

A practical focus on multi-food oral immunotherapy

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ABSTRACT

Approximately one-third of patients who present for oral immunotherapy (OIT) will be allergic to more than one food. Those patients with more than one food allergy have the option of sequential courses of single-food OIT or, in the right situation, combining several foods as part of multifeed OIT. The time and cost savings can be substantial. Treatment protocols used with multiple foods are basically the same as with single-food courses, so clinics proficient with single-food OIT can easily transition to multifeed OIT. Outcomes have been shown to be similar between the two approaches, so patients should be offered the opportunity to address their food allergies in one, more convenient OIT course.

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Oral immunotherapy (OIT) was introduced as single-allergen therapy, starting with peanut, but, over time, has evolved to the common practice of administering multiple allergens simultaneously.^{1–4} The use of more than one food in an OIT course is referred to as multifeed OIT. Combining foods in this fashion is an option for those with properly diagnosed food allergy to more than one, non-cross-reactive food. Each patient with multiple food allergies has a therapeutic decision to make with the treating physician to begin single-food or multifeed OIT, and, if the latter, how many and which foods to include in a given OIT course.

Factors that may influence the choice to pursue multifeed over single-food OIT include younger age, lower specific immunoglobulin E (IgE) to total IgE ratios, and a higher eliciting dose of food (historic or oral food challenge [OFC]).^{5–7} These patients are likely to tolerate the lower dose portion of the OIT protocol because they remain under their reactive threshold, which positions them well for a positive OIT experience. Multifeed OIT provides time and financial

efficiency over sequential single-allergen OIT courses, but the choice is an individualized decision for families to consider with their physician.

An OIT course typically takes 6–8 months to reach maintenance; therefore, eliminating one or more courses *via* combined food treatment offers significant savings of time and financial commitment. Preparation for multiple food OIT requires the same attention necessary to properly diagnose food allergy and establish patient and/or family commitment to OIT as would be undertaken if each food was being offered as single-food OIT. A patient with suspected cashew and walnut allergy who requires OFC to confirm the diagnosis would need those challenges whether doing sequential single-food OIT courses or a multifeed course. There could be a scenario wherein the history and testing of cashew was definitive for food allergy, but walnut with similar testing had never been eaten. Because this patient qualifies for cashew OIT, a lower threshold could be applied when it comes to requiring a risky walnut OFC, *i.e.*, walnut could simply be added to cashew in multifeed OIT. If walnut were the only suspected food, then OFC before single-food walnut OIT would be strongly encouraged. Selecting multifeed OIT is not an irreversible decision; if repeated reactions occur during a multifeed course, one or more foods can be held at a low dose or discontinued, and then resumed at a later date. The more common approach to the occasional dose reaction is to reduce both foods, in a similar fashion to single-food OIT, and then resume dosing per protocol.

Allergists have been using multiple inhalant allergens simultaneously in subcutaneous immunotherapy for most of the past century that this therapy has existed for allergic rhinoconjunctivitis. The concept is sound, and several studies have shown multifeed OIT to be as safe and effective as single-food therapy.^{3,4,8} These studies observed similar reaction rates, time to reach the maintenance dose, and likelihood of reaching maintenance (Table 1). Most commonly, two to three

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Table 1 Epinephrine use and outcomes in multifood OIT compared with single-food trials

	No. Patients	Age Range, y	sIgE, median, kU/L	Wheal Size, median, mm	Maintenance Dose, mg	Patients Who Reached Maintenance, %	Patients Who Used Epinephrine in the First Year, %
Sarasota ⁴							
Single food	162	0.6 – 36	53	15	750 – 2000	85	14
Multifood	77	0.9 – 19	32	15	750 – 3000	74	8
Palforzia ²⁰	372	4 – 17	69	11	300	79	14
Dallas peanut ²¹	67	0.75 – 16	19	ND	1500 – 3000	93	8
Canada peanut ²²	270	0.75 – 5	5	7	300 – 320	90	ND

OIT = Oral immunotherapy; sIgE = specific immunoglobulin E; ND = no data.

Table 2 Breakdown of foods used in a multifood oral immunotherapy trial*

	Cashew	Walnut	Peanut	Hazelnut	Egg	Milk	Sesame	Most Common Combinations			
								Cashew and Peanut	Cashew and Walnut	Cashew, Walnut, and Peanut	Cashew, Walnut, and Hazelnut
Patients, n (%)	51 (65)	41 (53)	39 (50)	13 (17)	13 (17)	8 (10)	4 (5)	15 (19)	9 (12)	10 (13)	9 (12)

*From Ref. 4.

foods are used (Table 2), although as many as five foods have been successfully administered simultaneously.³ Each additional food has the potential of making the combined dose too allergenic or, at the higher dose, disliked by the sheer volume of food being consumed. The dosing protocols are the same whether using single- or multifood treatment, although many clinicians will reduce the day-1 top dose by a dose step or two in light of the additional allergen exposure of the combined foods (Table 3). The buildup phase uses the same 1-week minimum time period between updose visits, although adjusting to a slower schedule for the more complex patient should be considered. The top, or maintenance dose, is the same as with single-food OIT. Although there may be some broad basophil hyporeactivity generated by OIT (see below), we adhere to the same dosing goals to ensure adequate protection against each treated food. With so much time saving built into the decision to use multifood OIT, adding a week or more between doses can be time well spent if it minimizes complications.

Multifood OIT can be particularly helpful with an allergy to tree nuts because tree nut cross-reactivity can be leveraged to decrease the number of nuts needed.^{9–12} OFCs in the subjects with multiple tree nut allergy showed a strong co-allergy between cashew and

pistachio, and between walnut and pecan with or without hazelnut.¹⁰ All 42 subjects who had pistachio positive OFC reacted to cashew OFC, whereas 10% of the subjects with cashew allergy tolerated pistachio.¹⁰ All 29 subjects allergic to pecan were also allergic to walnut, whereas 10% of the subjects who were allergic to walnut tolerated pecan.¹⁰ Thus, cashew and walnut are considered the dominant tree nuts, which results in them being the most common tree nuts used in OIT.¹⁰ Hazelnut is not as tightly correlated, but hazelnut allergens have high sequence identity with walnut vicilin (Cor a 11 and Jug r 6) (72%), legumin (Cor a 9 and Jug r 4) (73%), and pecan legumin (Cor a 9 and Car I 4) (71%).⁹

OIT to cashew will protect most patients against pistachio reactions, and walnut offers cross-immunotherapy for pecan, and, to some degree, for hazelnut and cashew as well.^{13,14} When offering cashew and/or walnut OIT, it is not necessary to use OFCs or other diagnostic testing to their cross-reactive nuts before OIT.^{15,16} In fact, the opposite was done, OFCs to pistachio after cashew OIT and pecan after walnut OIT to reassure these patients that the dominant nut indeed protects them against exposure to the cross-reactive nut.¹⁷ In this study, 94% of the subjects in cashew OIT passed the pistachio challenge and 97% of the subjects in walnut OIT passed the follow-up pecan challenge.¹⁷ Only one of the failed

Table 3 Sample dosing protocol for a patient in peanut and cashew multfood oral immunotherapy

	Cashew		Peanut		
	Dose	Cashew Protein per Dose, mg		Dose	Peanut Protein per Dose, mg
Cashew milk 1:100 (day 1)	0.3 mL, 0.9 mL, 2.7 mL	0.05, 0.15, 0.45	0.1 mg/mL flour (day 1)	1 mL, 3 mL	0.05, 0.15
1:10 Cashew milk (day 1)	0.6 mL	1	1 mg/mL flour (day 1)	1 mL, 2 mL	0.5, 1
1:10 milk	1.2 mL	2	10 mg/mL flour	0.4 mL	2
	1.9 mL	3.2	10 mg/mL flour	0.65 mL	3.25
	3 mL	5	10 mg/mL flour	1 mL	5
Cashew nut	0.03 g	6	Peanut	0.03 g	7.5
Cashew nut	0.05 g	10	Peanut	0.05 g	12.5
Cashew nut	0.08 g	16	Peanut	0.08 g	20
Cashew nut	0.13 g	26	Peanut	0.13 g	33
Cashew nut	0.2 g	40	Peanut	0.2 g	50
Cashew nut	0.32 g	64	Peanut	0.32 g	80
Cashew nut	0.5 g	100	Peanut	0.5 g	125
Cashew nut	0.8 g	160	~1 Peanut	0.8 g	200
~1 cashew	1.3 g	260		1.3 g	325
~1.5 cashews	2.1 g	420		2.1 g	525
Maintenance, ~2.5 cashews	3.4 g	680	Maintenance, ~3 peanuts	3 g	750

post-OIT challenges occurred at an eliciting dose of fewer than five nuts.¹⁷ Challenges to cross-reactive nuts can be done 1–3 months after reaching OIT maintenance, although, from these data, introducing the secondary nuts is often allowable at home.

Beyond the benefits of cross-reactivity protection, it has been shown that decreased basophil reactivity does not seem to be restricted to the allergen used in OIT. Basophils from the subjects undergoing peanut OIT had decreased reactivity when nonspecifically stimulated with an anti-IgE antibody.¹⁸ Such an effect may explain why, in a small study, walnut OIT provided desensitization to pecan, cashew, hazelnut, and pistachio in 7 of 8 patients and another study showed at least partial desensitization to hazelnut in 14 of 15 patients (at least a 10-fold increase in eliciting dose or tolerate > 1 g of protein).^{13,14} The decision to add hazelnut to walnut OIT should be based on a discussion with the family; unless large amounts of hazelnut are part of the family diet, even the partial protection provided by walnut OIT should be adequate for hazelnut, a nut often eaten in small quantities as a food flavoring.

CONCLUSION

Managing multfood OIT is more complex for the staff and the allergist, and the burden of additional foods being consumed regularly can be challenging

for the patient. However, the advantages for the patient far outweigh these manageable concerns. Clinics should be experienced in single-food OIT before undertaking multfood OIT.¹⁹ With the principles and protocols being the same between single- and multfood OIT, it should not take long for a clinic comfortable with single-food OIT to transition into offering multfood OIT to the appropriate patient.

CLINICAL PEARLS

- Multfood OIT is as safe and effective as single-food therapy
- Avoid patient and/or family burnout, cost, and time of sequential 6–8 month OIT courses; consider multfood OIT
- If a patient on multfood OIT starts reacting, slow the schedule, hold one food while up dosing the other(s), or discontinue a food

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