

7. Models of Dosing Schedules for CM and Egg OIT

7.1. Egg OIT

7.1.1. Product to be used

The preferred products contain only egg white, since the yolk does not contain allergenically active proteins:

- Pasteurized liquid egg white
- Dehydrated egg white
- Cooked egg white

Equivalences between egg products and natural egg must be considered in all cases (Table 1).

	Fresh Weight	Powder Weight	Protein Weight	Volume
Whole egg	60 g	10 g	6.6 g	45 mL
Egg white	19 g	4 g	3.3 g	30 mL

Table 1. Orientative Egg Product Equivalents (Average Amount)

7.1.2. Target dose of build-up phase

According to objective:

- Normal diet: up to 1 full serving
 - One raw egg white
 - One cooked egg (consider adding a quarter raw egg white to ensure desensitization to that amount of raw egg).
- Protection against accidental intake: There is no clearly defined threshold for ensuring protection. It is assumed that amounts of up to 300 mg of dehydrated egg white or 2.2 mL of pasteurized egg white (or 274 mg of egg white protein) can protect against food contamination and minor inadvertent intakes.

7.1.3. Standard OIT dosing schedules with pasteurized liquid egg white [1] (Table 2)

1. Grouped initial dosing schedules with 5 doses per day for 2 days. Thirty to 60 minutes between doses, and 2 hours with the patient under observation. Increments of 100% of the dose.
2. Continue administration once a day at home of the maximum tolerated dose reached on the second day.
3. Weekly increments of 30% of the dose.
4. Last dose of 33 mL (equivalent to 1 egg white).

Table 2. Standard OIT Dosing Schedules With Pasteurized Liquid Egg White (Modified From SEICAP, Vazquez-Ortiz et al[1])

	Dilution in Water	Dose, mL	Dose, mg of Protein	Increased Percentage
Week 1 / Day 1	1/1000	1 → 1 mL	0.11	100%
	1/1000	2 → 2 mL	0.22	
	1/1000	3 → 4 mL	0.44	
	1/100	4 → 0.8 mL	0.88	
	1/100	5 → 1.6 mL	1.76	
Week 1 / Day 2	1/100	1 → 3.2 mL	3.52	100%
	1/100	2 → 6.4 mL	7.0	
	1/10	3 → 1 mL	11	
	1/10	4 → 2 mL	22	
	1/1	5 → 0.4 mL	44	
Week 1 / Day 7	1/1	0.5		30%
Week 2	1/1	0.7		
Week 3	1/1	0.9		
Week 4	1/1	1.2		
Week 5	1/1	1.5		
Week 6	1/1	2		
Week 7	1/1	2.5		
Week 8	1/1	3.2		
Week 9	1/1	4.2		
Week 10	1/1	5.4		
Week 11	1/1	7		
Week 12	1/1	9		
Week 13	1/1	12		
Week 14	1/1	15.5		
Week 15	1/1	20		
Week 16	1/1	26		
Week 17	1/1	33		

7.1.4. OIT dosing schedules with cooked egg white (following the model of OIT with pasteurized liquid egg white) (Table 3).

1. Base product: 1 cooked egg white (large egg) and one 125-g CM yogurt (or soya in milk-allergic patients) mixed in a blender for 2 minutes to obtain a homogeneous mixture and an approximate volume of 150 mL (top up to 150 mL with a little water).

This 150-mL volume of base product contains an egg white equivalent to 3630mg of cooked egg white protein, ie, 24.2 mg of protein per mL.

2. Preparation of 1/100 and 1/10 dilutions in yogurt for the initial in-hospital phase:

- Dilution 1/10 in yogurt: 2.4 mg of cooked egg whiteprotein/mL
- Dilution 1/100 in yogurt: 0.24 mg of cooked egg whiteprotein/mL

3. Grouped initial dosing schedules with 5 doses a day during 2 days. One hour between doses and 2 hours with the patient under observation. Increments of 100%.

4. Continue administration once a day at home of the maximum tolerated dose recorded on the second day, and arrange a visit to continue dosing schedules in a week.

5. Use the base product for the home doses.

6. Weekly dosing schedules with increments of 30% of the dose.

7. Last dose: one cooked egg white.

Table 3. OIT Dosing Schedules With Cooked Egg White (Following the Model of OIT With Pasteurized Liquid Egg White)

	Dilution in Yogurt	Dose, mL	Dose, mg of Cooked Egg White Protein	Dose Increase
Week 1 / Day 1	1/100 1/100 1/100 1/100 1/100	1 → 0.5 mL 2 → 1 mL 3 → 2 mL 4 → 4 mL 5 → 8 mL	0.12 0.24 0.48 0.96 1.92	100%
Week 1 / Day 2	1/10 1/10 1/10 1/10 1/1	1 → 1.5 mL 2 → 3 mL 3 → 5 mL 4 → 10 mL 5 → 2 mL	3.6 7.12 12.5 24 48	100%
Week 1/ Day 7	1/1	2.5		30 %
Week 2	1/1	3.5		
Week 3	1/1	4.5		
Week 4	1/1	6		
Week 5	1/1	7.5		
Week 6	1/1	10		
Week 7	1/1	13		
Week 8	1/1	17		
Week 9	1/1	22		
Week 10	1/1	28		
Week 11	1/1	36		
Week 12	1/1	47		
Week 13	1/1	60		
Week 14	1/1	78		
Week 15	1/1	100		
Week 16	1/1	125		
Week 17	1/1	150		

7.1.5. Rush dosing schedules for egg-OIT [2](Table 4)

These dosing schedules may be useful in less severely affected patients without the described risk factors for adverse reactions.

Table 4. Rush Dosing Schedules for Egg OIT (García Rodríguez et al [2])

	Interval, Min	Egg White Dilution	Dose, mL of Pasteurized Egg White	Dose, mg of Egg White Protein
Day 1	30			
		1/1000	1	0.11
		1/100	0.5	0.55
		1/100	1	1.1
		1/100	5	5.5
		1/10	1	11
Day 2	60			
		1/1	0.2	22
		1/1	0.5	55
		1/1	1	110
Day 3	120			
		1/1	2	220
		1/1	3	330
Day 4	1 dose/d	1/1	4	440
Day 5		1/1	8	880
Day 6		Omelet	½ (15 mL)	1650
Day 7		Omelet	1 (30 mL)	3300

If the days are not consecutive, maintain the last tolerated dose on a daily basis at home, until the egg white dose is increased.

7.1.6. OIT dosing schedules with dehydrated egg white [3] (Table 5)

Table 5. OIT Dosing Schedules With Dehydrated Egg White (Escudero et al [3])

	Dose, mg of Dehydrated Egg White	Dose, mg of Protein
Week 1	10	7.8
Week 2	30	23.4
Week 3	75	58.5
Week 4	125	97.5
Week 5	250	195
Week 6	500	390
Week 7	1000	780
Week 8	2000	1560
Week 9	4000	3120

Daily doses with weekly increments

Dehydrated egg white: 4000 mg equivalent to 1 egg white (small egg)

7.2. Models of Dosing Schedule for Milk OIT

7.2.1. Standard milk-OIT dosing schedules [4] (Table 4)

1. Grouped initial dosing schedules with 5 doses per day for 2 days. Thirty to 60 minutes between doses, and 2 hours of observation. Increments of 100% of doses.
2. Continue administration once a day at home of the maximum tolerated dose recorded on the second day and arrange and arrange a visit to continue dosing schedules in a week.
3. Weekly dosing schedules with increments of 30% of doses.
4. Last dose 200 mL.

Table 4. Standard Milk OIT Dosing Schedules
(Modified from SEICAP, Martorell et al [4])

	Dilution in Water	Dose, mL	Dose Increment
Week 1 /Day 1	1/100 1/100 1/100 1/100 1/10	1 → 1 mL 2 → 2 mL 3 → 4 mL 4 → 8 mL 5 → 1.6 mL	100%
Week 1 /Day 2	1/10 1/10 1/10 1/1 1/1	1 → 1.6 mL 2 → 3.2 mL 3 → 6 mL 4 → 1.2 mL 5 → 2.5 mL	100%
Week 1 / Day 7	1/1	3.5	30%
Week 2	1/1	4.5	
Week 3	1/1	6	
Week 4	1/1	8	
Week 5	1/1	11	
Week 6	1/1	14.5	
Week 7	1/1	19	
Week 8	1/1	25	
Week 9	1/1	32	
Week 10	1/1	42	
Week 11	1/1	54	
Week 12	1/1	70	
Week 13	1/1	90	
Week 14	1/1	120	
Week 15	1/1	150	
Week 16	1/1	200	

7.2.2. Rush dosing schedules for milk OIT [5,6] (Table 7)

These dosing schedules may be useful in less severely affected patients without the risk factors described for adverse reactions.

Table 7. Rush Dosing Schedules for Milk OIT (Dosing Schedules Proposed by Bauer et al [5] and Modified for Clinical Application by Martorell et al [6])

Time	Monday	Tuesday	Wednesday	Thursday	Friday
8:30	1 mL, 1/100 ^a	16 mL, 1/100	2.4 mL, 1/1	32 mL, 1/1	100 mL, 1/1
9:30	2 mL, 1/100	3.2 mL, 1/10	4.8 mL, 1/1		
10:30	4 mL, 1/100	6 mL, 1/10	8 mL, 1/1	64 mL, 1/1	200 mL, 1/1
11:30	8 mL, 1/100	12 mL, 1/10	16 mL, 1/1		
12:30	16 mL, 1/100	2.4 mL, 1/1	32 mL, 1/1	100 mL, 1/1	

^aCM dilutions in water

7.3. Individualized Dosing Schedules for Milk And Egg OIT

Individualized dosing schedules may be indicated in patients who have reacted to medium or high doses of the food in the challenge tests. While this concept is not well defined, a cumulative dose of half a boiled egg or 50 mL of milk or more may be considered a medium to high tolerance threshold.

The starting dose in the build-up phase, in relation to the response threshold dose, has not been established. The last tolerated dose in the challenge test, or 50% of the threshold dose, is usually taken as reference.

7.4. Modification of the Dosing Schedules According to Severity of Reaction (Modified Clark and Ewan Severity Classification [7])

- Very mild reactions, grade 0:
 - Symptoms: oral itching, perioral erythema.
 - Treatment: consider antihistamines.
 - Plan: continue dosing schedules.
- Mild reactions, grade 1:
 - Symptoms: some wheals, localized angioedema, or mild and self-limiting abdominal pain (<15 minutes).
 - Treatment: antihistamines; systemic corticosteroids for angioedema.
 - Plan: repeat the dose next day.
- Mild reactions, grade 2:
 - Symptoms: urticaria/angioedema or erythema (generalized).

- Treatment: antihistamines; consider systemic corticosteroids and adrenalin if improvement is not achieved.
- Plan: on the next day, administer a lesser increment (eg, half) than that applied with respect to the tolerated dose.
- Mild reactions, grade 3:
 - Symptoms: skin (urticaria, angioedema, exanthema) and gastrointestinal (nausea, vomiting, abdominal pain) or rhinoconjunctivitis or dysphonia without dyspnea.
 - Treatment: antihistamines and corticosteroids; epinephrine if no prompt response or very intense and persistent abdominal pain.
 - Plan: repeat the previous tolerated dose and introduce smaller increments.
- Moderate reactions, grade 4:
 - Symptoms: laryngeal edema (dysphonia with dyspnea) or bronchospasm.
 - Treatment: inhaled β -agonists in case of bronchospasm. Epinephrine is indicated for laryngeal edema or no rapid bronchodilator response. Add systemic corticosteroids.
 - Plan: repeat the previous tolerated dose and introduce smaller increments.
- Severe reactions, grade 5:
 - Symptoms: intense dyspnea, desaturation, hypotension, altered level or loss of consciousness.
 - Treatment: epinephrine, oxygen therapy and fluid therapy. Symptomatic treatment according to clinical course. Support from the pediatric intensive care unit.
 - Plan: suspend procedure and consider resumption of OIT associated with omalizumab

7.5. Premedication

- In the event of oral itching or frequent skin reactions, premedication with an antihistamine may be considered and administered 1 hour before each dose.
- In the case of repeated abdominal pain, disodium cromoglycate, montelukast, and/or ketotifen should be considered on a daily basis.

- In asthmatic patients, consider introduction of base treatment with inhaled corticosteroids or in combination with long-acting β -agonists as premedication, or when bronchial symptoms appear.

(Level of evidence V. Grade of recommendation D: expert opinion).

References

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7. Clark AT, Ewan PW. Food allergy in childhood. *Arch Dis Child* 2003;88:79-81.