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The oral food desensitization in the Italian allergy centres

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Summary

Background. *Attempts aimed at inducing food tolerance through oral food desensitization (OFD) for the treatment of IgE-mediated food allergies are increasing. In Italy, a number of allergy centres offer this procedure.* ***Objective.*** *To collect information on how these centres are organized, how patients are selected, the methods used to administer OFD and how adverse reactions are managed.* ***Methods.*** *A questionnaire was e-mailed to all the Italian allergy centres offering OFD.* ***Results.*** *The survey shows a high degree of variability between centres. A correct diagnosis of food allergy is crucial for selecting patients for OFD. In the Italian allergy centres, oral food challenges are mostly open label (84%), but in 16% of cases they are single-blind (8%) or double-blind (8%). A high proportion of allergy centres (83%) offer OFD to children presenting forms of anaphylaxis triggered by traces - or very low doses - of food allergen. The majority of allergy centres (76%) enroll patients over 3 years of age, with 44% enrolling patients above the age of 5. Not-controlled asthma, unreliability of parents in the management of OFD and/or risk of adverse events, are the main reasons for exclusion from the procedure.* ***Conclusion.*** *Although OFD may sometimes be successful and may be considered a valid alternative to an elimination diet, further randomized controlled trials are needed, in order to clarify some controversial points, such as the characteristics of the child undergoing OFD, and the methods of food preparation and administration. Moreover, further studies should further investigate OFD safety, efficacy and costs.*

Introduction

Food allergy (FA) is a common condition, especially in children (1). Besides recommending avoiding the offending food (2), the induction of food tolerance through oral food desensitization (OFD) is proposed today for the treatment of the IgE-mediated forms of this condition (3-12). OFD is achieved through the administration of incremental doses of the offending food, which are progressively increased up to a predetermined top dose, or to the maximum tolerated dose. This method aims at inducing desensitization and, possibly, tolerance to the offending food.

There are numerous case reports and randomized controlled trials (RCTs) investigating OFD (3-12), but they are difficult to compare as they are not homogeneous in terms of the enrolled population, the offending food, its administration route, the dosage and the setting (home, hospital, day-hospital, outpatient clinic).
Up to May 2011, Brozek et al. (13) found that only 5 RCTs met the pre-established inclusion criteria. The RCTs analyzed (involving 218 patients) showed that OFD, compared to the elimination diet, increased the likelihood of achieving oral tolerance to cow's milk (CM). OFD adverse events included frequent local reactions, mild laryngospasm and mild asthma. Results obtained from observational studies were consistent with those obtained from RCTs. The safety of OFD represents a pivotal issue in patients treated with this active treatment for FA. Indeed, between 10% and 36% of patients could not complete the protocol due to adverse reactions (3-11,14). Although OFD may induce a variable level of desensitization, it remains unclear whether this therapeutic approach results in complete, long-lasting tolerance (15).
As the practice of OFD is quite common in Italy, we administered a questionnaire in the structures where OFD is practised, with the aim of taking a snapshot of the procedures concerning OFD adopted in Italy, in order to give targeted guidance on the standardization of this therapeutic procedure.

Materials and methods

This survey (conducted between April and November 2012) was conducted in the Italian allergy centres offering OFD, which are registered with the Italian Society of Pediatric Allergy and Immunology (SIAIP). In addition, an e-mail was sent to the main Italian pediatric allergy forums. A total of 55 allergy centres were thus identified and a questionnaire containing 26 multiple choice questions was e-mailed to them. The questions were divided into the following sections:

a. Type of services and availability of an anesthetist (questions 1-2, **table 1**)
b. Patient selection criteria (questions 3-7, **table 2**)
c. Methods of OFD execution (questions 8-15, **table 3**)
d. Management of adverse reactions occurring during OFD (questions 16-22, **table 4**)
e. Follow-up management (questions 23-26, **table 5**)

The data obtained were analyzed through descriptive statistical analysis.

Results

Type of service and availability of an anesthetist in the allergy centre (**table 1**). Twenty-four out of 55 allergy centres completed the questionnaire; 50% of them had treated 1-20 children and 37,5% between 21-100 children. Only 12.5% had treated more than 100 children. All the centres had an anesthetist on call in case of severe adverse reactions.
Patient selection criteria (**table 2**). While 75% of centres used OFD only for children with an IgE-mediated FA, a further 25% used it also for non-IgE-mediated conditions. As for the severity of symptoms, 68% considered the main indications for OFD to be anaphylaxis (even caused by traces of food), and children with partial tolerance. A lower proportion of allergists (32%) considered OFD only in children with severe conditions.
In terms of the diagnosis of FA, oral food challenge was open-label in 39% of cases, single-blind in 9% and double-blind in 9%. In 27.8% of the centres the diagnosis was based on clinical history and on the positivity of the skin prick test (SPT)/specific IgEs for the offending food. The age threshold for OFD was 6 years in 11.5% of the centres and 5 years in 38%. OFD was administered to children older than 3-4 years in 15.4% of the centres, and only in 8% of centres it was administered to children between 1-2 years old. The unreliability of parents (38.2%) and non-controlled asthma (32.7%) were the main criteria for exclusion from OFD. Anaphylaxis caused by the offending food resulted in exclusion from OFD in 12.7% of the allergy centres, and 9.1% of them also excluded patients living far from an emergency unit.
Methods of OFD execution (**table 3**). As regards the type of protocol adopted, 69.2% of the allergy centres used a slow protocol (over 2-6 months), while 15.4% used a rush protocol (lasting a

Table 1 *- Type of services and anesthetist availability.*

		Answer A	Answer B	Answer C	Answer D	Answer E	Answer F	Answer G
#1	Number of children submitted to OFD in the AC	1 to 5	6 to 10	11 to 20	21 to 50	51 to 100	101 to 200	> 200
		3 (12.5%)	2 (8.3%)	7 (29.2%)	5 (20.8%)	4 (16.7%)	2 (8.3%)	1 (4.2%)
#2	Availability of an anesthetist during the procedure	Yes	Yes, on request	NO				
		0 (0%)	24 (100%)	0 (0%)				

AC = Allergologic Centre

Table 2 *- Patient selection criteria for OFD.*

		Answer A	Answer B	Answer C	Answer D	Answer E	Answer F	Answer G
#3	Type of food related condition in children undergoing OFD	IgE-mediated FA	Not-IgE mediated (FPIES) condition	A + B				
		18 (75.0%)	0 (0.0%)	6 (25.0%)				
#4	Characteristics of patient undergoing OFD	Anaphylaxis induced by traces or very low doses	Partial tolerance	(A + B)				
		4 (16.0%)	4 (16.0%)	17 (68.0%)				
#5	FA diagnosis methods	Open-label OFC (A1) Single-blind OFC (A2) Double-blind OFC (A3)	Convincing clinical history for anaphylaxis + SPTs/IgEs positivity	Convincing clinical history in the previous year (indep. from SPT/IgEs for the offending food)	Suggestive clinical history of FA (NOT of anaphylaxis) in the previous year and SPT/IgEs+ for the offending food	Late clinical history of FA with negative SPT/IgEs		
		21(A1) (39.0%) 5 (A2) (9.0%) 5 (A3) (9.0%)	15 (28.0%)	0 (0.0%)	6 (11.0%)	2 (4.0%)		
#6	Age threshold for OFD	At diagnosis (any age)	After 1st year	After 2nd year	After 3rd year	After 4th year	After 5th year	After 6th year
		1 (3.8%)	2 (7.7%)	3 (11.5%)	4 (15.4%)	4 (15.4%)	9 (34.6%)	3 (11.5%)
#7	Exclusion criteria	Anaphylaxis induced by the offending food	Not-controlled asthma	Physical activity-induced asthma	Atopic dermatitis	Concomitant not-food-dependent allergy	Unreliability of parents	Excessive distance from the ED
		7 (12.7%)	18 (32.7%)	0 (0.0%)	1 (1.8%)	3 (5.5%)	21 (38.2%)	5 (9.1%)

FA = Food Allergy
OFC = Oral Food Challenge
ED = Emergency Department

few days) and 15.4% used a mixed protocol (rush + slow). As regards the dosage, 56% of the allergy centres allowed home administration of incremental doses of the offending food, while 44% only incremented the doses in the hospital setting. The oral route was most frequently used (84%), with sublingual administration being less common (16%). OFD was administered to patients with allergy to CM (42.9%), egg (37.5%), wheat (10.7%), fish (5%), peanut (1,8%) and hazelnut (1,8%), that were mostly administered uncooked. Some allergy centres administered the food in a wheat matrix (21.4%) or as a baked food (28.6%). In terms of the initial dosage of the food, in 37.4% of the centres a dosage lower than the one provoking a reaction in the oral food challenge was used. In 7.5% of the centres, the initial dosage was based on the clinical history or on the SPT end-point (11.2%). Dosage administration was mainly carried out in day-hospital settings (46.7%) or at home after day-hospital or hospital admission (23.3%), or directly at home in the case of slow increments. However, major increments or doubled doses were administered in a day-hospital setting (20%). In a small proportion of centres, OFD was administered during hospitalization (6.7%) or in the outpatient clinic (3.3%). During home administrations, 54.8% of allergists were available on their mobile phones 24 hours per day, while 9.7% were available in specific time slots. Nineteen percent of the allergy centres communicated with families via e-mail, compared to 9.7% of patients, who in case of need, were obliged to refer to the emergency department of the structure responsible for their OFD administration.

Management of adverse reactions in the course of OFD (**table 4**). The main criterion for the interruption of OFD was the occurrence of anaphylaxis triggered by the administration of low doses (24.7%) followed by non-controlled asthma (22.4%).

Table 3 *- Methods of OFD execution.*

		Answer A	Answer B	Answer C	Answer D	Answer E	Answer F	Answer G
#8	Type of protocol	Rush (rapid. in a few days)	Slow (2 to 6 months or more)	Mix (Rush + Slow)				
		4 (15.4%)	18 (69.2%)	4 (15.4%)				
#9	OFD increment method	Dose increase in hospital setting (not at home)	Dose increase in hospital setting and at home					
		11 (44.0%)	14 (56.0%)					
#10	Administration routes	Sublingual (without swallowing)	Sublingual (with subsequent swallowing)	Epicutaneous	Oral			
		2 (8.0%)	2 (8.0%)	0 (0.0%)	21 (84.0%)			
#11	Food	Cow's milk	Egg	Wheat	Fish	Peach	Peanut	Hazelnut
		24 (42.9%)	21 (37.5%)	6 (10.7%)	3 (5.4%)	0 (0.0%)	1 (1.8%)	1 (1.8%)
#12	Food preparation	Raw	Cooked	In wheat matrix	Freeze-dried			
		21 (47.6%)	12 (28.6%)	9 (21.4%)	1 (2.4%)			
#13	Initial dose criteria	Very low predetermined dose (decreasable if clinical history of anaphylaxis with low doses)	Based on the SPT wheal diameter	Based on the SPT end points	Based on the specific IgEs level	Lower than the one provoking a reaction in the OFC	Lower than the one based on the clinical history	
		10 (37.4%)	0 (0.0%)	3 (11.2%)	0 (0.0%)	10 (E1) (37.4%) 1.75 (E2) (6.5%)	2 (7.5%)	
#14	Setting	Day-Hospital regimen	Hospital admission regimen	At home after Day- Hospital and/or Hospital admission	At home for slow increments and in Day-Hospital for major increments or doubled doses	Outpatient clinic		
		14 (46.7%)	2 (6.7%)	7 (23.3%)	7 (20.0%)	1 (3.3%)		
#15	At-home patient management and communication with the AC	Parents can call the doctor on mobile 24 hours a day	Parents can call the doctor on mobile in specific time slots	Parents can only refer to the AC during opening hours	Only email communications	Parents can bring the patient to the ED (where data of all children undergoing OFD are available)	Other	
		17 (54.8%)	2 (6.5%)	1 (3.2%)	6 (19.4%)	3 (9.7%)	2 (6.5%)	

AC = Allergologic Centre OFC = Oral Food Challenge ED = Emergency Department

Twenty percent of the allergy centres considered the parents' ability to manage possible adverse events to be crucial.

If the child presents mild to moderate reactions during OFD, 53.8% of the allergy centres continue the procedure with lower doses of the food, which are later incremented if no adverse symptoms occur. In 15.4% of the allergy centres the trigger dose is administered until the symptoms disappear. Some of the allergy centres administer antihistamines (11.5%) or interrupt the protocol, but in such cases the maximum tolerated dose is maintained (11.5%). To the contrary, some other centres step back and prescribe allergen avoidance (3.8%).

Table 4 *- Management of adverse reactions occurring during OFD.*

		Answer A	Answer B	Answer C	Answer D	Answer E	Answer F	Answer G
#16	OFD interruption criteria after adverse reactions	Non-controlled asthma following OFD administration	Systemic anaphylaxis following very low doses	After 12 months, impossibility to achieve a minimum dose able to protect from reactions occurring after consumption of food traces	Inability of parents to manage adverse events	Repeated ED admissions		
		19 (22.4%)	21 (24.7%)	16 (18.8%)	17 (20.0%)	12 (14.1%)		
#17	OFD management in case of mild to moderate reactions	The trigger dose is re-administered without increment, and is increased after symptoms disappear	The dose is decreased of some steps and is increased when symptoms disappear	The dose is administered with wheat matrix	The patient is pre-treated with antihistamines for few days	The protocol is interrupted and the maximum tolerated dose is maintained	The protocol is interrupted and the children is prescribed an elimination diet	
		4 (15.4%)	14 (53.8%)	1 (3.8%)	3 (11.5%)	3 (11.5%)	1 (3.8%)	
#18	OFD management in case of moderate to severe reactions and/or anaphylaxis	The trigger dose is re- administered without increment, and it is increased after symptoms disappear	The dose is reduced of some steps and is increased when symptoms disappear	The dose is reduced of some steps; the patient is pre-treated with antihistamines and when the symptoms disappear the dose is increased more slowly	The protocol is interrupted and the maximum tolerated dose is maintained	The protocol is interrupted and the children is prescribed an elimination diet for the offending food		
		1 (3.8%)	12 (46.2%)	4 (15.4%)	4 (15.4%)	5 (19.2%)		
#19	Drugs used in case of adverse reactions	Nebulized epinephrine (A1) Epinephrine IM (A2)	Nebulized Cortisone (B1) Cortisone IM (B2) Cortisone IV (B3) Cortisone OS (B4)	Antihistamine IM (C1) Antihistamine IV (C2) Antihistamine OS (C3)	inhaled β2-agonists			
		10 (A1) (8.1%) 23 (A2) (18.5%)	4 (B1) (3.2%) 8 (B2) (6.5%) 13 (B3) (10.5%) 13 (B4) (10.5%)	7 (C1) (5.6%) 8 (C2) (6.5%) 19 (C3) (15.3%)	19 (15.3%)			
#20	Antihistamine administration during OFD	Only in case of adverse reactions (possibly associated with other drugs)	During the whole protocol, independently from the subject	During the whole protocol, only in high-risk subjects				
		18 (78.3%)	1 (4.3%)	4 (17.4%)				
#21	Antihistamine molecule	Cetirizine	Oxatomide	Chlorpheniramine	Other			
		20 (87.0%)	1 (4.3%)	1 (4.3%)	1 (4.3%)			
#22	Extra-dietary factors affecting OFD	Physical activity	Respiratory tract infections	Gastroenteric infections	Fasting	Drugs	Pollinic season	Other
		20 (24.4%)	18 (22.0%)	18 (22.0%)	4 (4.9%)	10 (12.2%)	11 (13.4%)	1 (1.2%)

ED = Emergency Department

Table 5 *- Follow-up management.*

		Answer A	Answer B	Answer C	Answer D	Answer E	Answer F
#23	Management after achievement of the maximum dose	Daily consumption of the maximum tolerated dose	Daily consumption of the food (not necessarily the amount achieved through the protocol)	Occasional consumption allowed (never beyond 2 days)	Occasional consumption allowed (never beyond 4 days)	Occasional consumption allowed (never beyond 7 days)	Free consumption allowed
		5 (18.5%)	8 (29.6%)	5 (18.5%)	4 (14.8%)	0 (0.0%)	5 (18.5%)
#24	Management after achievement of a partial tolerance	Daily consumption of the maximum tolerated dose	Daily consumption of the food (not necessarily the amount achieved through the protocol)	Occasional consumption allowed (never beyond 2 days)	Occasional consumption allowed (never beyond 4 days)	Occasional consumption allowed (never beyond 7 days)	Free consumption allowed
		5 (18.5%)	8 (29.6%)	5 (18.5%)	4 (14.8%)	0 (0.0%)	5 (18.5%)
#25	Adverse reactions following an occasional consumption of the food	Reactions that had occurred previously, equally or less severe	Reactions that had occurred previously, but more severe (including anaphylaxis)	Reactions different from those that occurred previously	No reactions		
		4 (36.4%)	0 (0.0%)	0 (0.0%)	7 (63.6%)		
#26	OFD immunological evaluation	Yes, at the completion on the protocol	Yes, at the completion on the protocol and every 6 months	Yes, at the completion on the protocol and annually	Yes, at the completion on the protocol and periodically at predetermined time intervals	No, never	
		2 (8.3%)	4 (16.7%)	5 (20.8%)	9 (37.5%)	4 (17.7%)	

In the case of severe reactions or anaphylaxis during OFD, lower doses were administered in 46.2% of cases, and were subsequently increased if the patient did not experience any symptoms. Some of the allergy centres pre-treated the patient with an antihistaminic drug and then slowly increased the doses (15.4%), whereas some others preferred to prescribe allergen avoidance (19.2%).

Treatment of adverse events was usually appropriate to the type of reaction.

Physical activity, respiratory tract infections and gastroenteric infections (24.4%, 22% and 22% respectively) were considered the main factors that could facilitate adverse reactions during OFD.

Follow-up management (**table 5**). If the top dose of the protocol was tolerated, 48% of the allergy centres prescribed daily consumption of the food, against 18.5%, which prescribed a free diet. When the acquired tolerance was partial, daily consumption of the food was the most common prescription (69.2%).

Children who had ingested the food occasionally during the follow-up did not have adverse reactions (63.6%) or reported reactions that had already occurred previously (36.4%). No anaphylaxis was reported.

Discussion

Type of services and availability of an anesthetist in the AC (**table 1**). All the centres rely on an anesthetist who does not participate to the procedure but is ready to intervene on request. This is important for the safe execution of OFD. In patients with a high risk of severe adverse reactions, an anesthesiologic visit before the procedure is considered useful.

Patient selection criteria (**table 2**). The majority of the centres offer OFD only to patients with exclusively IgE-mediated FA. Nevertheless, 25% also administer OFD to patients with not-IgE-mediated forms (FPIES, allergic enteropathy, eosinophilic forms). According to current evidence, even if OFD in the IgE mediated food allergy is still considered an experimental approach, there are no recommendations for the administration of OFD to patients with not-IgE mediated forms (16) and it should be done exclusively in the context of research protocols

with the purpose of verifying its efficacy. A high proportion of the allergy centres (83%) offer OFD to children presenting forms of anaphylaxis triggered by traces or very low doses of the food allergen. Even though this is a dangerous procedure, most allergy centres consider, according to evidence (6), that the long-term benefits of OFD are higher than the risks and disadvantages, because of the need for daily food consumption.
A correct diagnosis of FA is crucial for the selection of patients for OFD. In the Italian allergy centres OFD is mostly open label (84%) but in 12% of the centres the diagnosis is based on a suggestive clinical history of IgE-mediated FA, combined with positive SPTs and/or specific IgEs. This is reasonable when the reaction is immediate and clearly associated with food ingestion or when oral food challenge is too risky (4,17,18). Although double-blind, placebo controlled oral food challenge is still considered the gold standard in FA diagnosis, in some circumstances a single-blind or open-label oral food challenge is accepted (19). Considering the complexity of OFD the etiology should, in any case, be very accurately investigated.
The majority of the allergy centres (76%) enroll patients above the age of 3 and 44% above the age of 5. However, some of the allergy centres offer OFD even to children below the age of 2. The first approach considers the chance that food tolerance is achieved with age (13,20,21). The second takes into account the reduced quality of life of children with FA and their families, especially when the allergy is severe (22).
Not-controlled asthma, unreliability of parents for the management of OFD and/or risk of adverse events are the main reasons for exclusion from the procedure. Indeed, families have to respect the protocol accurately and take note of adverse reactions, trigger doses and circumstances that may facilitate the reactions. Moreover, families must be able to manage potential adverse events, both by adjusting food doses and by administering appropriate drugs. All these aspects underline the crucial role of families in the management of OFD.
Methods of OFD execution (**table 3**). Most of the allergy centres adopt a slow desensitization protocol (69.2%), which is sometimes associated with an early rush phase (15.4%). A smaller proportion of them adopt a rapid rush method (15.4%). Indeed, the dose increase is not always gradual and some allergy centres (44%) increase food doses only in controlled settings and the dosage achieved in hospital is then maintained in the following period, at home.
As far as the initial dose is concerned, about half of the allergy centres start with a predetermined, very low dose, decreasing it if an adverse reaction intervenes. However, some centres establish the first dose based on the SPT wheal diameter, or on the specific IgEs level. It is difficult to propose precise doses and time intervals for the progressive increment. Indeed, there are no comparative observations evaluating the different administration protocols. Gradual and proportional food administration should always be accurately respected and empirical and irregular approaches should be avoided, in order to guarantee an appropriate safety level (23).
Though the majority of the centres adopt the oral administration route, some are exploring the sublingual route. Even if the tolerance may be elicited by different food administration routes, the oral one seems to offer better results than the sublingual route, because it imitates what happens in natural food consumption and permits the use of much higher food doses (24).
In 80% of the centres, children submitted to OFD are allergic to CM and/or egg. To a smaller extent, desensitization to wheat is also practiced, while desensitization to foods such as peanut and hazelnut is still negligible, since the prevalence of these allergies in Italy is low.
Food is administered uncooked in 47.6%, and cooked in 28.6% of the centres. Food in wheat matrix is administered in 21.4% and freeze-dried food in 2.4% of the centres. Food preparation is still a controversial aspect of OFD, particularly with respect to egg. Consequently, while some protocols use raw egg (10,11), other protocols using freeze-dried egg have also been used (25). The possibility of inducing tolerance towards cooked egg proteins contained in cooked products would allow children to considerably broaden their diet, since children only occasionally consume uncooked egg. The risk connected with different cooking methods (poaching, frying, baking) still needs to be evaluated and the different cooking methods should be standardized (26).
Management of adverse reactions during OFD (**table 4**). Since the majority of the allergy centres also administer OFD to patients with previous history of anaphylaxis (**table 2**, 68%), care-givers should take into account possible severe adverse reactions, which may necessitate management with an appropriate therapy. Moreover, children undergoing OFD in hospital settings should receive venous access for the prompt administration of an intravenous therapy. Drugs should be prepared before administering the food dose, ready for use. Moreover, parents should always receive a copy of an action plan for drug interventions at home. After applying the action plan instructions, parents should keep in touch with the pediatrician (possibly via mobile phone).
Drugs used in case of OFD adverse reactions (intramuscular epinephrine and/or steroids) have to be chosen according to the severity of the reaction (27). As mild to moderate reactions are more frequent, antihistamines were among the most widely administered drugs. During the treatment at home, allergy centres often try to minimize the risk of adverse reactions through the daily administration of doses which are much smaller than those tolerated in hospital. Nevertheless, some protocols establish a gradual and constant food introduction at home too (4,11). Parents should be also alerted about the possibility that some

factors, such as physical exercise, respiratory and gastroenteric infections, and the administration of gastro-damaging drugs may induce the loss of food tolerance and trigger possible severe adverse reactions (28).

Follow-up management (**table 5**). When the protocol is completed, one problem is how to continue consuming the tolerated food, even in the case of partial tolerance. Indeed, while some subjects may reach a definitive food tolerance, others maintain tolerance to the offending food only if they consume it constantly, even if not daily (5,7). Some children who consumed the food occasionally, reported the occurrence of previously experienced reactions (36.4%). This finding is consistent with current literature (5), but is a very controversial point. The occasional consumption of the food should be allowed only if a significant decrease of specific IgEs or of the SPTs intensity is observed. In our opinion, subjects who, at the completion of the protocol, tolerate the food but show a high persistence of specific IgEs, should be prescribed daily consumption. Indeed, specific IgEs decrease and reduction of SPTs reaction intensity are the most reliable indicators of the efficacy of OFD. Furthermore, as we already pointed out, OFD is highly specific and IgEs decrease regards only the food to which the subject is allergic and for which he/she has been submitted to OFD (29).

The child who has reached food tolerance through OFD must be monitored by means of outpatient controls over time, in order to establish whether the achieved tolerance is persistent or not (30).

Conclusion

Our survey shows significant differences in the way the Italian allergy centres conduct OFD. Indeed, although this procedure often results in clinical success, and in selected patients may be considered a valid alternative to the elimination diet, further and appropriately designed RCTs are still needed before OFD can be considered a routine procedure in specialized centres. In addition to OFD safety, efficacy and costs, RCTs should be aimed at defining indications, food preparation methods and administration protocols. Moreover, in our opinion, further studies should also better investigate achievement of a definitive food tolerance, through an evaluation of specific immunological parameters during OFD.

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