A practical focus on fish and shellfish oral immunotherapy

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ABSTRACT

Although fish and shellfish allergies represent common worldwide allergies, with anaphylaxis being reportedly frequent, treatment approaches, e.g., oral immunotherapy (OIT), are uncommonly performed. A review of the limited literature is discussed here. Both practical and immunologic challenges are common with seafood OIT, including taste, odor, unclear and potentially inconsistent cross-reactivity, and alteration of protein concentration during the cooking process as well as other concerns. Ongoing attempts at standardization of this OIT process should be considered. The experienced OIT physician may consider this treatment in patients who are motivated to begin OIT.

(J Food Allergy 4:148–150, 2022; doi: 10.2500/jfa.2022.4.220016)

The prevalences of finned fish and shellfish allergies have been reported to be 1% and 3%, respectively, with variability reported for different ages, ethnicities, and geographic regions.[1–3] Although finned fish allergy may be common in both pediatric and adult patients, shellfish allergy is typically more common among adults and may develop after years of eating these foods. Although fish and shellfish are normally easy to avoid due to stringent labeling and lack of widespread use compared with other allergens (*e.g.*, nuts, peanut, milk, or egg), reactions due to ingestion are not uncommon. Furthermore, fish allergens can be aerosolized *via* steam during cooking and can trigger severe allergic reactions if inhaled.[4] When ingested, these allergens can cause severe reactions, with shellfish being one of the most frequent triggers of anaphylaxis in adult populations worldwide.[3]

Fish and shellfish allergies tend to be lifelong conditions, particularly if they are identified in childhood.[2] When considering the risk of severe reactions with accidental exposures and the nutritional benefits of including fish in the diet, alternative therapies, such as hypoallergens, subcutaneous immunotherapy with recombinant allergens, or food immunotherapy, may represent a valid option in selected patients.[5–7] Unfortunately, limited data have been published with regard to finned fish or shellfish oral immunotherapy (OIT). Early approaches used boiled cod in a suspension to desensitize patients.[7,8] More recent publications used a lyophilized white fish, hake in a suspension initially, followed by ingestion of actual fish for maintenance.[9,10] Similarly, for shellfish, limited data have been reported, with one paper identifying only three patients, all of whom used omalizumab as an adjunctive therapy as part of a multifood OIT treatment.[11] Currently, to our knowledge, there are no published studies that outline detailed methods or results for shellfish desensitization without an adjuvant.

SPECIFIC CHALLENGES AND CONSIDERATIONS

There are several significant challenges for desensitizing either finned fish and shellfish. The first concern is immunologic cross-reactivity. For example, if a patient has shrimp, crab, and lobster allergy, does OIT for shrimp lead to similar desensitization for the other crustaceans? Does this then extend to mollusks? Many thousands of fish, crustaceans, and mollusks have been identified, and the determination of allergic cross-reactivity may be inconsistent. In fish allergy, parvalbumin is the major allergen and the basis of different degrees of cross-reactivity, depending on its concentration in the different species, with a high concentration in cod and hake, and lower concentrations in other species, *e.g.*, swordfish or tuna.[12] However, other allergenic proteins, *e.g.*, enolase aldolase and triosephosphate isomerase, may be responsible for reactions that compromise the degree of desensitization to other species.[13] The allergenic profile of shrimp

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D.P. Mack has provided consultation and speaker services for Aimmune. P.R. del Rio has provided speaker services for Aimmune. M. Woch has no conflict of interest to disclose pertaining to this article

No external funding sources reported

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*This manuscript is part of the **Journal of Food Allergy** collection of published works referred to as the "Oral Immunotherapy Manual." The contents of this work reflects the opinion(s) of the author(s) and is not intended to replace published guidelines or the clinician's medical advice in the doctor-patient relationship*

is more complex, with four main proteins that cause allergy (*i.e.,* tropomyosin, arginine kinase, myosin light chain, and sarcoplasmic protein) and these being differentially represented in other shellfish.[14]

In two publications, the investigators suggest that treatment with one type of fish can lead to potential cross-protection for other fish species due to desensitization to parvalbumin but, given the differing allergenic proteins among fish species, this may not be generalizable.[9,15] In one report, a single patient, with oral food challenge–confirmed allergy to both cod and salmon, who was treated with cod was also desensitized to salmon, and both allergies were confirmed before treatment.[15] However, in the other report, baseline oral challenges were not consistently performed on the other species to determine true allergy, therefore, firm conclusions could not be made.[9] There are no reported similar data for crustaceans or mollusks. Importantly, there have been numerous reports of improper identification of fish in supermarkets.[16] If there is limited cross-protection, then a change in species may be a significant risk factor for a reaction. Further studies are needed to identify the degree of cross-protection, although the degree of cross-protection is dependent on the patient's sensitization, *e.g.,* tropomyosin versus arginine kinase.

Practically, the second reported barrier is potential aversion and distaste. Although distaste and aversion are commonly reported for many foods during OIT, these foods may be particularly challenging for many patients because masking fish or shellfish is especially difficult because of the odors.[17] The masking of flavor has been described by using orange juice, yogurt, and vegetable puree. Mixing the fish with condiments, *e.g.,* ketchup, may also be an option. The final major issue is portability. If using fresh fish or shellfish, participants will always require a ready supply that has been handled properly to avoid poisoning. Similarly, this places an additional burden on families when traveling to ensure that the product is shelf stable. Options to address this problem can include dried fish and/or shellfish, flours, powders, and even jerky; however, detailed reports that demonstrate the effectiveness of these products have been limited.[11]

DOSE PREPARATION

Whereas, at higher doses, fish can be weighed with a common kitchen scale, at low doses, a few approaches have been used, including dried cod extract, lyophilized hake extract, baked cod, and boiled cod solutions. One group used a dosing protocol with readily available cod. To prepare a boiled cod solution, boiled cod was whisked in water and then serial dilutions were necessary to obtain the ultralow doses. Serial dilutions can lead to significant variability in protein concentration if not performed with precision. However, others authors have described higher starting doses, and some analytical balances may be sufficient to weigh doses similar to the U.S. Food and Drug Administration-approved peanut product.

Table 1 **Published protocol of lyophilized hake (a white fish) oral immunotherapy***

	Dose, mg of lyophilized extract of hake	Dose, mg of protein
Day 1 in the hospital	0.006	0.003
Doses hourly	0.012	0.006
	0.027	0.0135
	0.054	0.27
	0.111	0.0555
Day 2 in the hospital	0.111	0.0555
Doses hourly	0.225	0.1125
	0.45	0.225
	0.9	0.45
	1.8	0.9
Dose maintained at home	3	1.5
With escalation once a week in the hospital	4.5	2.25

**Adapted from Ref. 10.*

Finned fish and shellfish protein concentrations can differ significantly among species; therefore, consistent use of a similar product or species may be most important during the buildup phase. Some commercially available extracts (*e.g.,*. Stallergenes-Greer, Lenoir, NC, USA) may use different species in varying concentrations. Similarly, the shell on shrimp and crustaceans should be taken into consideration and the protein concentrations should be determined for shelled crustaceans. One of the challenges with cooking fish and shellfish products is that the weight of the fish or shellfish may be dependent on the amount of water in the product. Handling, freezing, thawing, and cooking these products can alter the amount of water, which therefore affects the actual total protein concentration of the fish. Furthermore, although major fish and shellfish allergens are heat resistant, some other proteins are labile to this process (*e.g.,* enolases and aldolases in fish or arginine kinase in shrimp); therefore, seafood OIT should always be carried out by using the same processing.[18]

As such, the use of lyophilized products could be a good solution in terms of safety, precise protein amount, and reproducibility; however, producing the extract is not easy and requires having the support from a dedicated team to produce the product.[9,10] Another protocol, which uses lyophilized hake, is reported in Table 1.

Dried fish and shellfish may represent a more reasonable long-term option and can be found online. These products can be ground into a shelf-stable powder. Fish jerky may also be an option for salmon and other fish. Care must be taken to ensure proper refrigeration and storage of cooked fish and shellfish, and should be ingested within 3 days to prevent spoilage and toxin production in fish.[19] Cooked fish and dried powders can also be stored in a suitable freezer for long-term use.

Published Dosing Schedules

The protocol in Table 1 has been reported with lyophilized hake (a white fish).[10]

CONCLUSION

Unfortunately, the level of evidence for fish or shellfish OIT is not nearly as robust as for other foods. Although some practitioners may attempt this approach because of the inherent difficulties with standardization, which may represent a high risk for allergic reactions, especially in the home setting, we recommend that this type of OIT be considered only in select patients and for experienced OIT providers.

CLINICAL PEARLS

- Fish and shellfish OIT is uncommonly performed, with numerous barriers documented.
  - Taste and odors
  - Inherent aversion
  - Shelf-stable products
  - Unclear species cross-desensitization
- Fish and shellfish OIT may be considered in the patient who is highly motivated and with experienced OIT providers.
- A lyophilized fish product may be a reasonable option for desensitization.
- Further research is recommended to safely offer this therapeutic approach to more patients.

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