay of the diagnostic process. The history relies on the patient's recollection of events surrounding the development of symptoms. Unfortunately, this assumes the patient was able to identify the offending food, which is not always easy with complex foods with multiple and sometimes “hidden” allergenic ingredients.

Prick skin testing with the food in question provides a rapid, relatively safe and inexpensive method for screening patients with a history suggestive of IgE-mediated fish and/or shellfish hypersensitivity. It is extremely important that caution be exercised in interpreting skin test results when the history is poor, because potential cross-reacting allergens may result in positive skin tests with unclear clinical

Table 2. Potential cross-reacting allergens

Origin	Allergen name	Molecular weight (kD)
<i>Gadus callarias</i>	Parvalbumins	
Baltic cod	Gad c 1	12.3
<i>Gadus morhua</i>	Gad m 1	11.5
Atlantic cod		
<i>Salmo salar</i>	Sal s 1	14.1
Atlantic salmon		
<i>Rana esculenta</i>	Ran e 1	11.9
Edible frog	Ran e 2	11.7
	Tropomyosins	
<i>Metapenaeus ensis</i>	Met e 1	32.8
Greasyback shrimp		
<i>Penaeus aztecus</i>	Pen a 1	36
Brown shrimp		
<i>Penaeus monodon</i>	Pen m 1	38
Black tiger shrimp	Pen m 2 (arginine kinase)	40
<i>Penaeus indicus</i>	Pen i 1	34
Shrimp		
<i>Charybdis feriatus</i>	Cha f 1	34
Crab		
<i>Homarus americanus</i>	Hom a 1	33
Lobster		
<i>Panulirus stimpsoni</i>	Pan s 1	34
Lobster		
<i>Todarodes pacificus</i>	Tod p 1	38
Squid		
<i>Helix aspera</i>	Hel as 1	36
Snail		
<i>Haliotis midae</i>	Hal m 1	49
Abalone		
<i>Blomia tropicalis</i>	Blo t 10	33
Mite		
<i>Dermatophagoides farinae</i>	Der f 10	33
American house dust mite		
<i>Dermatophagoides pteronyssinus</i>	Der p 10	36
European house dust mite		
<i>Periplaneta americana</i>	Per a 7	37
American cockroach		
<i>Lepisma saccharina</i>	Lep s 1	36
Silverfish		

relevance [48••]. In the future, recombinant parvalbumins and tropomyosins may become useful tools in the diagnosis of fish and shellfish allergy [27••]. On a submolecular level, the use of selected epitopes may yield more precise in vitro testing for predicting seafood allergy.

Radioallergosorbent testing (RAST) has generally been considered a less sensitive and more expensive method for the diagnosis of food allergy compared with the skin prick test. However, improved methods, such as the Pharmacia CAP-RAST FEIA (Pharmacia-Biotech, Freiburg, Germany) are being developed. In a study by Sampson and Ho [11], the performance characteristics of the Pharmacia CAP System FEIA for fish allergy were good. Diagnostic IgE levels were identified at 20 kU(A)/L for fish allergy. This level is predictive of clinical reactivity with more than 95% certainty. Importantly, the CAP-RAST FEIA can determine the risk for a systemic reaction without the need for a confir-

matory double-blind, placebo-controlled food challenge (DBPCFC) for several important foods. Although the diagnostic levels of IgE for predicting crustacean allergy have yet to be determined, the Pharmacia CAP-RAST FEIA is a safe and predictive test when considered in combination with the clinical history for the diagnosis of food allergy. The Pharmacia CAP-RAST FEIA also eliminates the potential risk for a systemic reaction, which might result from the DBPCFC, or, rarely, may occur in the exquisitely sensitive patient during prick skin testing.

Management

The only proven therapy for fish and shellfish hypersensitivity is strict avoidance. Unfortunately, strict avoidance is not always possible. As a result, new approaches to the treatment of food allergy are being investigated and developed. Immunotherapy for food allergy was first described

by Freeman in 1930 [50]. Freeman reported the first successful case of rush immunotherapy for a patient with fish allergy and poorly controlled asthma. More recently, Casimir *et al.* [51] desensitized a young girl with a standard rush immunotherapy protocol with codfish. After the rush therapy, the child was submitted to uncooked codfish odors without any reaction. Even with an accidental ingestion of codfish, no reaction was observed.

Although a few cases of successful rush immunotherapy with foods have been described, this form of therapy is very risky compared with other forms of immunotherapy and should be considered experimental [52,53]. Caution must also be observed in patients receiving inhalant immunotherapy, because the risk for developing hypersensitivity to certain cross-reacting food allergens may be increased. van Ree *et al.* [54] demonstrated that house dust mite immunotherapy is accompanied by the induction of IgE against foods, including tropomyosin-reactive IgE. In that report, food allergy was observed in patients who had IgE antibodies against this cross-reactive allergen that were manifested by oral allergy symptoms. Induction of IgE during mite immunotherapy might occasionally cause allergy to foods of invertebrate animal origin.

Many alternative approaches, including food-allergen plasmid DNA vaccines, mutated less allergenic recombinant food proteins, and anti-IgE with or without conventional immunotherapy are under study. These novel approaches to fish and shellfish allergy offer the potential of safely desensitizing patients with less risk for systemic reaction.

Conclusions

Fish and shellfish are extremely important in the American diet and economy, but they continue to be leading causes of food hypersensitivity. As our understanding of the mechanisms involved and the identification of seafood allergens and potential cross-reacting allergens advance, our approach to diagnosis and management of this difficult problem will continue to improve. Although a vast amount of knowledge has been gained during the past decade, continued research in this area is essential for the development of safer and more effective methods of diagnosis and management of fish and shellfish hypersensitivity.

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