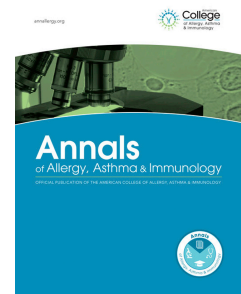


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Reintroduction of foods after a negative oral food challenge – a two year follow up

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Oral food challenges (OFCs) are the gold standard in the diagnosis of food-related allergic symptoms and can help determine if a food can be safely reintroduced into the diet.¹⁻³ Following a negative OFC, patients are recommended to regularly consume the food.^{1,4} While data are limited, there are multiple published cases of recurrence of peanut allergy after a negative OFC when there is infrequent consumption.^{1,4,5} In 2015 van der Valk et al. found that among a group of Dutch patients, successful reintroduction was as low as 56% due to a number of patients having reactions to the food even after a negative OFC.⁶ In contrast, a 2019 study by Weinberger et al. found that 85% successfully reintroduced peanuts in the diet.⁷ Our aim was to identify rates of and barriers to reintroduction, contrast rates among different allergens, and identify rates of recurrence of food allergy over a two-year period among those who have negative OFCs.

We conducted a telephone-based survey of pediatric patients who underwent hospital-based OFCs between January 1, 2013 and June 30, 2016. These patients were referred by six community-based allergists and all patients lived in Minnesota or Wisconsin, with most living in the Minneapolis-St. Paul metro area. All OFCs were performed by a nurse practitioner experienced in OFCs with both positive and negative outcomes determined by objective and subjective symptoms as outlined by the PRACTALL consensus report for OFCs.⁸ The study was institutional review board approved and Fisher's exact test and chi-square analysis were used for proportion comparisons (IBM SPSS Statistics for Macintosh, Version 25.0, Released 2017).

A total of 261 families were contacted by phone following an initial letter explaining the intended study. Of the families successfully contacted (46%), the majority (88%) elected to participate. Reintroduction data were obtained for 103 OFCs (39% overall response rate). The

mean age was 6.93 $\pm$ 4.74 years. Allergens included: peanut (44), tree nuts (19), egg (14), milk (6), fish or shellfish (6), and fewer than four of each of: baked milk, beef, chicken, coconut, fruits/vegetables, sesame, soy, and wheat. Most patients completed one OFC, however three completed two, two completed three, and one completed each of five and seven OFCs.

Regarding the timing and frequency of reintroduction of foods, 98% of 103 patients reintroduced the food at any point, 86% consumed the food at any frequency one month after, and 83% at each of one and two years after the OFC. Twenty-five percent consumed the food every 1-3 days, 39% about 1-2 times per week, 24% about once per month, and 4% several times per year (Table 1a). Among the 13 patients who consumed the food several times per year or less, reasons cited for infrequent consumption include: not part of routine (including dislike of taste/texture) - 77%, anxiety or fear - 46%, and family member with allergy - 23%. Significantly more patients failed to consume tree nuts than peanuts at one month following the OFC (32% versus 7% non-ingestion rate, $p=0.019$). Among the 44 peanut-allergic patients, 82% consumed peanut at least once per week and 91% consumed peanut at least once per month (Table 1b). Peanuts were reintroduced at least weekly significantly more than non-peanut allergens ($p=0.002$) and both fish/shellfish and tree nuts were reintroduced at least weekly significantly less than other allergens ($p=0.016$ and <0.001 , respectively) (Table 1b). Adolescents were less likely than younger children to consume a food at least weekly (40% versus 72% ingestion rate, $p=0.004$) (Table 1b).

With respect to subsequent allergic reactions, 7 of 103 patients in our study self-reported having or possibly having had an allergic reaction to the food in the years following the negative OFC;

however, none had symptoms suggestive of an IgE-mediated reaction with every ingestion. All of the patients were six years old or younger. Four patients reported hives, and one toddler had vomiting or diarrhea. None reported respiratory symptoms and none sought medical care for the reaction. All continued to consume that food 1 and 2 years after the OFC and when contacted were consuming the potential allergen at least once per week, despite initial concern for reaction following the OFC.

In summary, we completed a two-year follow up of negative oral food challenges to identify rates of and barriers to reintroduction among a community-based population. Overall, our study shows peanut has relatively high reintroduction rates, tree nuts and seafood have relatively lower reintroduction rates, children 10 or younger reintroduce more frequently than adolescents, two-thirds of pediatric patients reintroduce at least weekly and nearly 90% reintroduce foods at least monthly after a negative OFC. The most common barrier to reintroduction is that the food is not part of the patient's routine and that they dislike the taste and/or texture, similar to previously published data showing patient preference and anxiety being the most common reasons cited.^{6,9} Regular reintroduction is important because case reports suggest children who inconsistently consume peanut after a negative OFC may be at increased risk of recurrent allergy.^{4,5} There is not a universally recognized optimal frequency of consumption to prevent a possible recurrence of allergy, although common practice is to encourage at least weekly consumption.¹ A unique aspect of our study is that it discusses differences in reintroduction among non-peanut allergens and differentiates reintroduction rates by age. Children may undergo food challenges to foods that they have no interest in eating in the future and perhaps this also contributes to failure to reintroduce over time. The failure to regularly ingest tree nuts and seafood may be due to their

smaller weekly per capita consumption in the general American population, cited as being 23-36% less than that of peanut and egg by the United States Department of Agriculture.¹⁰ Reintroduction data targeting specific food allergens and age groups is important for the allergist when deciding whether to pursue an OFC and to help shape anticipatory guidance before and reintroduction recommendations after a negative OFC. It is important when discussing whether or not to pursue an OFC that physicians also discuss the need to maintain the food in the diet over time. While our study found significant differences in reintroduction among some ages and allergens, a larger study is needed to more concretely define differences in reintroduction rates among all different ages and less common allergens. Additionally, there continues to be a paucity of data defining at exactly what frequency foods need to be eaten after passing a challenge, as many published recommendations regarding frequency of reintroduction are largely based on historical norms.

We also sought to identify IgE-mediated food allergic reactions to the tested allergen following the negative OFC. It is noteworthy that among patients in our study, none reported a classic food-related reaction requiring ongoing strict avoidance. However, a limitation of our study is that we did not have access to follow up allergist notes that may have better elucidated the symptoms described by families. Additionally, while the majority of families we reached participated, there may have been differences between the response group and those unwilling or unable to participate in the study. We were unable to evaluate these differences based on limited information available.

In conclusion, our data suggests that there may be differences in rates of reintroduction among various allergens and ages, common barriers to reintroduction, and low risk of IgE-mediated food allergy to the tested food following a negative OFC, and this knowledge may prove particularly helpful to the allergist when counseling a family and deciding whether or not to proceed with an OFC.

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Table 1a: Reintroduction rate and frequency of consumption over two years from oral food challenge. Table 1b: Reintroduction at least every week and every month among different allergens and ages.

Table 1.

A.

	Number of patients
Reintroduction at some point after negative OFC	101 (98%)
Eating at 1 month post OFC	89 (86%)
Eating at 1 year post OFC	86 (83%)
Eating at 2 years post OFC	86 (83%)
Felt child had more food options after negative OFC *	86 (83%)
Consume food every 1-3 days *	26 (25%)
Consume food at least weekly *	66 (64%)
Consume food at least monthly *	91 (88%)
Consume food at least several times per year *	95 (92%)
Thought did or may have had allergic reaction after OFC * (*when contacted 2-5 years after negative oral food challenge)	7 (7%)

B.

	Number consuming at least every week	Number consuming at least every month
Milk (n=6)	6 (100%) $p=0.093$	6 (100%) $p=1.0$
Egg (n=14)	12 (86%) $p=0.127$	14 (100%) $p=0.201$
Peanut (n=44)	36 (82%) $p=0.001$	40 (91%) $p=0.550$
Fish or Shellfish (n=6)	1 (17%) $p=0.016$	5 (83%) $p=0.558$
Tree nut (n=19)	4 (21%) $p<0.001$	13 (68%) $p=0.010$
0-4 years old (n=36)	25 (69%) $p=0.405$	32 (89%) $p=1.0$
5-10 years old (n = 42)	31 (74%) $p=0.088$	37 (88%) $p=1.0$
11-18 years old (n=25)	10 (40%) $p=0.004$	22 (88%) $p=1.0$

* p -values represent significance of difference in number consuming food at least every week and at least every month between that specific allergen and all other allergens or between that specific age group and all other ages.