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ORIGINAL ARTICLE

Frequency of positive oral food challenges and their outcomes in the allergy unit of a tertiary-care pediatric hospital

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Abstract

Introduction and objective: The oral food challenge (OFC) is the gold standard to diagnose food allergy (FA); however, it is not a procedure free from the risk of having significant allergic reactions, even life-threatening.

The aims of our study were to evaluate the frequency of positive OFCs performed in children with a suspected diagnosis of IgE- and non-IgE-mediated (food protein-induced enterocolitis syndrome (FPIES)) FA and how the failed challenges were managed.

Materials and methods: A retrospective chart review was done on all children who have had OFCs in a tertiary-care pediatric allergy unit from 2017 to 2019.

Results: 682 patients were enrolled and 2206 challenges were performed: 2058 (93%) for IgE-mediated FA and 148 (7%) for FPIES. There were 262 (11.8%) challenge failures. The transfer to the emergency department was required 3 times (1.1%). None of the failed challenges resulted in death or hospitalization and 13.3% challenges did not require any treatment.

Conclusions: Our findings confirm that food challenges can be performed safely in a specialized setting by well-trained personnel; all food challenge reactions, even the most serious, were reversible, thanks to a prompt recognition and treatment that generally did not worsen over time.

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Introduction

The oral food challenge (OFC) is the gold standard to diagnose IgE- and non-IgE-mediated food allergy (FA). Moreover, OFC is performed to verify whether tolerance to the offending food has been achieved.[1] However, the OFC carries the risk of significant allergic reactions which may require a prompt treatment.[2,3] The rate of systemic reactions depends on the inclusion criteria of the enrolled population[1]: in children with IgE-mediated FA, Perry et al.[2] have identified 28% of severe reactions, of which 11% have required epinephrine administration. Similar data were found in a Japanese multicentric study: allergic reactions occurred in 44.6% cases, but epinephrine administration was necessary in 7.1%-positive OFCs.[4]

In children with food protein-induced enterocolitis syndrome (FPIES), Wang et al.[5] reported 18% of positive OFCs, of which 72.2% required intravenous (IV) drug administration; instead, Pena et al. study[6] reported 39 positive OFCs, but severe reactions that required an IV treatment were fewer than 10%.

Because of its features, the OFC should be performed in specialized centers with emergency care facilities and by trained healthcare professionals who are responsible for managing adverse reactions.[1]

The aims of our study were to evaluate the frequency of positive OFCs performed in children with a suspected diagnosis of FA in a tertiary-care pediatric hospital and how the failed challenges were managed.

Material and methods

All the children, referred to the Allergy Unit of Meyer Children's Hospital in Florence (Italy), with suspected IgE-mediated FA and FPIES were retrospectively enrolled from 2017 to 2019. The suspicion of IgE-mediated FA was based on the suggestive clinical history as well as on the cutaneous tests results [Skin Prick Tests (SPTs) and Prick by Prick (PbP)] and the serum-specific IgEs (s-IgEs) to trigger food allergens. The SPTs were performed using commercial allergen extract (Alk Abellò, Milan, Italy), and the PbP technique was performed by using fresh food when the commercial allergen extract was not available. The positive result for SPT and PbP was considered when the mean of wheal diameter was ≥3 mm. The detection of s-IgEs was performed for the available allergenic foods by using ImmunoCAP (Thermo Scientific, Uppsala, Sweden) and was considered positive for a value ≥0.10 kU/L. The allergic tests (SPT or PbP and/or s-IgE) performed for each offending food are summarized in Tables 1 (for IgE-mediated FA) and 2 (for non-IgE-mediated FA).

For IgE-mediated FA, the OFC consisted in the administration of incremental doses of food protein every 20 minutes until a final dose equivalent to an "age-appropriate" portion was tolerated following the PRACTALL Consensus[7] and the EAACI guidelines.[8] The OFC was considered positive if there were objective symptoms like hives, angioedema, vomiting, diarrhea, bronchospasm, rhinitis, and conjunctivitis within 2 hours after administration of the last food dose, which is the frame-time of observation in the hospital setting. Patients were observed for 2 hours after the final dose. If there was a reaction, patients were observed for a minimum of 2 hours, until objective signs of the reaction had resolved. The diagnosis of FPIES was based on the criteria of the latest international guidelines.[9] When the criteria for diagnosing FPIES were not met, children with suspected FPIES underwent diagnostic OFC as soon as possible after recovering from the reaction. The OFC was performed with the trigger food from 12 to 18 months after the last FPIES episode to verify whether tolerance to the offending food had been achieved. Moreover, patients who have had FPIES to liquid and/or solid food underwent OFCs with moderate-high risk foods (legumes, rice, wheat, poultry, red meat, fish, milk, soy, egg, banana), never eaten before. An IV access was always secured. The OFC procedure was performed following the protocol described by Barni S. et al.[10] It consisted in administering 25% of the full dose, calculated as 0.3 g of food protein per kilogram of body weight, and, in the absence of adverse reactions, the remaining dose was administered 4 hours later, followed by another 4 hours of observation. The OFC was considered positive

Table 1 The offending food tested in the IgE-mediated oral food challenges and the allergic tests (skin prick test or prick by prick and/or serum-specific IgE) performed.

Family groups N (%)	Specific food	All OFCs N (%)	Positive OFC N (%)	SPT	PbP	s-IgE
Tree nuts 637 (30.9%)	*Walnut*	155 (24)	25 (10)	×	✓	✓
	Hazelnut	128 (20)	32 (13)	×	✓	✓
	Almond	105 (16.4)	4 (1.6)	×	✓	✓
	Pine nut	91 (14.2)	17 (6.9)	×	✓	✓
	Pistachio	78 (12.2)	7 (2.8)	×	✓	✓
	Cashew	76 (11.9)	4 (1.6)	×	✓	✓
	Brazil nut	4 (0.6)	0 (0)	×	✓	✓
Milk 517 (25.1%)	*Cow's milk*	466 (90.1%)	44 (17.7)	×	✓	✓
	Goat's milk	16 (3)	1 (0.4)	×	✓	✓

(Continued)

Table 1 (Continued)

Family groups N (%)	*Specific food*	All OFCs N (%)	Positive OFC N (%)	SPT	PbP	s-IgE
	Donkey's milk	13 (2.4)	0 (0)	×	✓	✓
	Infant formula	10 (1.9)	0 (0)	×	✓	×
	Soy milk	8 (1.5)	0 (0)	×	✓	✓
	Sheep's milk	4 (0.8%)	1 (0.4)	×	✓	✓
Egg 361 (17.5%)	*Hen's egg*	361 (100)	49 (19.8)	✓	×	✓
Legumes 189 (29.6%)	*Peanut*	144 (76)	14 (5.7)	×	✓	✓
	Lentils	15 (8)	1 (0.4)	×	✓	✓
	Beans	11 (5.8)	0 (0)	×	✓	✓
	Chickpeas	9 (4.7)	1 (0.4)	×	✓	✓
	Lupin	7 (3.7)	0 (0)	×	✓	✓
	Soy bean	3 (1.6)	0 (0)	×	✓	✓
Fish and shellfish 133 (6.4%)	*Shrimp*	40 (30)	0 (0)	×	✓	✓
	Tuna	21 (15.7)	0 (0)	×	✓	✓
	Sole	14(11.2)	0 (0)	×	✓	✓
	Cod	12 (9)	0 (0)	×	✓	✓
	Swordfish	8 (6)	0 (0)	×	✓	✓
	Salmon	8 (6)	0 (0)	×	✓	✓
	Clam	7 (5.2)	0 (0)	×	✓	✓
	Squid	4 (3)	0 (0)	×	✓	✓
	Octopus	4 (3)	0 (0)	×	✓	✓
	Trout	4 (3)	0 (0)	×	✓	✓
	Mussel	3 (2.2)	0 (0)	×	✓	×
	Hake	3 (2.2)	0 (0)	×	✓	✓
	Sea bream	3 (2.2)	0 (0)	×	✓	✓
	Plaice	2 (1.5)	0 (0)	×	✓	✓
Fresh fruit 84 (4%)	*Kiwi*	24 (28.5)	1 (0.4)	×	✓	✓
	Peach	13 (15.4)	0 (0)	×	✓	✓
	Wild berries	10 (11.9)	0 (0)	×	✓	×
	Apple	8 (9.5)	0 (0)	×	✓	✓
	Strawberry	5 (5.9)	0 (0)	×	✓	✓
	Plum	5 (5.9)	0 (0)	×	✓	✓
	Apricot	4 (4.7)	0 (0)	×	✓	✓
	Orange	4 (4.7)	2 (0.8)	×	✓	✓
	Grapes	3 (3.5)	0 (0)	×	✓	✓
	Banana	3 (3.5)	0 (0)	×	✓	✓
	Pear	3 (3.5)	0 (0)	×	✓	✓
	Cherries	2 (2.3)	0 (0)	×	✓	✓
Cereals 57 (2.7%)	*Wheat*	37 (64.9)	7 (2.8)	✓	×	✓
	Corn	13 (22.8)	0 (0)	✓	×	✓
	Rice	5 (8.8)	0 (0)	✓	×	✓
	Oat	1 (1.8)	0 (0)	✓	×	✓
	Barley	1(1.8)	2 (0.8)	✓	×	✓
Meats 32 (1.5%)	*Rabbit*	17 (53.1)	0 (0)	✓	×	✓
	Turkey	10 (31.3)	0 (0)	✓	×	✓
	Chicken	3 (9.4)	0 (0)	✓	×	✓
	Veal	1 (3.1)	0 (0)	✓	×	✓
	Pork	1 (3.1)	0 (0)	✓	×	✓
Vegetables 28 (1.3%)	*Tomato*	15 (53.6)	0 (0)	×	✓	✓
	Celery	8 (28.6)	0 (0)	×	✓	✓
	Spinach	5 (17.9)	0 (0)	×	✓	✓
Seeds 20 (1%)	*Sesame*	12 (60)	7 (2.8)	×	✓	✓
	Sunflower	6 (30)	0 (0)	×	✓	✓
	Linseed	2 (10)	0 (0)	×	✓	✓

The percentage of the family group is calculated on the total number of performed challenges, the percentage of the specific food is calculated on the number of the performed family groups' challenge.
Legend: s-IgE: serum-specific IgE; SPT: skin prick test; PbP: Prick by Prick; ×: not performed; ✓: performed.

Table 2 The offending food tested in the non-IgE-mediated oral food challenges and the allergic tests (skin prick test or prick by prick and/or serum-specific IgE) performed.

Family groups N (%)	Specific food	All OFCs N (%)	Positive OFCs N (%)	SPT	PbP	s-IgE
Milk 27 (18.4)	*Cow's milk*	27 (100)	5 (35.7)	×	✓	✓
Egg 16 (10.8)	*Hen's egg*	16 (100)	3 (21.4)	✓	×	✓
Fish	*Sole*	8 (72.7)	3 (21.4)	×	✓	✓
11 (7.4)	*Shrimp*	1 (9)	1 (7.1)	×	✓	✓
	Plaice	1 (9)	1 (7.1)	×	✓	✓
	Swordfish	1 (9)	1 (7.1)	×	✓	✓
Meats	*Rabbit*	3 (27.3)	0 (0)	✓	×	✓
11 (7.4)	*Turkey*	3 (27.3)	0 (0)	✓	×	✓
	Chicken	3 (27.3)	0 (0)	✓	×	✓
	Veal	2 (18.2)	0 (0)	✓	×	✓
Cereals	*Rice*	3 (42.9)	0 (0)	✓	×	✓
7 (4.7)	*Corn+tapioca*	3 (42.9)	0 (0)	✓	×	✓ (only corn)
	Wheat	1 (14.3)	0 (0)	✓	×	✓
Fresh fruit	*Banana*	5 (83.3)	0 (0)	×	✓	✓
6 (4.1)	*Pear*	1 (16.7)	0 (0)	×	✓	✓
Legumes	*Soy bean*	4 (66.7)	0 (0)	×	✓	✓
6 (4.1)	*Lentils*	2 (33.3)	0 (0)	×	✓	✓

The percentage of the family group is calculated on the total number of performed challenges, the percentage of the specific food is calculated on the number of the performed family groups' challenge.
Legend: s-IgE: serum-specific IgE; SPT: skin prick test; PbP: Prick by Prick; ×: not performed; ✓: performed.

according to the diagnostic criteria of the international guidelines of FPIES.[8] The OFC symptoms were classified into mild, moderate, and severe according to Niggemann's classification[11] for IgE-mediated FA and to the diagnostic criteria guidelines for FPIES.[9] All data were collected in a database. For each patient, the following items were registered: date of birth, sex, SPT/PbP and s-IgE results to the culprit food, food tested during OFC, OFC outcome, clinical manifestations during positive OFC, administered drugs and route of administration, and the access to the emergency department (ED) (yes/no). Written informed consent was obtained from the children's parents for all procedures performed. The audit code issued by our hospital (Meyer Children's University Hospital) is IR904-17-23411.

Descriptive data were expressed as mean values ± standard deviation (SD). The means were compared using the Student's t-test, and the percentages were compared using a chi-square test. All the significance tests were two-sided, and a P-value of <0.05 was considered statistically significant. The SPSS 14.0 package for Windows (SPSS Inc., Chicago, IL) was used for the statistical analysis.

Results

Six-hundred and eighty-two patients [440 males (64.5%) and 242 females (35.5%)] were enrolled, and 2206 OFCs were performed: 2058 (93%) for IgE-mediated FA and 148 (7%) for FPIES.

IgE-mediated FA

Six-hundred and twenty-eight of 682 (92%) patients presented IgE-mediated FA: 415 males (66%) and 213 females (34%) with a median age of 8.7 years ± 8.4 SD (range 1 to 18 years). One-hundred and seventy-six patients of 628 (28%) patients presented FA to multiple foods. Two-hundred and twenty-five patients (35.8%) were affected by atopic dermatitis (AD), 114 patients (18.2%) by asthma, 167 patients (26.6%) by allergic rhinitis, and 397 (63.2%) had a family history of allergy.

Before the OFC, cutaneous tests were performed in all children, while s-IgEs were detected in 565 (90%) patients. The results of SPTs and s-IgE to each culprit food are summarized in Table 3.

Two-thousand and fifty-eight OFCs were performed (696 OFCs for diagnostic purpose, 1362 OFCs for follow-up) in 628 children. For each child, a mean of 3.4 OFCs (range 1 to 17) was performed: 511/628 (81.3%) children underwent from 1 to 5 OFCs, 111/628 (17.6%) more than 5 OFCs and the 6/628 (1.8%) more than 10 OFCs. The offending foods are described in Table 1.

Two-hundred and forty-eight (12%) of 2058 challenges were positive (58 diagnostic OFCs and 190 follow-up OFCs)

Table 3 The results of SPT and s-IgE to the offending foods in children with IgE-mediated food allergy.

Family groups	*Specific food*	N (%)	SPT or PbP mean ± SD (range) mm	s-IgE mean ± SD (range) KU/l
Milk	*Cow's milk*	109 (17.4)	5.3 ± 2.2 (3-18)	27.3 ± 4.6 (0.12-100)
	Goat's milk	5 (0.8)	7.2 ± 6.8 (3-20)	19.6 ± 5.2 (0-18-54.6)
	Donkey's milk	4 (0.6)	5 ± 2.7 (3-8)	16.8 ± 6.3 (0.2-28.9)
	Infant formula	3 (0.5)	6.9 ± 3.2 (3-10)	np
	Soy milk	4 (0.6)	5.2 ± 1.4 (3-7)	23.4 ± 4.9 (0.38-40.1)
	Sheep's milk	1 (0.2)	6 ± 0 (6-6)	19.9 ± 0 (19.9-19.9)
Egg	*Hen's egg*	99 (15.8)	5.3 ± 2.8 (3-13)	7.08 ± 6.9 (0.13-100)
Fish and shellfish	*Shrimp*	14 (2.2)	4.3 ± 1.2 (3-10)	11.9 ± 7.4 (0.21-33.8)
	Tuna	8 (1.3)	4.7 ± 3.8 (3-7)	5.3 ± 2.8 (0.28-11.4)
	Sole	7 (1.1)	3.8 ± 2.2 (3-5)	1.8 ± 1.2 (0.30-3.4)
	Cod	4 (0.6)	3 ± 0.5 (3-3)	0.4 ± 0.8 (0.24-1.8)
	Swordfish	2 (0.3)	3 ± 0.8 (3-3)	1.6 ± 0.6 (0.80-3.8)
	Salmon	4 (0.6)	4 ± 1.2 (3-5)	6.3 ± 2.4 (1.9-10.4)
	Clam	2 (0.3)	3 ± 0 (3-3)	0.8 ± 0.5 (0.31-3.2)
	Squid	2 (0.3)	3 ± 0 (3-3)	1.9 ± 0.8 (0.28-4.1)
	Octopus	1 (0.2)	3 ± 0 (3)	2.1 ± 0 (2.1-2.1)
	Trout	1 (0.2)	3 ± 0 (3-3)	3.2 ± 0 (3.2-3.2)
	Mussel	1 (0.2)	3 ± 0 (3-3)	np
	Hake	1 (0.2)	3 ± 0 (3-3)	3.1 ± 0 (3.1-3.1)
	Sea bream	1 (0.2)	3 ± 0 (3-3)	3.2 ± 0 (3.2-3.2)
	Plaice	1 (0.2)	3 ± 0 (3-3)	1.8 ± 0 (1.8-1.8)
Fresh fruit	*Kiwi*	13 (2)	5.2 ± 1.8 (3-13)	14.7 ± 5.6 (0.68-36.8)
	Peach	6 (0.9)	3.8 ± 2.1 (3-7)	6.1 ± 4.8 (0.25-28.7)
	Wild berries	2 (0.3)	3.5 ± 0.6 (3-4)	np
	Apple	4 (0.6)	3.5 ± 2.8 (3-5)	5.8 ± 2.7 (0.85-11.9)
	Strawberry	3 (0.5)	4.2 ± 1.1 (3-7)	6.6 ± 3.4 (1.2-15.7)
	Plum	3 (0.5)	3.7 ± 2.3 (3-6)	3.3 ± 1.2 (0.7-5.9)
	Apricot	2 (0.3)	3.5 ± 0.6 (3-4)	3.9 ± 0.6 (0.3-8.7)
	Orange	2 (0.3)	3.5 ± 0.7 (3-4)	3.5 ± 0.7 (0.5-7.6)
	Grapes	1 (0.2)	3 ± 0 (3-3)	1.6 ± 0 (1.6-1.6)
	Banana	5 (0.8)	3.3 ± 0.6 (3-4)	7.2 ± 4.2 (0.7-35.6)
	Pear	1 (0.2)	3 ± 0 (3-3)	1.7 ± 0 (1.7-1.7)
	Cherries	1 (0.2)	3 ± 0 (3-3)	1.3 ± 0 (1.3-1.3)
Tree nuts	*Walnut*	95 (15)	5.8 ± 2.3 (3-18)	23.5 ± 4.6 (0.10-100)
	Hazelnut	83 (13.2)	8.6 ± 6.4 (3-20)	18.9 ± 3.2 (0.28-100)
	Almond	31 (5)	5.3 ± 1.4 (3-11)	8.7 ± 4.3 (0.32-40.8)
	Pine nut	21 (3.3)	6.2 ± 2.8 (3-17)	14.3 ± 3.2 (0.15-100)
	Pistachio	11 (1.8)	8.4 ± 3.2 (3-18)	7.8 ± 3.8 (0.18-100)
	Cashew	9 (1.4)	5.7 ± 0.9 (3-14)	5.2 ± 1.2 (0.21-58.7)
	Brazil nut	1 (0.2)	3 ± 0 (3-3)	4.6 ± 0 (4.6-4.6)
Legumes	*Peanut*	23 (3.7)	8.3 ± 3.4 (3-20)	7.4 ± 2.1 (0.10-100)
	Lentils	2 (0.3)	9.5 ± 0.6 (9-10)	2.1 ± 0.6 (0.10-28.9)
	Beans	2 (0.3)	7 ± 0.6 (6-8)	6.3 ± 0.6 (0.38-11.5)
	Chickpeas	2 (0.3)	5.5 ± 0.6 (5-6)	2.2 ± 0.6 (0.21-4.78)
	Lupin	1 (0.2)	6 ± 0 (6-6)	2.9 ± 0 (2.9-2.9)
	Soy bean	2 (0.3)	8.6 ± 2.8 (3-17)	5.7 ± 1.7 (0.10-21.4)
Cereals	*Wheat*	8 (1.3)	4.1 ± 1.8 (3-5)	14.8 ± 3.8 (0.91-41.5)
	Corn	2 (0.3)	3 ± 0 (3-3)	11.2 ± 0.6 (0.76-22.3)
	Rice	2 (0.3)	3.5 ± 0.6 (3-4)	6.7 ± 0.6 (1.3-10.2)
	Oat	1 (0.2)	3 ± 0 (3-3)	9.3 ± 0 (9.3-9.3)
	Barley	1 (0.2)	3 ± 0 (3-3)	5.7 ± 0 (5.7-5.7)

(Continued)

Table 3 (Continued)

Family groups	Specific food	N (%)	SPT or PbP mean ± SD (range) mm	s-IgE mean ± SD (range) KU/l
Meats	*Rabbit*	2 (0.3)	3.5 ± 0.6 (3-4)	1.2 ± 0.6 (0.11-0.86)
	Turkey	1 (0.2)	3 ± 0 (3-3)	0.2 ± 0 (0.2-0.2)
	Chicken	1 (0.2)	3 ± 0 (3-3)	0.26 ± 0 (0.26-0.26)
	Veal	1 (0.2)	3 ± 0 (3-3)	0.7 ± 0 (0.7-0.7)
	Pork	1 (0.2)	3 ± 0 (3-3)	0.18 ± 0 (0.18-0.18)
Vegetables	*Tomato*	1 (0.2)	5 ± 0 (5-5)	48.3 ± 0 (48.3-48.3)
	Celery	1 (0.2)	3 ± 0 (3-3)	11.4 ± 0 (11.4-11.4)
	Spinach	1 (0.2)	3 ± 0 (3-3)	0.23 ± 0 (0.23-0.23)
Seeds	*Sesame*	3 (0.5)	9.8 ± 2.5 (3-10)	21.8 ± 4.7 (2.67-22.8)
	Sunflower	1 (0.2)	4 ± 0 (4-4)	5.1 ± 0 (5.1-5.1)
	Linseed	1 (0.2)	3 ± 0 (3-3)	9.4 ± 0 (9.4-9.4)

Legend: SD: standard deviation; PbP: prick by prick; s-IgE: serum-specific IgE; SPT: skin prick test.

in 181 children. The offending foods and the demographic characteristics of patients with positive OFCs are summarized in Tables 1 and 5, respectively. Fifty-two of 628 patients (8.3%) had more than one positive OFC. Older children were significantly more likely to fail an OFC than younger children (10.8 vs 6.9 years; p=0.01), as those affected by AD (69% vs 53%; p=0.03) and asthma (58% vs 37%; p=0.002), whereas children with rhinitis were not more likely at risk to have a positive OFC (41% vs 39%; p=0.3). Four-hundred and fifty-three reactions to different offending foods were reported. The cutaneous symptoms were the most common (174 OFCs, 70.2%), followed by gastrointestinal ones (169 OFCs, 68.1%). Respiratory symptoms were present in 109 OFCs (43.9%). The neurologic symptom (drowsiness) was present in one OFC (0.4%). No cardiovascular symptoms were presented by children. Anaphylaxis occurred in 15 of 628 (2.4%) children, in particular, the culprit foods were tree nuts in 8 (53.3%) children (3 hazelnuts, 3 walnuts, and 2 pine nuts), milk in 5 (33.3%) children, and egg in 2 (13.3%) children. One child required 2 epinephrine IM administration in 2 different OFCs with cow's milk. A statistically significant difference of the epinephrine use in relation to the offending food was not found.

The symptoms that occurred during a positive OFC were compared between milk, egg, and tree nuts: respiratory symptoms occurred significantly higher in milk OFCs (p=0.005) than in egg [55 (22.2%) vs 13 (5.2%), p=0.005) and tree nuts OFCs [55 (22.2%) vs 30 (12%), p=0.0002]; gastrointestinal symptoms occurred significantly higher in tree nuts OFCs than in egg and milk OFCs [52 (21%) vs 34 (13.7%) vs 32 (12.9%), p=0.0002] as well as cutaneous symptoms [51 (20.6%) vs 34 (13.7%) vs 33 (13.3%), p=0.02)]. The characteristics of symptoms varied by food were summarized in Figure 1.

According to Niggemann's classification,[11] mild reactions (Grade I-IIa) occurred 130 times (52.4%), moderate reactions (Grade IIb) occurred in 41 cases (16.5%), and severe reactions (Grade IIIa-IIIb) occurred 77 times (31%). The severity of reactions during failed OFCs varying by food is reported in Table 4. The SPT and s-IgE values and the type of food were not predictive of OFC reaction severity.

The treatment was necessary in 218 (88%) of 248 children with positive OFC.

Antihistamines were administered in 110/248 OFCs (44.3%), corticosteroids in 98/248 OFCs (39.5%), beta-2 agonists in 27/248 OFCs (10.8%), and epinephrine in 16/248 OFCs (6.4%). Fifty children (19.8%) required a single drug administration.

The routes of administration were in 171 cases per os (78.4%), in 31 cases (14.2%) inhaled, and in 16 cases (7.3%) IM. Epinephrine was always administered IM. None required IV therapy.

Only one child was transferred to the ED due to clinical observation after an anaphylaxis episode, in two different occasions.

FPIES

Fifty-four of 682 patients (8%) were enrolled: 28 males (52%) and 26 females (48%) with a median age of 6 months ± 3.90 SD (range 20 days to 12 months).

The age of the first episode of FPIES was ≤1 month in 2 children (4%), from 2 months to 6 months in 29 (56%) children, and from 7 to 12 months in 21 children (40%). The offending foods were 83: 27 (32%) cow's milk (CM), 16 (19%) egg, 11 (13%) fish [8 sole, 1 shrimp, 1 plaice, and 1 swordfish], 11 (13%) meat [3 rabbit, 3 turkey, 3 chicken, and 2 veal], 7 (8.4%) cereals [3 rice, 3 corn and tapioca, and 1 wheat], 6 (7.2%) fresh fruit [5 banana and 1 pear], and 6 (7.2%) legumes [4 soy and 2 lentils].

Thirty-seven patients (68.5%) presented FPIES to a single food, while 17 (31.5%) patients had FPIES to multiple foods. For each child a mean of 1.6 offending foods (range 1-11) was reported.

The SPT/PbP and/or s-IgE performed for each specific food are summarized in Table 2.

The PbP/SPTs to the culprit food were performed in all patients; s-IgEs were requested in 53 (98%) patients. The SPT/PbP was positive in 8 children (14.8%), and s-IgEs were positive in 10 children (18.5%). Ten patients (18.5%) presented atypical FPIES.

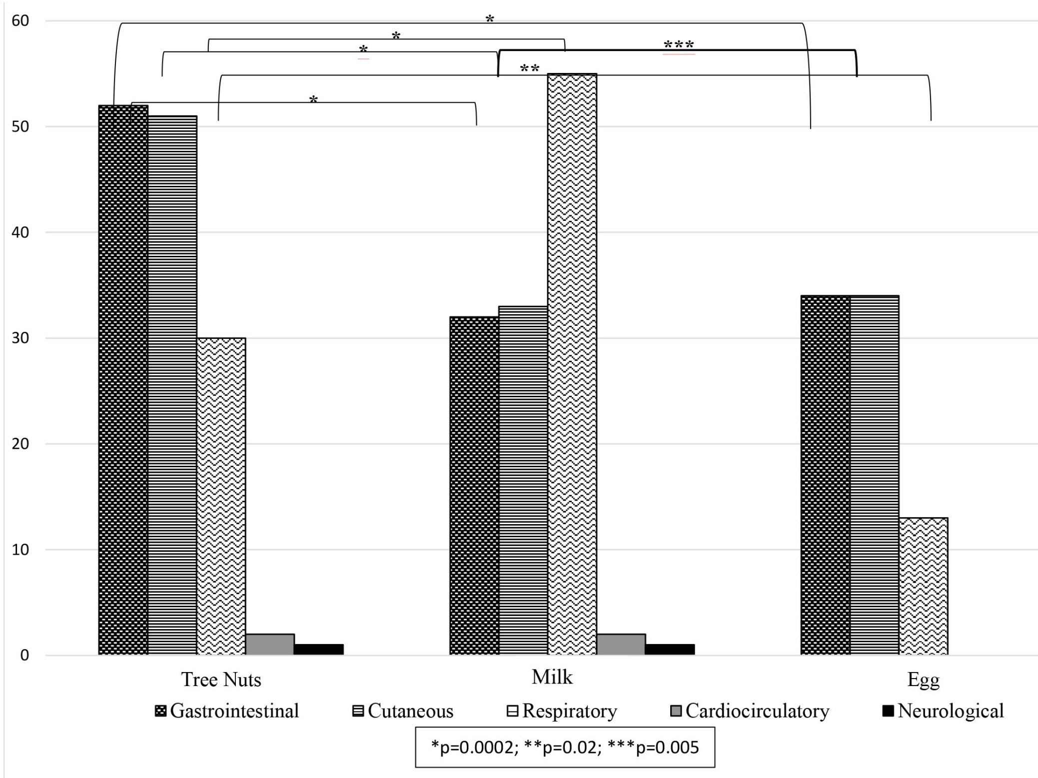

Figure 1 Clinical characteristics of positive oral food challenges in children with IgE-mediated food allergy.

One-hundred and forty-eight OFCs were performed in 54 children: 46 patients (85.2%) underwent from 1 to 5 OFCs and 8 (14.8%) more than 5 OFCs. For each patient, a mean of 4.5 OFCs (range 1–11) was performed. Sixty-seven OFCs (45.3%) were performed to introduce the medium- to high-risk foods in hospital, 60 (40.5%) to verify the achievement of tolerance to the offending food, and 21 (14.2%) OFCs were diagnostic with a mean age of 4.7 months ± 3.09 SD (range 3 to 6 months).

Fourteen of 148 (9.5%) OFCs were positive (10 diagnostic OFCs and 4 OFCs to verify the achievement of tolerance) in 12 children. The offending foods and the demographic characteristics of patients with positive OFCs are summarized in Tables 2 and 5, respectively.

All patients (100%) presented vomiting: 8 children (57.2%) in association with lethargy and pallor and in 6 children (42.8%) in association with lethargy and diarrhea.

According to the international guidelines for FPIES classification,[9] mild reactions occurred in 6 OFCs (42.8%) [2 times (33.3%) with egg, 2 (33.3%) with CM and 2 (33.3%) with fish], moderate reactions occurred in 3 OFCs (21.4%) [2 cases (66.6%) with fish and 1 (33.3%) with CM], and severe reactions occurred in 5 OFCs (35.7%) [2 (40%) with fish, 2 (40%) with CM and 1 (20%) with egg].

The therapy was administered in 9 patients of 14 (70%): 8 children (47%) received physiological solution IV, of which 4 (50%) in association with IV corticosteroid and 6 (75%) in association with an antiemetic. Five patients (42.8%) did not require any treatment.

Only one child was transferred to the ED due to persistent vomiting, hypotonia, and drowsiness despite the therapy given in Allergy Unit.

Discussion

To our knowledge, our single-center retrospective study represents the one with the highest number of OFCs (2206) performed; moreover, it involves a considerable number of children (682) with IgE- or non-IgE-mediated FA including in the analysis all the tested foods and not only the three "big ones," i.e., CM, egg, and tree nuts.

Table 4 The severity of reactions during failed oral food challenges in IgE-mediated food allergy.

	Milk (n=74)	Egg (n=49)	Tree nuts (n=90)	Cereals (n=9)	Seeds (n=7)	Fresh fruit (n=3)	Legumes (n=16)	Total (n=248)
Mild	30 (40.5%)	37 (75.5%)	31 (34.4%)	5 (55.5%)	5 (71.4%)	2 (66.6%)	13 (81.2%)	130 (52.4%)
Moderate	15 (20.2%)	5 (10.2%)	23 (25.5%)	1 (11.1%)	0 (0%)	0 (0%)	3 (18.7%)	41 (16.5%)
Severe	29 (39.1%)	7 (14.2%)	35 (38.8%)	3 (33.3%)	2 (28.5%)	1 (33.3%)	0 (0%)	77 (31%)

Table 5 Demographic characteristics of children with positive OFCs (IgE-mediated and non-IgE-mediated food allergy).

	IgE-mediated food allergy	Non-IgE-mediated food allergy
	Positive OFCs (n=248)	Positive OFCs (n=14)
Male, n (%)	154 (85.1)	10 (83.3)
Median age at first reaction (months ± SD)	1176 months (±19.04)	6.5 months (± 3.8)
Atopic dermatitis, n (%)	155 (85.6)	2 (16.7)
Asthma, n (%)	66 (36.5)	0 (0)
Rhinitis, n (%)	68 (37.6)	0 (0)
Family history of allergy, n (%)	159 (87.8)	7 (58.3)
Concomitant non-IgE-mediated food allergy to different food group, n (%)	0 (0)	5 (41.7)
Concomitant IgE-mediated food allergy to different food group, n (%)	117 (64.6)	0 (0)

For IgE-mediated FA, our population was composed by 66% of males like those of Akuete et al.'s[12] study according to the epidemiology of FA which mainly affects males. In our study, the mean age of children at the moment of OFC was higher than in other Italian, American, and Asian studies[13,14,15] [8.7 years ± 8.4 SD (range 1–18 year) vs 5 years]. This result is due to the fact that, being a third-level hospital with 50% extra-regional attractiveness, often the patients who come to our observation have already been evaluated by other allergy centers and come to our allergy unit for diagnosing an FA. OFCs, however, were performed most commonly in the range from 5 to 10 years (204, 32.5%). One-hundred and seventy-six (28%) patients presented FA to multiple foods, and 2058 OFCs were performed with a mean of 3.4 OFCs for each patient.

Differently from previous studies, in our population SPT/PbP sizes and s-IgEs levels did not predict the severity of reactions of the OFCs.[2,16,17,18] In particular, in Perry et al. study,[2] there was a statistically significant trend to have a more serious reaction with an increase in the level of s-IgE only for peanut. Likewise, in Abram et al.[16] and DunnGalvin et al.'s studies,[18] both SPT size and s-IgE level were significantly correlated with challenge failures especially for peanut.

Furthermore, we have not detected any correlation between the tested foods and the severity of the reactions during the OFC, similarly to Perry et al.'s study,[2] whereas in Jarvinen et al.'s study,[19] severity reactions were mainly associated with peanut and tree nuts.

Similarly to Abrams et al.[16] and Itazawa et al.'s[4] studies, we found a significant correlation between the age of children, the rate of atopy, and failed OFCs: older children, in fact, were more likely to fail an OFC than younger ones like those affected by AD and asthma.

OFCs were mostly performed with tree nuts (637 OFCs, 30.9%), milk (517 OFCs, 25.1%), and egg (361, 17.5%) in accordance with an international trend: in Europe and Asia,[20] the most tested foods were CM, egg, wheat, soy, and tree nuts. Twenty (1%) OFCs were performed with seeds and 2.8% of these were positive with sesame seeds. The data confirm the significant prevalence's increase of this allergy especially in industrialized countries and the high risk of an adverse reaction after their intake. According to the heterogeneity of trigger foods based on the geographical origin of the cohorts, hazelnut is more common in Europe, while walnut and cashew are mainly found in USA cohorts, whereas Brazilian nut, almond, and walnut are mainly found in UK.[21] Although peanut is considered a high-risk food which can lead to severe and fatal reactions such as anaphylaxis,[16] in our study, adverse reactions to peanut were reported 13.8% times, and it never caused anaphylactic reaction.

Comparing our results to those reported in Abrams et al.[16] and Itazawa et al.'s studies,[4] a significant difference is found in the positivity rate of OFCs: 12% versus 33% versus 44.6%, respectively.

The reason for this finding may be partially related to the fact that some authors[4] considered the OFCs as positive in those children with really mild and subjective symptoms. On the other hand, our result is similar to that reported by Fleischer et al.'s study[22] in which 11% of the OFCs were positive.

We found that anaphylaxis occurred in 6.4% of the positive OFCs (0.8% of 2058 OFCs), this rate is much lower than the one found by Abrams et al. (19%)[16] but barely higher than in Akuete et al. (2%)[12] and Calvani et al.'s study (2.4%).[23]

The food mostly tested during OFC was tree nuts like in Abrams et al.'s study.[16] On the contrary, Perry et al.'s study revealed that the prevalence of severe reactions was with egg (38%), wheat (33%), and milk (27%).[2]

The milk ranked in second place with 25.1% of the performed OFCs (n=517); similarly to Akuete et al.'s study, milk is one of the most common trigger foods due to its high incidence in Western children.[12] Egg followed the same trend, causing an adverse reaction in 19.8% OFCs (n=49). The Japanese study conducted by Itazawa et al.[4] actually found egg at the first place of challenged foods.

During positive OFCs, cutaneous symptoms were the most common (70.2%) like in Abrams et al.[16] and in Perry et al.'s studies[2] followed by gastrointestinal symptoms (68.1%) and then respiratory symptoms (43.9%). It is encouraging that no cardiovascular symptoms were observed as these symptoms are the most common life-threatening ones during an allergic reaction.

In our study, a significant correlation between the clinical manifestations in failed OFCs and the offending food was found: respiratory symptoms (71.4%) occurred more frequently in OFCs performed with milk. Our results are in contrast with those found in Noone et al.'s study,[24] in which the prevailing symptoms presented by children who underwent OFCs with CM were gastrointestinal (93.7%). In our population, the gastrointestinal symptoms (51.4%) occurred more frequently with tree nuts in contrast with the findings of Abrams et al.[16] that highlighted a clear prevalence of cutaneous symptoms (100%), whereas in a Canadian cohort,[16] respiratory symptoms (40%) occurred after the administration of tree nuts.

According to Niggeman's classification,[11] severe reactions occurred in 31% of children in our population, similarly to Perry et al. study[2] (28%) and to Benhamou's study[25] (37%), although the last one is composed by children with an IgE-mediated allergy to egg.

In our population, the therapy was necessary in 88% (218/248) of patients; epinephrine was used in 2.5% of children and in 6.4% of positive OFCs, and it was always administered IM. We found a considerable discordance between the occurrence of severe reactions (31%) and the administration of epinephrine (6.4%). This result can reflect the fact that OFCs have always been performed in a hospital setting by a highly qualified staff: the medical presence in some cases allowed the adoption of a wait-and-see approach. A similar condition was found in Perry et al.'s study[2]: severe reactions occurred in 28% of the OFCs, but epinephrine administration was administered in 11%. Moreover, a Japanese multicentric study[4] found 2258 positive OFCs, of which 991 (43.9%) were classified as grade 1, 736 (32.6%) were classified as grade 2, 340 (15.1%) were classified as grade 3, and 191 (8.5%) were classified as grade 4–5. Epinephrine was administered only in 7.1% (n = 160) of positive OFCs (44.5% of patients with grade 4–5 of anaphylaxis).

In our population, only one case of transfer to the ED due to anaphylaxis has been documented.

It is worth discussing separately our results related to FPIES, due to its unique characteristics. Although FPIES is defined as a rare disease,[26,27] in our study population, 7.7% of children were affected by FPIES. Although literature suggested that FPIES is prevalent in males,[28] our cohort was almost equally composed by males (51.9%) and females (48.1%). Akin to Blackman et al.'s study,[29] the mean age of the first FPIES episode was 6.7 months ± 3.9 SD of age. Geography returns to play a major role in the incidence of FPIES trigger foods: Nomura et al.'s study[30] and the international guidelines for FPIES[8] prove the heterogeneity of the offending foods according to the geographical origin of the cohort due to different diet habits (i.e., the time of introduction of a food in children's diet).

CM, for example, is the most common trigger food in Italy, USA, and Greece,[31,32,33] confirming the results of our population; rice ranks first in Australia[33,34] and is becoming increasingly frequent in the USA.[29] Fish is prevalent in Mediterranean countries, i.e., Italy, Spain, and Greece,[31,35,36,37] but in our cohort, it was not as widespread as egg (19%). Similarly to Miceli Sopo S. et al.'s study,[38] also among our patients with FPIES to fish (n = 11, 13%), the main trigger fish was the sole (n = 8, 73%).

Cutaneous tests were negative in 85.2% of children. Ten patients (18.5%) presented atypical FPIES in accordance with the incidence of atypical FPIES in other European studies (15.7%).[37] Fourteen of 148 OFCs were positive (9.5%) in 12 children, and 93% of patients presented vomiting which is the hallmark of FPIES.[39,40]

Therapy administration was necessary in 9 patients of 14 (70%): 8 children received physiological solution IV, of which 4 (50%) in association with IV corticosteroid and 6 (75%) in association with an antiemetic. Only one case of serious FPIES that required transfer to the ED has been documented.

The limitations of our study are, first of all, based on the collection of retrospective data and that OFCs are open challenges instead of double-blind placebo controlled, which would be the gold standard to diagnose IgE- and non-IgE–mediated FA. However, its strength is represented by the great number of performed OFCs in a high number of children with a great food variability.

Considering all performed OFCs, 11.8% (262/2206) were positive: the transfer to the ED was required 3 times (1.1%), one case due to a severe FPIES and the other two cases due to anaphylaxis. None of the failed OFCs resulted in death or hospitalization, and 13.3% OFCs did not require any treatment.

In conclusion, our findings confirm that OFCs can be performed safely in a specialized setting by well-trained personnel. We found that all allergic reactions, even the most serious, were reversible, thanks to a prompt recognition and treatment that generally did not worsen over time.

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Conflict of interest

The authors declare not to have conflict of interest.

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