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Seafood graded oral food challenge outcomes in a pediatric tertiary care center

Zachary E. Rubin^{a*}, Hongjie Gu^b and Brooke I. Polk^a

ABSTRACT

Background: There are sparse data regarding the predictors of positive oral food challenges and reaction severity for seafood in children.

Objective: Identify clinical characteristics in children with seafood allergy who were most likely to experience a negative oral food challenge (OFC).

Methods: A retrospective chart review was performed for children who had a graded OFC to seafood at a pediatric tertiary care center from 2008 through 2019.

Results: Sixty-three (60% male; average age 8 years; range 1–21 years) OFCs were performed, of which 21 were fish and 42 were shellfish. There were 10 (16%) positive OFCs and positive OFC rate was similar between fish (19%) and shellfish (14%). Forty-three children who underwent OFC had a reported history of IgE-mediated symptoms. Five of six children who had a history of anaphylaxis had a negative OFC. There was no difference in positive OFCs due to age, history of atopy, or initial allergic reaction history. The clinical characteristics of the positive OFCs were similar between fish and shellfish. A positive skin prick test to fish or shellfish did not increase the risk of a positive OFC. While the positive OFC rate did not differ for the shellfish food-specific IgE (FslgE) level, there was a significant difference for fish (median <0.34 kU_A/L vs. 1.63 kU_A/L for pass and fail, respectively; $P = 0.023$).

Conclusion: A retrospective study of OFCs to seafood showed that the rate of a positive OFC was low. While seafood allergy is thought to be rarely outgrown, children who have a low FslgE and/or skin testing can successfully tolerate seafood.

Keywords: Food allergy, Seafood, Fish, Shellfish, Oral food challenge, Outcomes, Anaphylaxis, Sensitization

INTRODUCTION

Though the true prevalence of seafood allergy is not known, a systematic review estimated the worldwide prevalence of fish and shellfish allergy at 0.3 and 0.5%, respectively.¹ In the United States,

fish allergy is thought to affect 2.7% of adults and 0.2% of children, and shellfish allergy prevalence is reported at 9% for adults and 2% for children.¹ The incidence of seafood allergy is increasing, which may be due to the growing consumption of seafood worldwide. The 2018 Food and

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<http://doi.org/10.1016/j.waojou.2020.100121>

Received 18 December 2019; Received in revised form 6 March 2020; Accepted 31 March 2020

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Agriculture Organization of the United Nations report showed that global fish consumption per capita has risen from 9.0 kg in 1961 to 20.5 kg in 2017.² Despite being among the most common foods to provoke anaphylaxis,³ seafood is not as well-studied as other food allergens. The natural history of seafood allergy is not well understood, although it is believed that most seafood allergies are persistent.⁴ A small study performed in Canada reported a resolution rate of 0.6% per person-year for fish and 0.8% per person-year for shellfish.⁵

Food allergy is typically diagnosed by taking a detailed history and obtaining skin prick testing (SPT) and serum food-specific IgE (FSIgE) levels. Oral food challenges (OFCs) are the gold standard procedure to determine the diagnosis and resolution of a food allergy, but they are time-consuming, resource-intensive, and place the patient at risk for a severe allergic reaction.⁶ FSIgE levels have been used as decision points to predict negative OFCs.⁷⁻¹⁰ In most situations, pediatric patients are considered appropriate OFC candidates if the likelihood of a negative OFC is less than 50%, especially to determine the resolution of a known food allergy.¹¹ While Perry et al. reported that a FSIgE of ≤ 2 kU_A/L (or ≤ 5 kU_A/L for peanuts without a history of a reaction) are associated with a $\leq 50\%$ likelihood of reacting to eggs, milk or peanut during an OFC,¹² these values have not been established for fish or shellfish.

There have been recent efforts to incorporate additional clinical and laboratory data along with FSIgE levels to more effectively evaluate food allergy.^{7,13-15} This approach may help more accurately identify those patients who would benefit from an OFC in order to confirm resolution of their food allergy. However, seafood has been mostly overlooked in these studies. Our purpose was to identify clinical characteristics in children with fish or shellfish allergy who were most likely to experience a negative OFC.

METHODS

Study population

The study population included patients aged 21 years or younger who underwent graded OFC to fish or shellfish in a midwestern United States

pediatric tertiary care hospital from January 2008 to July 2019. OFCs were performed to evaluate whether a patient had become tolerant to a food that was previously documented as a food allergy or to determine the significance of a positive FSIgE without clinical history of a reaction to a food (reported as "sensitization"). Patient selection for OFC was based upon the allergists' clinical opinion and family interest in the challenge. Although no specific SPT or FSIgE cutoffs were used as inclusion criteria for an OFC, the general practice was to select patients with low or undetectable FSIgE levels, likely due to the conventional belief that fish and shellfish allergies are persistent.

Oral challenges

OFCs were supervised by allergists and nursing staff and scheduled within one year from the collection of FSIgE levels. From January 2008 to March 2019, the OFC protocol was adopted from Bock et al.¹⁶ These challenges were administered in 11 escalating doses every 15 min for a cumulative dose of 16.4 g food, with final dose of 8 g food (~1600 mg protein for fish and 1900 mg protein for shellfish). Protein content totaled 3-4 g for fish and shellfish. Our OFC protocol was streamlined in March 2019, to align more closely with PRACTALL guidelines, resulting in a 7-dose protocol (cumulative dose 28 g (1 oz portion), final dose 18.9 g which equates to 6-7 g protein for fish and 5-7 g for shellfish).⁶ This protocol was implemented in 6 patients.

Challenge outcomes were classified as positive, negative or equivocal based on the clinician's judgement. If the patient displayed objective symptoms of an IgE-mediated reaction (e.g. urticaria, vomiting, wheezing, anaphylaxis), the challenge was classified as a positive OFC. If the patient refused to complete the OFC, then the result was classified as equivocal. Clinical reactions were divided into the following categories: urticaria, angioedema, gastrointestinal symptoms, and anaphylaxis. Positive OFCs were treated based on the severity of the reaction and were recorded in the chart.

Data collection and statistical analyses

A retrospective cross-sectional analysis of relevant clinical data was performed. De-identified

Male, n (%)	38 (60.32%)
Female, n (%)	25 (39.68%)
Average age (years)	8.08 ± 4.69
Caucasian, n (%)	35 (55.56%)
African American, n (%)	17 (26.98%)
Hispanic, n (%)	3 (4.76%)
Asian, n (%)	1 (1.59%)
Other ethnicity, n (%)	7 (11.11%)
Fish allergy, n (%)	21 (33.33%)
Shellfish allergy, n (%)	42 (66.67%)
Allergic rhinitis, n (%)	40 (63.49%)
Asthma, n (%)	34 (53.97%)
Atopic dermatitis, n (%)	20 (31.75%)
Multiple food allergies ^o , n (%)	31 (49.21%)

Table 1. Patient demographics (N = 63). ^oDefined as food allergy to one or more different types of foods other than fish or shellfish

demographics, clinical history, laboratory results, and challenge outcome were recorded in a database. Follow-up telephone surveys were conducted to determine whether children continued to consume foods that resulted in a negative OFC after the OFC was completed. This study was Institutional Review Board exempt as analysis of de-identified data constitutes non-human subject research.

SPT (Stallergenes Greer, Cambridge, MA) and FSIGe (ImmunoCAP®, Phadia, Uppsala, Sweden) levels were recorded from the closest date before OFC. As wheal diameter was not available for some patients referred from external allergists, SPT results were recorded as either positive or negative. Positive SPT results were defined as a mean wheal diameter greater than or equal to 3 mm above that achieved with the saline control or if SPT was reported as positive from a referring allergist. Laboratory-reported FSIGes of <0.34 kU_A/L and <0.10 kU_A/L were recorded as 0.34 and 0.10, respectively.

Quantitative variables were presented as mean ± standard deviation or median with first and third quartiles, whereas qualitative variables were presented as n (%). Pearson's Chi-square test

and Fisher's exact test were used to detect the association between categorical variables. ANOVA test or Kruskal-Wallis test were used to compare distributions of continuous variables among three groups. Logistic regression analyses were performed to assess potential predictors for failures in oral food challenges. All data analyses were performed by SAS® (SAS Institute Inc., Cary, NC, USA) 9.4 version. A p value < 0.05 was considered significant.

RESULTS

Study population characteristics

Sixty-three OFCs were performed, of which 21 were fish (4 cod, 7 salmon, 4 tilapia, 4 tuna, 1 catfish, 1 flounder) and 42 were shellfish (36 shrimp, 2 scallop, 1 lobster, 3 crab). Patients' characteristics are listed in Table 1. Most patients were male (60%) and Caucasian (56%) with a mean age of 8 years at the time of the OFC. Most patients had allergic rhinitis (63%) and asthma (54%), but fewer patients had atopic dermatitis (32%). Roughly one half of patients had multiple food allergies documented.

Predictors of oral food challenge outcomes

Of the 63 OFCs, 49 (78%) did not experience a clinical reaction and were negative, whereas 10 (16%) had a clinical reaction and 4 (6%) refused to complete the challenge. Among the 10 positive OFCs, 4 were fish (1 salmon, 2 tilapia, 1 tuna) and 6 were shellfish (5 shrimp, 1 lobster). The comparisons of patients' clinical characteristics between those who experienced a positive OFC and those who experienced a negative OFC and those who were equivocal are listed in Table 2. Based on the initial clinical reaction, most patients experienced a negative OFC if their presenting history was urticaria (18/49). Of the 20 patients who had an

OFC based on sensitization, 15 passed. Five (4 shrimp, 1 salmon) of six patients with a history of anaphylaxis experienced a negative OFC. There was no statistically significant difference between these groups based on age, sex, co-morbid allergic disease or initial presenting reaction to the food. Table 3 lists the clinical characteristics between positive fish and shellfish OFCs. The rate of positive OFCs between fish and shellfish and the type of clinical reaction during OFC were similar. There were two cases of anaphylaxis in the fish group (1 tilapia, 1 salmon) and two cases in the shellfish group (2 shrimp) that required treatment with epinephrine. One case of

	Negative (N = 49)	Positive (N = 10)	Equivocal (N = 4)	Total (N = 63)	p-value
Average Age (years)	8.20 ± 4.90	8.50 ± 4.33	5.50 ± 2.38	8.08 ± 4.69	0.5238
Male (%)	28/49 (57.14%)	6/10 (60%)	4/4 (100%)	38/63 (60.32%)	0.3001
Female (%)	21/49 (42.86%)	4/10 (40%)	0/4 (0%)	25/63 (39.68%)	
Overall atopy (%)	40/49 (81.63%)	10/10 (100%)	4/4 (100%)	54/63 (85.71%)	0.3946
Asthma (%)	26/49 (53.06%)	6/10 (60%)	2/4 (50%)	34/63 (53.97%)	0.9011
Allergic rhinitis (%)	30/49 (61.22%)	6/10 (60%)	4/4 (100%)	40/63 (63.49%)	0.3930
Atopic dermatitis (%)	13/49 (26.53%)	5/10 (50%)	2/4 (50%)	20/63 (31.75%)	0.2486
Multiple food allergies (%)	22/49 (44.90%)	5/10 (50%)	4/4 (100%)	31/63 (49.21%)	0.1397
Initial reaction	Negative (N = 49)	Positive (N = 14)	Equivocal (N = 4)	Total (N = 63)	p-value
Urticaria	18/49 (36.73%)	6/10 (60%)	1/4 (25%)	25/63 (39.68%)	0.4532
Angioedema	9/49 (18.37%)	2/10 (20%)	0/4 (0%)	11/63 (17.46%)	>0.9999
Sensitization	15/49 (30.61%)	2/10 (20%)	3/4 (75%)	20/63 (31.75%)	0.1368
Gastrointestinal	4/49 (8.16%)	1/10 (10%)	0/4 (0%)	5/63 (7.94%)	>0.9999
Anaphylaxis	5/49 (10.20%)	1/10 (10%)	0/4 (0%)	6/63 (9.52%)	>0.9999

Table 2. Patient demographics based on OFC results

	Fish (N = 21)	Shellfish (N = 42)	Total (N = 63)	p-value
Positive challenge (% per food)	4/21 (19.05%)	6/42 (14.29%)	10/63 (15.87%)	0.8870
Negative challenge (% per food)	16/21 (76.19%)	33/42 (78.57%)	49/63 (77.78%)	
Equivocal (% per food)	1/16 (4.76%)	3/42 (7.14%)	4/63 (6.35%)	
Reaction	Fish (N = 4)	Shellfish (N = 6)	Total (N = 10)	p-value
Anaphylaxis	2/4 (50%)	2/6 (33.33%)	4/10 (40%)	>0.9999
Urticaria	2/4 (50%)	3/6 (50%)	5/10 (50%)	>0.9999
Angioedema	0/4 (0%)	1/6 (16.67%)	1/10 (10%)	>0.9999
Gastrointestinal symptoms	0/4 (0%)	1/6 (16.67%)	1/10 (10%)	>0.9999

Table 3. Positive OFC characteristics

anaphylaxis to shrimp required two doses of epinephrine and subsequent transfer to the emergency room, but there were no hospitalizations.

SPT data were available for 43 patients and FSIgE levels were available for all 63 patients included in the study. SPT results were not significantly different among positive, negative and equivocal OFCs (Table 4). A significant difference was detected among median FSIgE levels for negative (<0.34 kU_A/L) and equivocal (<0.34 kU_A/L) OFCs versus positive (1.63 kU_A/L) OFCs for fish ($p = 0.023$) but not for shellfish ($p = 0.2724$). Mean FSIgE levels of fish were higher among positive fish OFCs compared to negative OFCs. A logistic regression model shows that a cutoff level of 1.99 kU_A/L was associated with an 85% negative challenge rate (17/20 = 85%), and the negative predictive value (NPV) was 82.35%.

Of the 49 negative OFCs, no patient returned with symptoms of food allergy related to the challenge food. Forty-one families were contacted by telephone successfully. Thirty-six of these children (88%) did not have reactions to the seafood that was previously tested; all but 5 of these children consumed their challenge food regularly. Five children (12%) do not consume the seafood that resulted in a negative OFC. Of these, 1 child reported experiencing tongue itching after consuming cod within one week after the OFC while another child reported experiencing a perioral and hand rash upon contact with shrimp. Three children completely refused to consume the questioned seafood even though the OFC was completed successfully.

DISCUSSION

Limited research has been devoted to the prevalence and natural history of seafood allergy.

	Negative	Positive	Equivocal	p-value
Skin test to fish (% positive)	5/11 (45.45%)	1/1 (100%)	-	>0.9999
Skin test to shellfish (% positive)	11/24 (45.83%)	3/5 (60%)	2/2 (100%)	0.5640
Skin test to fish (wheal size)	0 (0-2.5)	15	-	0.0764
Skin test to shellfish (wheal size)	0 (0-3)	0 (0-5)	4.5 (4-5)	0.1695
Fish-specific IgE (kU/L)	0.34 (0.34-0.64)	1.63 (1.31-7.55)	0.34	0.0233
Shellfish-specific IgE (kU/L)	0.34 (0.34-0.34)	0.34 (0.34-0.34)	0.34 (0.1-0.34)	0.2724

Table 4. SPT and FSIgE results for negative versus positive OFCs

We intended to identify clinical characteristics in children with seafood allergy who were most likely to experience a negative OFC. This study is unique because of its focus on clinical characteristics of children who were most likely to experience a negative seafood OFC. Seafood is an important cause of anaphylaxis, and an estimated 6% of children in the United States consume seafood at least two times per week.¹⁷ Previous retrospective reviews mainly focused on milk, egg, peanut, and tree nuts.¹⁸⁻²⁰

In our retrospective cohort, 78% of children with a suspected seafood allergy experienced a negative OFC. This high rate goes against the conventional wisdom that seafood allergy rarely resolves.⁴ A cohort study of self-reported resolution of fish and shellfish allergy suggested resolution of fish allergy in only 1 of 38 subjects (2.6%) and shellfish allergy resolution in 1 of 26 subjects (3.9%).⁵ Turner et al. reported that seafood allergy resolved in 4% of their pediatric cohort.²¹ A recent prospective analysis of seventeen Thai adults, however, found that almost half of shrimp-allergic subjects passed repeat OFC after ten years of avoidance.²² History of anaphylaxis was an exclusion criteria in this study. Notably, five out of six patients in our cohort with a history of anaphylaxis after ingestion of seafood had a negative OFC, and this high rate of resolution has not been reported in the literature previously. This indicates that anaphylaxis should not be a contraindication to future fish or shellfish OFC.

To the authors' knowledge, this is the first cohort study to definitively document negative OFCs to clinically diagnosed fish or shellfish allergy in childhood. Most of our cohort (43 of 63 OFCs) had a known prior diagnosis of fish or shellfish allergy, and 34 of these 43 patients passed his/her OFC. Though our pass rate aligns with a large cohort of open OFCs by Lieberman et al., in which 88% of fish and 89% of shrimp challenges passed, that study did not include baseline characteristics, clinical history, or SPT/FSIgE values for fish or shellfish, so it is not possible to discern what proportion of patients had a known allergy or whether that allergy was outgrown.²³ Additionally, while another retrospective cohort by Abrams et al. included 10 fish OFCs and 14 shellfish OFCs,

baseline data or outcomes specific to fish or shellfish were not reported.¹⁹

Our cohort had a high rate of atopy, but atopy did not increase the risk of a positive challenge. This finding differs from previous studies,^{12,19} which may be due to OFCs only being offered to patients with low FSIgE levels. Age was not a significant risk factor for a positive OFC. Previous studies investigating other foods have reported that age was not a significant risk factor as well.^{7,20,23} Therefore, age may not need to be considered as a selection criterion for administering an OFC.

The overall rate of anaphylaxis during OFC in this study was 6% (4 of 63 OFCs), with a rate of 10% (2 of 21) for fish and 6% (2 of 42) for shellfish. Anaphylaxis during OFC to fish or shellfish was not reported in the Lieberman et al. pediatric study, though 11% of OFCs in the Thai adult study resulted in anaphylaxis.^{22,23} Risk factors for anaphylaxis could not be determined because only 4 patients received epinephrine in our study. There were no hospitalizations in our study, consistent with previous retrospective studies.^{19,24} Similar to other studies, there was no detectable association between initial reaction at presentation and OFC outcome.

A significant difference for fish FSIgE was detected between negative OFCs and positive OFCs, which was not detected for shellfish. Based on the results of univariate logistic regression for positive fish and shellfish OFCs, we were unable to determine the 50% NPV cutoff points for FSIgE levels. Sampson et al. reported the >95% positive predictive value for fish was 20 kU_A/L.¹⁰ However, to our knowledge the 50% NPV has not been determined for fish or shellfish in previous studies. We would have more likely been able to determine these values if we performed more OFC with higher FSIgE levels. This may explain why logistic regression analysis for shellfish OFC showed that the probability of a positive OFC decreased with increasing FSIgE levels.

There were limitations to our study, including its retrospective design and midwestern U.S. pediatric population. However, previous studies investigating OFC outcomes use retrospective data collection.^{7,10,14,18-20} Selection bias occurred because patients who were selected for OFC had

low FSIGe levels. The challenges were open and not double-blind placebo-controlled (DBPC) challenges, which are the gold standard, so there is a higher chance for a falsely negative OFC. However, DBPC challenges are time-consuming and expensive, and open OFCs are considered an adequate alternative in the office setting.^{6,7,23} No patient returned with symptoms of food allergy related to the food challenged, but 2 individuals in our telephone follow-up of 41 negative OFCs reported reactions to the food challenged in our clinic within one week after the challenge was completed, so 4.9% of those OFCs were falsely negative. We adopted newer OFC protocols through the PRACTALL guidelines to help reduce the false-negative rate, and none of the 6 OFCs performed with this newer protocol resulted in a false-negative OFC. Eight individuals (19.5%) either completely refused to consume the food previously tested or consume the food less than once per week. Previous studies have reported that between 20 and 30% of previously allergic patients continue a food avoidance diet despite a negative challenge.^{25,26} Post-challenge guidance is essential to address food avoidance barriers and follow-up after OFCs needs to be strengthened to improve expanding children's diets.

While the inclusion of patients with sensitization and no documented history of fish or shellfish allergy may be considered a limitation, this is a realistic patient for the practicing allergist who sees growing numbers of patients with laboratory findings of sensitization ordered by outside providers. Although 20 OFCs were performed in patients with sensitization as the presenting history, sensitization only explains 31% (15/49) of the negative OFCs, and one quarter of patients presenting with sensitization were proven allergic by OFC. We were unable to determine any significant difference in challenge outcomes based on SPT even when we removed patients who did not have SPT performed at our clinic. There were 4 equivocal OFCs because these patients refused to complete the challenge. It is unknown whether these children truly would have had a clinical reaction, so their food allergy could not be resolved. Therefore, we analyzed these equivocal OFCs separately to prevent the positive challenge rate from being falsely elevated. Because of the small sample size, we were unable to perform subgroup

analysis of the types of fish and shellfish. In the future, more OFCs will need to be included in the analysis to increase the power since most of the challenges were negative.

Overall, OFC failures occurred in only 16% of our patients to seafood and clinical characteristics were similar between children who had positive, negative and equivocal OFCs. Those with history of anaphylaxis to fish or shellfish did not have a higher failure rate. Fish challenges were more likely to be negative if FSIGe level was <2 kU_A/L. Since most reactions were mild and only 6% of challenges resulted in anaphylaxis, offering OFCs to seafood is most likely safe in patients with low to undetectable FSIGe levels. Therefore, providers may be more willing to offer seafood OFCs to children. Few children were offered seafood OFCs in our clinical practice over the previous 11 years, so administering more OFCs will help guide the decision to perform an OFC for children with seafood allergy.

Abbreviations

SPT: Skin prick testing; FSIGe: food-specific IgE; OFC: oral food challenge

Funding

None.

Consent for publication

All authors consent to publication of this work.

Potential competing interests

The authors report no competing interests.

Ethics statement

This study was Institutional Review Board exempt as analysis of de-identified data constitutes non-human subject research. Anonymous follow-up telephone surveys were conducted - with verbal consent from at least one of the patients' parents - to determine whether children continued to consume foods that resulted in a negative OFC after the OFC was completed.

Acknowledgements

None.

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