Variations in protocol development during oral immunotherapy

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ABSTRACT

Oral immunotherapy (OIT) protocols are not standardized, and a wide heterogeneity exists in the literature. OIT protocol variables include the initiation approach (fixed dose versus oral food challenge), buildup speed (slow versus fast), target maintenance dose (low versus high target dose), type of food used, and use of adjuvants among other variables. Most protocols start with an initial escalation day, which is a series of extremely low doses to safely identify the patients who are most allergic, followed by a buildup period over several months to years until the final target maintenance dose is achieved. Doses are generally increased every 1–2 weeks by a factor of 1.25 to 2 and are adapted based on the patient's symptoms. Protocols are increasingly favoring low-maintenance doses over traditional high maintenance doses, although this needs to be discussed and adapted based on the patient's preferences. Accelerated OIT schedules with using a short treatment of omalizumab can be considered in severe food allergy cases.

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Oral immunotherapy (OIT) generally consists of three separate stages: initial dose escalation, updosing or buildup phase, and maintenance phase. The initial dose escalation is conducted in a clinical setting where increasing doses of allergen are administered to identify the highest tolerated dose. The patient then enters the buildup phase, starting with daily ingestion of the highest tolerated dose, with weekly to every other week dose increases in the clinic until the maintenance dose is reached.[1] Protocol variables include the initiation approach (fixed dose versus threshold challenge), buildup approach (frequency of visits, percentage dose increase per visit), and target maintenance dose (low versus high target dose), among other variables. Knowledge and experience with multiple protocols will likely contribute to increasing the comfort and flexibility of OIT providers and help tailor protocols based on the patient's needs and preferences. This article will focus on describing existing OIT protocol variables and may provide a basis for clinicians wishing to develop an expertise in OIT. OIT studies with the protocols used are summarized in Tables 1 and 2.

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FIXED DOSE VERSUS THRESHOLD CHALLENGE FOR INITIATION

Initiation of OIT is generally achieved with one of the three following approaches: (1) initial dose escalation, which is graded oral food challenge (OFC), up to a defined low quantity of protein (generally up to 6 to 12 mg of protein); (2) standard graded OFC up to a maximum quantity of food (*i.e.*, regular portion); and (3) single-dose OFC. Target cumulative doses during initial dose escalations have been prescribed, up to 500 mg, but today have more commonly been capped at 6–12 mg. In most randomized controlled trials, OIT starts with an initial low-dose escalation, which is typically a series of doses starting with 0.1–0.5 mg of protein and going no higher than 6 mg of protein (Table 1).[1] One example is the Consortium for Food Allergy Research seven-step initial day food escalation, which starts at 0.1 mg of peanut protein and increases doses every 30 minutes up to a final dose of 6 mg of peanut protein (Table 3).[2] The patient begins daily dosing at home by using the last tolerated dose or the final dose if no reaction occurs.

A second option when initiating OIT is to perform a standard graded OFC (*i.e.*, up to a regular portion of food) based on existing OFC protocols.[3,4] One option is to use the Practical Allergy OFC protocol, starting at 3 mg of protein and increasing doses every 20 minutes to 10, 30, 100, 300, 1000, 3000 mg up to a total cumulative dose of 4443 mg of protein.[4,5] Other protocols have

Table 1 **Summary of OIT protocols used for peanut, egg, and milk (studies with $N > 50$ patients included)**

Studies	Design	N	Age (Range)	IDE*	Build-up phase			Maintenance Dose	DSS (ITT)	SU (ITT)
					Dose increase intervals	% increase and steps	Length			
Peanut										
Anagnostou *et al.*,[13] 2014	RCT	99	7–16 y	No IDE:2 mg pp	2 wk	100–150; 9	16 wk	800 mg pp	84	NA
Wasserman *et al.*,[58] 2014	RCR	352	3–24 y	Site 1: 0.001–20.5 mg pp	1 wk	25–150; ND	104 days to >1 y	415–8000 mg pp	85	NA
				Site 2: 0.1–6 mg pp	2 wk					
				Site 3: 0.1–20 g pp	1 wk					
				Site 4: 0.13–1040 mg pp	1 wk					
				Site 5: 0.1–25 mg pp	4 wk					
Tang *et al.*,[59] 2015	RCT	62	1–10 y	0.1–12 mg pp in 8 steps	2 wk	25–100; 16	8 mo	2000 mg peanut flour with *Lactobacillus*	90	82%
Kukkonen *et al.*,[14] 2017	Non–randomized controlled, open-label trial	60	6–18 y	No IDE: 0.1 mg pp	1–2 wk	33–150; 19	34 wk	800 mg pp	67	NA
Bird *et al.*,[60] 2018	RCT	55	4–26 y	0.5–6 mg pp	2 wk	20–100; 10	Median 22 wk	300 mg pp		NA
Vickery *et al.*,[61] 2018	RCT	551	4–17 y	0.5–6 mg pp	2 wk	20–100; 11	6 mo	300 mg pp	67.2	NA
Nachshon *et al.*,[20] 2018	RCR	145	3.9–6.7 y	Day 1: 0.1–50 mg pp	1 mo	First updosing: 300% over 4 days	Median 8.7 mo	1200–3000 mg pp	77.9 (3000 mg)	NA
				Day 2: 50–3000 mg pp		Second updosing: 200% over 3 days			91.7 (≥300 mg)	
				Day 3: dose before and 2 maximum tolerated starting doses		Third and fourth updosing: 100% over 2 days				
				Day 4 : 2 maximum tolerated starting doses		Rest: 50%				
Reier-Nilsen *et al.*,[15] 2019	RCT	77	5–15 y	No IDE: 5 mg pp initially, lowered to 1 mg pp after $n = 26$	2 wk	50–100 initially, followed by 20–44; 25	11.5–18 mo	5000 mg pp	21.1	NA
Wasserman *et al.*,[10] 2019	RCR	270	4–18 y	2 protocols: 0.001–10 mg pp in 26 steps; 0.002–2.05 mg pp in 10 steps	1–2 wk	NA (doses twice a day)	NA	3000 mg pp	79	57.9%

Table 1 **Continued**

Studies	Design	N	Age (Range)	IDE*	Build-up phase			Maintenance Dose	DSS (ITT)	SU (ITT)
					Dose increase intervals	% increase and steps	Length			
Soller *et al.*,[9] 2019	RCR	270	15-33 mo (IQR)	3 options: (1) no IDE: 12 mg pp; (2) 0.1-6 mg PP IDE; (3) no IDE: 10 mg pp	2 wk	25-100	3.7-5.1 mo	300-320 mg pp	90	NA
Chinthrajah *et al.*,[41] 2019	RCT	120	7–55 y	0.5–6 mg	2 wk	12–108; 22 (lower percentage increase as buildup progresses)	42–60 wk	4000 mg pp	85	13% (52 wk)
Afinogenova *et al.*,[62] 2020	RCR	783	3.5–48.3 y	0.1–3 mg pp	2 wk	33–50; 18	9 mo	2.5–15 peanuts	89	NA
O'B Hourihane *et al.*,[63] 2020	RCT	175	4–17 y	0.5–6 mg pp	2 wk	20–100; 11	20–40 wk	300 mg pp	58	NA
Egg										
Morisset *et al.*,[64] 2007	RCT	90	1–8 y	No IDE: 1 g of egg yolk daily	1 wk	NA; 4 g of yolk and 4 g of egg white after 1 mo	3 mo	Daily intake of cream desserts and flan, 6 mo total	69	NA
Burks *et al.*,[65] 2012	RCT	55	5–11 y	0.1–50 mg of egg white powder in 10 steps	2 wk	10–50	10 mo	2 g of egg–white powder (~1/3 egg)	55	28%
Fuentes-Aparicio *et al.*,[66] 2013	RCT	72	4–15 y	Day 1: 1–18 mg PPE; day 2: 30 mg PPE	1 wk	25–100; 12	3 mo planned -> 1 mo observed	10 g PPE (~1 egg)	92.5	NA
Vazquez-Ortiz *et al.*,[67] 2014	Non–randomized controlled, parallel group intervention study	82	5–18 y	Day 1: 0.2–1 mL of 1/100 LEW in water; day 2: 0.2–2 mL of 1/10 LEW in water; day 3: 0.4 mL undiluted	1 wk	25–40, up to 30 mL LEW	16 wk	1 raw egg	80	NA
Escudero *et al.*,[68] 2015	RCT	61	5–17 y	0.08–140 mg EWP in 12 steps every 20 min	1 wk	2–10–fold increases	Median 32.5 days	2.808 g EWP	93	37%
Martin-Munoz *et al.*,[23] 2019	RCT	101	6–9 y	From 1 mL of 1/1000 diluted pasteurized egg white (0.11 mg protein) to 0.4 mL of undiluted pasteurized egg white (44 mg protein) in 8 steps	Weekly plus daily or weekly only	30% weekly plus 5% daily (PI) vs 30% weekly (PII)		30 mL pasteurized egg white (3.3 g EWP, ~1 egg)	84.21% (96.15% PI vs 75.8% PII)	NA

Table 1 **Continued**

Studies	Design	N	Age (Range)	IDE*	Build-up phase: Dose increase intervals	Build-up phase: % increase and steps	Build-up phase: Length	Maintenance Dose	DSS (ITT)	SU (ITT)
Kim *et al.*,[69] 2020	Randomized, open-label trial	50	3.5–16.8 y	0.1–25 mg of egg white powder	2 wk	NA	NA	2.5 g of egg white powder (2 g EWP)	7.4% (baked egg); 56.5 % (raw egg OIT)	11.1% (baked egg); 45.3% (raw egg OIT)
Palosuo *et al.*,[12] 2021	Randomized, open-label trial	50	6–17 y	No IDE: 0.1 mL of egg white powder 1 mg/mL in water (0.1 mg EWP)	1–2 wk	50–100; 16	8 mo	12 g of egg-white powder (=1 g of egg protein)	44	
Milk										
Morisset *et al.*,[64] 2007	RCT	60	1.1–6.5 y	No IDE; start with 1 mL CM	Every day for the first week, followed by every 1 week	100%	6 wk	250 mL whole CM	88.9	NA
Longo *et al.*,[70] 2008	RCT	97	5–17 y	10-day rush IDE: starting with 0.5 mg of CM protein (= 5 drops of 1/10 dilution in water) up to 20 mL of milk	2 days (at home)	1 mL increase every other day	12 m	150 mL of whole CM	36	NA
Martorell *et al.*,[71] 2011	RCT	60	2–3.5 y	Day 1: 1, 2, 4, 8 mL of 1/100 CM dilution followed by 1.6 mL 1/10 dilution every hour; day 2: 1.6, 3.2, 6, 12 of 1/10 CM dilution followed by 2.5 mL pure CM	1 wk	25–50; 16	12 m	200 mL of whole CM	90%	NA
Levy *et al.*,[21] 2014	RCR	280	4–27 y	Day 2: 2 highest tolerated doses on day 1, followed by 2 doses formulated midway between the last tolerated dose and the eliciting dose; day 3: dose before and 2 maximum tolerated starting doses; day 4: 2 maximum tolerated starting doses	1 mo	3 monthly rounds of 4 day of IDE followed by monthly 50% increases	Median 188 days	240 mL of 3% fat CM	61.5	NA

Table 1 **Continued**

Studies	Design	N	Age (Range)	IDE*	Build-up phase			Maintenance Dose	DSS (ITT)	SU (ITT)
					Dose increase intervals	% increase and steps	Length			
Kauppila *et al.*,[11] 2019	RCR	296	5–17 y	No IDE; start with 0.5 mg CMP (= 5 drops of 1/10 dilution in water)	1–2 wk	100;15	4–6 m	200 mL CM	56	NA
De Schryver *et al.*,[72] 2019	RCT	52	6–18 y	Day 1: 1–2–4–8 mL of CM diluted 1/100 with water every hour, last dose of 1.6 mL of CM diluted 1/10 with water; day 2 (if no reaction on day 1): 1.6–3.2 to 6.4–12 mL of CM diluted 1/10 with water every hour, with last dose of 2.5 mL undiluted CM	1 wk	25–50; 16	Mean 26 wk	200 mL whole CM	73.2	NA

*CM = cow's milk; CMP = cow's milk protein; DSS = desensitization; EWP = egg-white protein; IDE = initial dose escalation; IQR = interquartile range; ITT = intention to treat; LEW = liquid egg white; NA = not available; ND = no data; OIT = Oral immunotherapy; PI = pattern 1; PII = pattern 2; pp = peanut protein; PPE = powdered pasteurized egg; RCR = retrospective chart review; RCT = randomized controlled trial; SU = sustained unresponsiveness; wk = weeks; y = years. *IDE in 1 day unless specified.*

fewer steps.[6] The starting dose for OIT is usually the last tolerated dose or between one-tenth to one-fourth of the OFC threshold, depending on the severity of the reaction.[5,7] The advantage of using this strategy is that some patients (high threshold reactors) may be able to tolerate a higher dose than the 6–12 mg of protein described previously, and this will allow them to reach the maintenance dose faster and save them a significant number of visits. It is also more practical for the OIT provider because patient's with higher thresholds can leave with a quantifiable dose of food (*e.g.,* one-fourth peanut) instead of powders, which have to be prepared with a precision scale.[8] The disadvantage of this approach is that the protocol might overestimate the threshold dose by inducing temporary desensitization and is time and resource consuming. In addition, there potentially is a higher risk of anaphylaxis than with the previously described low-dose OFC due to the higher cumulative dose ingested. This approach is generally favored when a high reactivity threshold is suspected or to confirm the food allergy before OIT is provided when the diagnosis is unclear.

In clinical practice, a final possibility is to start OIT with a fixed dose of allergen[9–11] if the patient has a recent positive OFC result or a recent clear-cut reaction to the allergen with a high likelihood of food allergy based on skin-prick tests and/or allergen-specific immunoglobulin E (sIgE). This fixed dose can be based on clinical judgment (*e.g.,* history of reaction to trace amounts, severe reaction, sIgE levels) and generally varies between 0.1 and 12 mg of protein.[9,11–15] The advantage of performing single-dose OFC is that it is less resources-intensive and less strenuous in young children who have a strong aversion to the food. If tolerated, the patient pursues this dose daily at home until the next updosing visit. There, however, is a small but non-negligible risk that the patient will have a systemic reaction to the chosen dose, especially if the dose is in the upper 5- to 12-mg range. In a recent systematic review, 4.5% of patients with peanut allergy reacted with anaphylaxis at a dose of 5 mg of peanut protein.[16] Patients with a history of reaction to trace amounts of allergen and/or with suspected severe food allergy should undergo standard initial dose escalation starting in the submilligram range, as previously described.

Irrespective of the chosen approach, OIT initiation should always be performed by trained providers who have experience in treating anaphylaxis and with the appropriate equipment and infrastructure.[8] Once the tolerated dose is identified, dosing precautions are given with concern about the avoidance of cofactors to lower the risk of reacting to doses at home with a personalized action plan for management of allergic reactions.[17]

FREQUENCY OF ESCALATION

After OIT initiation, patients enter the buildup phase and continue daily ingestion of doses until the following dose escalation. These updosings are generally performed at the clinic, with a few studies reporting home updosings.[7,18] The frequency of updosings in OIT randomized controlled trials generally varies from weekly to every other week (Table 1). However, there is no contraindication in clinical practice to increase intervals (to lower resource constraints and for patient convenience purposes), with some studies reporting longer intervals, ranging from 1 month[19–21] up to 3 months.[22] Interestingly, a randomized controlled open-label Spanish study that assessed children undergoing egg OIT found that weekly (30% increments) plus daily (5% increments) updosings led to a statistically significant higher desensitization rate (96%) than updosing on a weekly basis only (30% increments) (76%), and a shorter buildup period.[23] Further studies are needed to validate this strategy, and the criterion standard so far is to maintain the same dose at home between updosings.

DOSE INTERVAL INCREASES

At each updosing visit, doses are generally increased by a factor of 1.25 to 2 (Table 1), although many protocols exist in the literature. Some protocols initially start by doubling doses (*e.g.,* 6–12 mg, 12–25 mg, 25–50 mg) but eventually slow down when higher doses are reached, to prevent potential adverse effects associated with an exponential increase (*e.g.,* 1.25 times increase per visit starting from 100 mg of peanut protein).[2] In clinical practice, there does not seem to be any further risk to pursue 50% to 100% increases all the way through to the maintenance dose. Symptom-driven updosing is potentially the most beneficial for patients (*i.e.,* adapting the dose increases based on a patient's symptoms rather than by following a fixed protocol).[1] There is no predetermined buildup calendar, and doses are increased based on a patient's reported symptoms since the previous updosing visit or initiation. One example of symptom-driven updosing is described in the Double-Blind, randomized controlled trial comparing two dosages of Omalizumab to placebo to accelerate a symptom-driven Oral immunotherapy schedule for the treatment of Multiple food allergies (BOOM) OIT clinical trial protocol (Table 4).[24]

FAST VERSUS SLOW

One important variable during OIT is the time required to achieve the maintenance dose. On one hand, too rapid updosings can lead to breakthrough reactions; on the other hand, too slow updosings can lead to unnecessary visits to the clinic and cause patients and their families to become discouraged with therapy. In conventional OIT protocols, the buildup phase generally lasts many months to years (median time ranges from 20

Table 2 **Summary of low-dose OIT protocols for peanut, egg, milk, and wheat**

Study	Type of Food	*N*	Age Range, y	IDE*	Increase, %#	Intervals, wk#	MD	DSS (ITT), %	SU (ITT), %
Vickery *et al.*,[2] 2017	Peanut	40	0.75–3	0.1–6 mg every 30 min in 7 steps	25–100	2	300/3000 mg pp	85% 76%	85%/71%
Nagakura *et al.*,[55] 2018	Peanut	24	5–18	Rush 5-day buildup in the hospital: 8–133 mg with doses twice daily	30–50	4	133 mg pp	92	33
Blumchen *et al.*,[5] 2019	Peanut	62	3–17	None: based on eliciting dose of OFC	10–20	2	125 vs 250 mg pp	74.2	NA
Yanagida *et al.*,[50] 2016	Egg	33	3–13	Rush 5-day buildup in hospital: 62–194 mg of protein	NA	NA	194 mg of scrambled egg protein (1/32 egg)	76.2	71 (1/32 egg); 33 (1/2 egg)
Maeta *et al.*,[51] 2018	Egg	11	3–8	1, 2, 4, and 10 LAC at 20-min intervals	10–100	1	79–110 mg BEP	63.6	NA
Takaoka *et al.*,[52] 2019	Egg	33	Median age 6	1, 2, 4, and 10 LAC at 20-min intervals	20	1	79–110 mg BEP	33.3	NA
Maeta *et al.*,[53] 2021	Egg	31	Median age 6	1, 2, 4, and 10 LAC at 20-min intervals	NA	NA	79–110 mg BEP	35.5	NA
Yanagida *et al.*,[48] 2015	Milk	37	5–17	Rush 5-day buildup in hospital	0.1–0.5 mL/visit up to the MD	0.7	3 mL/25 mL	58.3 (3 mL); 33.3 (2 5 mL)	NA
Miura *et al.*,[49] 2021	Milk	33	5.6–9.4	Rush 5-day buildup in hospital	0.1–0.5 mL/visit up to the MD	0.7	3 mL	NA	27 (1 y); 52 (2 y); 61 (3 y)
Takaoka *et al.*,[37] 2020	Milk	33	5–15	Rush buildup in hospital witd 20% increase per dose (no. days NA)	NA	NA	100 mL 20 mL	65 90	NA
Sugiura *et al.*,[19] 2020	Milk	50	4–7	0.2–5 g or mL of food in 5 steps, starting dose was based on symptom severity	10–50%	4	565 mg EWP	35.9 (overall)	NA
	Egg	133					165 mg CMP		
	Wheat	45					130 mg WP		

BEP = baked egg protein; CMP = cow's milk protein; DSS = desensitization; EWP = egg white protein; IDE = initial dose escalation; ITT = intention to treat; LAC = low egg-allergen cookies (7.9–11 mg of EW protein); MD = maintenance dose; NA = not applicable; OFC = oral food challenge; OIT = Oral immunotherapy; pp = peanut protein; SU = sustained unresponsiveness; WP = wheat protein; wk = weeks; y = years.

**In 1 day unless specified.*

#During the updosing phase of OIT.

to 60 weeks[25]), with some protocols up to 85 weeks,[26] whereas rush protocols can allow patients to arrive at the maintenance dose as fast as 1 to 7 days.

Nonadjuvanted rush OIT protocols have been described for egg,[27–29] peanut,[30,31] milk,[32–37] and wheat.[38] In rush OIT protocols, the patients are admitted to the hospital for a short period of time (generally 5–7 days), during which doses are gradually increased and adjusted based on patients' tolerance. One example is the study by Staden *et al.*[34] about rush OIT to milk, in which doses start at 1:100 of the eliciting dose and are doubled every 2 hours with three to five doses a day up to a dose of 120 mL over a period of 3 to 7 days. Doses are adjusted, depending on reactions during updosings (repeated if there is a subjective symptom, reduced by one step if there are mild skin symptoms, reduced by two steps if there is a severe reaction).[34] Nonadjuvanted rush protocols are generally resource intensive that require hospitalization and may be associated with a higher rate of adverse effects compared with protocols with more gradual updosing,[1] although head-to-head trials are needed.

Rush protocols combined with omalizumab have improved the safety profile of rush OIT and can be useful in severe cases.[1,26] Omalizumab-accelerated OIT has been performed for peanut,[39–41] milk,[42–44] eggs,[45] and multiple foods[46,47] in patients at high risk. These studies generally consist of pretreatment with omalizumab at least 2 months before initiating OIT and an accelerated initial dose escalation over 1 day. An example of omalizumab-accelerated initial dose escalation is illustrated in Table 5 and was adapted from the multifood OIT protocol by Bégin *et al.*[1,46]: the starting dose is 5 mg of protein and doses are increased every 30 minutes up to a dose of 1200 mg of protein. Although omalizumab-accelerated OIT reduces adverse reactions and can increase rates of desensitization compared with nonadjuvanted rush protocols, it does not seem to improve sustained unresponsiveness.[41]

LOW- VERSUS HIGH-DOSE TARGET

Traditionally, OIT clinical trials have aimed for low versus high target dose situated between 300 and 4000 mg of protein (Table 1). However, clinical trials with lower maintenance doses have been increasingly performed in recent years because they are believed to be safer in patients with severe food allergies,[19] and studies have shown that high target doses do not necessarily improve long-term outcomes of OIT.[2,37] Low-dose OIT is defined as OIT with a target maintenance dose much less than a full portion.[19] Protocols have been reported for milk,[19,37,48,49] egg,[19,50–53] peanut,[5,54–56] and wheat,[6,19,57] and are described in Table 2. Low-dose OIT target maintenance doses vary between 2 and 20 mL for milk,[19,37,48,49] between 125 and 250 mg of peanut protein,[2,5,55] 194 mg of scrambled egg protein (1/35 whole egg)[50] to 79–110 mg of baked egg protein,[51–53] and 52–53 mg of wheat protein.[19,57]

Table 3 **Example of oral immunotherapy initial dose escalation***

Initial Dose Escalation		
Step	**Protein Amount, mg**	**Increase, %**
1	0.1	—
2	0.2	100
3	0.4	100
4	0.8	100
5	1.5	100
6	3	100
7	6	100

**Adapted from Ref 2.*

There are little data available that compared low versus high target doses in OIT. In a recent randomized controlled trial by Nowak-Wegrzyn *et al.*,[6] there was no significant difference in the rate of desensitization to 4.4 g of vital wheat gluten between low target dose (1.4 g; $n = 23$ [52%]) and high target dose (2.7 g; $n = 21$ [57%]). In addition, there was no difference in dosing symptoms between both groups. Takaoka *et al.*[37] compared a low (20 mL) and high (100 mL) maintenance dose target in children undergoing milk OIT.[37] There was no difference in the primary efficacy end point (milk OFC threshold after 6 months on the maintenance dose) in the low-dose group versus the high-dose group. However, the 100-mL group reported a significantly higher number of severe symptoms than the 20-mL group during the maintenance phase.[37] Vickery *et al.*[2] compared high- and low-dose OIT in 40 children ages 9 to 36 months with peanut allergy. Seventeen of 20 (85%) in the 300-mg peanut protein arm achieved sustained unresponsiveness to 5 g of peanut protein compared with 12 of 17 (71%) in the 3000-mg peanut protein arm. There were no differences found in T-cell or basophil responses between those subjects on the low and those on the high maintenance dose,[56] which suggests no additional benefit of higher maintenance dosing on long-term immunomodulation.

When considering the lack of evidence that a high maintenance dose leads to improved sustained unresponsiveness, the final target dose should be discussed and adapted based on the patient's needs and personal goals (*i.e.*, protection against traces versus unrestricted integration of the food into the daily diet).[1] An example for which a high-dose target might be beneficial is the case of a patient who enjoys the taste of the ingested allergen and wishes to pursue foods with concentrated forms of the protein (*e.g.*, peanut butter), in which higher doses are needed (8 peanuts is the equivalent of only 2 teaspoons of peanut butter). The risk of pursuing a higher dose target

Table 4 **Example of symptom-driven updosing rules*#**

OIT Symptoms Since the Last Updosing	Management
No symptoms at all	Updose as planned; double the next planned percentage updosing
Transient mild (COFAR grade 1)	Updose as planned; keep next planned percentage updosing the same
Transient moderate (COFAR grade 2) or persistent mild (COFAR grade 1)	Updose as planned; decrease next planned percentage updosing by half
Persistent moderate symptoms (COFAR grade 2) or severe local symptoms (COFAR grade ≥ 3) or systemic reaction	Do not updose; return to previously tolerated dose; decrease next planned percentage updosing by half

OIT = Oral immunotherapy; COFAR = Consortium for Food Allergy Research.

**Adapted from Ref. 24.*

#On the first updosing visit after the initial dose escalation, if eligible for updosing, the patient will attempt to double his or her current daily food dose (100% increase); in the subsequent visits, if the patient reports no symptoms at all, then he or she can double the percentage of planned updosing (up to a maximum of 200% [for protocols without omalizumab, a maximum increase of 100% is preferred]); if the patient experiences only transient mild symptoms (COFAR 1 grade [65], e.g., oral pruritus), then the patient continues the same percentage of updosing; if the patient reports transient moderate (COFAR grade 2) or persistent mild (COFAR grade 1) symptoms, then the percentage of updosing is decreased by half; if the patient reports persistent moderate symptoms (COFAR grade ≥ 2) or severe local symptoms (COFAR grade ≥ 3) or one systemic reaction, then the daily food dose is lowered by half or to the last tolerated dose, no updosing is performed, and the next updosing percentage is lowered by half. Patients who react on updosing remain on the same dose that they were taking at home and a reattempt updosing at half the percentage increase of the failed updose at the next visit. If updosing fails again, then the percentage increase will again be decreased by half at each subsequent visit until the updose is tolerated (e.g., if a subject reacts at a 100% increase, then the next planned increase will be 50%). In the event in which the updosing rules dictate increasing to a percentage updosing that was previously failed, then the subject must repeat one additional uneventful visit with the current percentage updosing before proceeding to this new percentage increase, e.g., a patient for whom a previous 100% updosing increase failed would need to tolerate two consecutive updosing visits at 50% with no symptoms at home before proceeding to the 100% updosing.

Table 5 **Example of omalizumab-accelerated initial dose escalation protocol***

Step	Protein Amount, mg	% Increase
1	5	—
2	15	+200
3	50	+233
4	150	+200
5	300	+100
6	600	+100
7	1200	+100
8	2400	+100
9	4800	+100
10	9600	+100

**Adapted from Refs 1, 46.*

is that patients may develop an aversion to the food, which may ultimately lead to treatment cessation. Adherence to peanut OIT was significantly improved with a lower maintenance dose in a study that compared a maintenance dose of 1200 mg (4 peanuts) and 3000 mg (10 peanuts) of peanut protein, with no significant difference in maintaining desensitization to 10 peanuts.[20] In addition, a fixed high-dose target is not optimum in younger children because they are often incapable of integrating large quantities of foods into their diet.

In conclusion, although more data are needed, these seems to be no benefit on long-term outcomes in pursuing a higher target dose in patients undergoing OIT. In addition, higher maintenance doses may be associated with increased adverse reactions and lower compliance. However, the maintenance dose target ultimately requires a patient-centered approach that explores the patient's preferences and personal goals for undergoing this treatment.

CLINICAL PEARLS

- OIT protocols generally consist of an initial dose escalation day, buildup phase, and maintenance phase.

- The initial dose escalation identifies the highest tolerated dose, which is then pursued daily at home.
- During the buildup phase, doses are generally increased every 1–2 weeks by a factor of 1.25 to 2 until the maintenance dose is achieved. The buildup phase protocol should be adapted based on the patient's symptoms and evolution throughout treatment.
- A low versus a high maintenance dose target needs to be discussed with patients and their families, and adapted based on their preferences and personal goals (*i.e.,* protection against traces versus unrestricted integration of the food in their daily diet) when considering that a higher maintenance dose has not been shown to improve long-term outcomes of OIT.
- Rush OIT protocols with omalizumab can be considered in severe cases.

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