Original Article

Oral Food Challenge Protocols in Food Protein-Induced Enterocolitis Syndrome: A Systematic Review

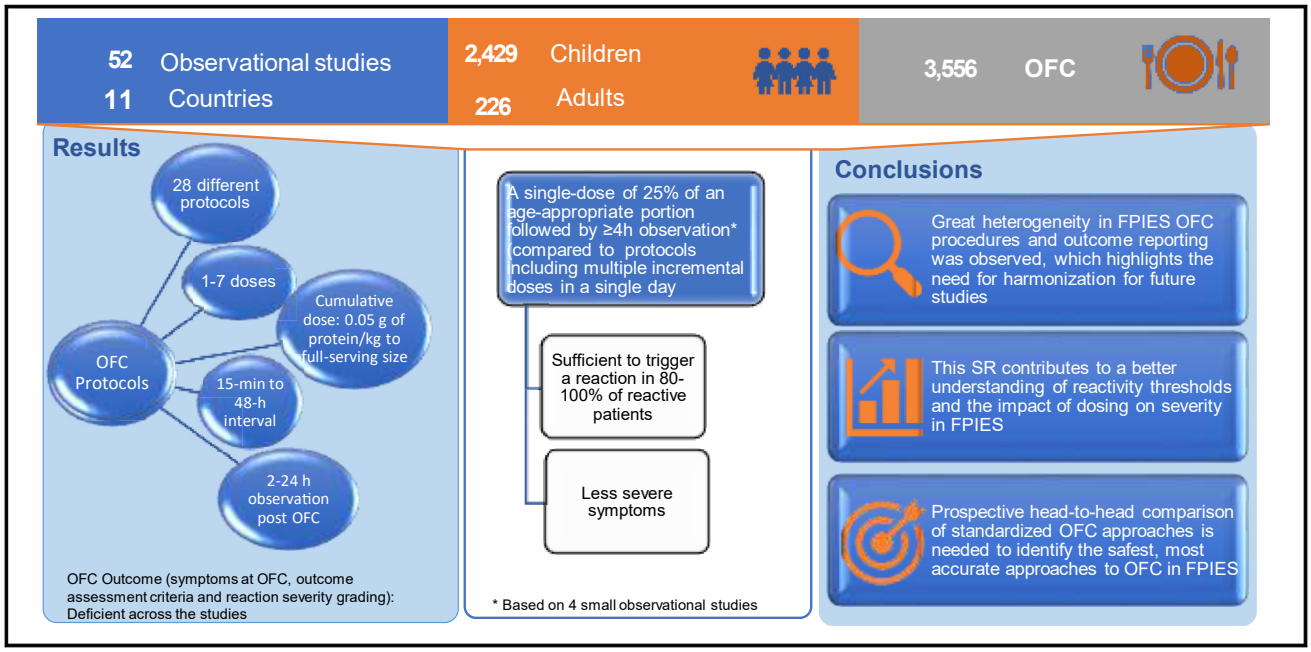
Tayseer Ibrahim, MD, MSc[a], Laura Argiz, MD[b,c], Sonsoles Infante, MD, PhD[d], Stefania Arasi, MD, MSc[e], Ulugbek Nurmatov, MD, MSc, PhD[f], and Marta Vazquez-Ortiz, MD, PhD[g] *Doha, Qatar; Pamplona and Madrid, Spain; Rome, Italy; and Cardiff and London, United Kingdom*

What is already known about this topic?. The current food protein-induced enterocolitis syndrome (FPIES) consensus-recommended oral food challenge (OFC) protocol involves administering 0.3 g protein/kg (maximum of 3 g) in three equal doses over 30 minutes, which is not evidence-based.

What does this article add to our knowledge? The optimal OFC procedure and outcome assessment for patients with FPIES remain unclear. In four small observational studies, administering 25% of an age-appropriate portion followed by at least a 4-hour observation triggered reactions in 80% to 100% of cases and was associated with less severe reactions compared with protocols using multiple (generally larger) doses within a single day.

How does this study impact current management guidelines? Current guideline recommendations may not reflect the safest methods for conducting and assessing OFCs in FPIES. An OFC protocol that starts with 25% of an age-appropriate portion followed by at least 2 to 4 hours of observation may be safer. Further studies are needed to validate this finding.

VISUAL SUMMARY



[a]Allergy and Immunology Division, Department of Medicine, Hamad Medical Corporation, Doha, Qatar
[b]Department of Allergy, Clínica Universidad de Navarra, Pamplona, Spain
[c]RICORS Red De Enfermedades Inflamatorias (REI)— RD21/0002/0028, Madrid, Spain
[d]Pediatric Allergy Unit, Hospital General Universitario Gregorio Marañón, Gregorio Marañón Health Research Institute, IiSGM, Madrid, Spain

Abbreviations used
AAP- Age-appropriate portion
FPIES- Food protein-induced enterocolitis syndrome
OFC- Oral food challenge

BACKGROUND: Oral food challenges (OFCs) are essential for the diagnosis and follow-up of acute food protein-induced enterocolitis syndrome (FPIES) because no diagnostic or prognostic biomarkers are available. However, the optimal OFC procedure remains unclear.
OBJECTIVE: This systematic review aimed to assess OFC procedures' design and clinical outcomes in patients with FPIES.
METHODS: We searched 10 databases for studies published in English between 1978 and February 2024 involving children or adults undergoing OFC for FPIES. Critical appraisal followed Effective Public Health Practice Project parameters.
RESULTS: In total, 52 studies met inclusion criteria, all observational studies. Of these, 35 were judged to have strong methodological quality. There was great heterogeneity in OFC procedures, particularly in cumulative dose, number, size, and timing between doses. Oral food challenge outcome reporting was often inadequate, especially regarding reaction symptoms and severity grading. In single-dose OFC protocols, most children reacted after at least 2 hours. Four small studies showed that a single dose of 25% of an age-appropriate portion was sufficient to trigger reactions in 80% to 100% of cases, and this was associated with less severe reactions. Owing to methodological heterogeneity and insufficient outcome reporting, further assessment of the OFC protocol characteristics associated with safer outcomes was not possible.
CONCLUSIONS: There is significant heterogeneity in FPIES OFC practices. Current recommendations for OFC procedures and outcome assessments have limitations and should be revisited, because this may affect patient safety and diagnostic accuracy. Future studies should focus on standardizing clinical outcomes and generating evidence to support safer, more accurate OFC protocols in FPIES. **(J Allergy Clin Immunol Pract 2025;13:814-32)**

Key words: *Food protein-induced enterocolitis syndrome; Oral food challenge; Food allergy; Tolerance development; non−IgE-mediated food allergy; Systematic review*

INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) is a delayed non−IgE-mediated food allergy primarily affecting infants, characterized by profuse and repetitive vomiting 1 to 4 hours after ingesting the culprit food. Other symptoms may include lethargy, pallor, and diarrhea.[1]

Food protein-induced enterocolitis syndrome can be severe. Up to 20% of patients present with hypotension or shock.[1]

Since Powell's first description in the 1970s,[2] our understanding of FPIES has expanded. However, no specific biomarkers exist for diagnosing FPIES, leading to the development of clinical diagnostic criteria.[1,3-7]

The first FPIES international consensus published in 2017 established the following criteria for acute FPIES diagnosis: vomiting within 1 to 4 hours of ingesting the culprit food (in the absence of IgE-mediated allergy symptoms) as the major criterion, plus three or more minor criteria (repetitive vomiting after ingestion of the same or a different food on a separate occasion, extreme lethargy, marked pallor, diarrhea, hypothermia, the need for intravenous fluid support, or emergency department attendance in a suspected reaction).[1] Thus, FPIES diagnosis depends mainly on clinical history. Given the lack of a diagnostic test, oral food challenges (OFCs) are crucial for confirming the diagnosis in unclear cases, assessing tolerance to related foods, and determining FPIES resolution.[1]

Generally, FPIES has a favorable prognosis in children. However, predicting resolution is challenging without prognostic biomarkers. Tolerance development varies by allergens, geographic location, and population.[8-10] Therefore, regular evaluation by OFCs is essential to determine FPIES resolution in children.

No tests are available to guide safe food introduction in infants with FPIES, which often leads to parental anxiety.[11] The prevalence of multiple food FPIES (and the implicated foods) also varies by region, with rates ranging from 27% to 35% in the United States, United Kingdom, and Australia to 6% in Southern Europe.[9,12-14] To prevent unnecessary dietary restrictions and ensure safe food introductions, OFCs or supervised feeds may be warranted.[1]

Recent reports described FPIES in adults with clinical presentations differing from those in children. In adults, vomiting occurs in approximately 60% of cases, and abdominal pain, nausea, and diarrhea are more commonly reported. This limits using the most accepted FPIES diagnostic criteria and OFC outcome assessment criteria (classically developed for children) in adults. Nonetheless, the resolution of adult-onset FPIES has been observed, underscoring the potential utility of OFCs in adult follow-up.[15,16]

Direct evidence on the optimal cumulative dose, number of doses, and intervals between doses is lacking. It remains unclear what eliciting dose triggers mild but definitive symptoms or whether larger doses may affect reaction severity, leading to significant variability in OFC protocols.[17,18]

The 2017 FPIES consensus recommends an OFC protocol involving a cumulative protein dose of 0.06 to 0.6 g (usually

[e]Allergy Unit, Department of Pediatric Medicine, Bambino Gesù Children's Research Hospital, IRCCS, Rome, Italy
[f]Division of Population Medicine, School of Medicine, Cardiff University, Cardiff, United Kingdom
[g]Section of Inflammation, Repair and Development, National Heart and Lung Institute, Imperial College London, London, United Kingdom
Open Access funding provided by the Qatar National Library.
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication April 3, 2024; revised December 20, 2024; accepted for publication December 24, 2024.
Available online December 31, 2024.

Corresponding author: Tayseer Ibrahim, MD, MSc, Allergy and Immunology Division, Hamad Medical Corporation, Al Rayyan Road, Doha, Qatar. E-mail: tayseer444@yahoo.com.
2213-2198

https://doi.org/10.1016/j.jaip.2024.12.033

0.3 g food protein/kg body weight) given in three equal doses over 30 minutes. The maximum dose is 3 g protein or 10 g total food (or 100 mL liquid), followed by 4 to 6 hours of observation. Lower starting doses and/or longer intervals between doses were advised for patients with a history of severe reactions.[1]

Given the potential for severe reactions during OFCs, the consensus recommended conducting OFCs under medical supervision, with immediate access to fluid therapy and prolonged monitoring.[1] In addition, because the management of reactions includes intravenous treatments (fluids, ondansetron, and corticosteroids), experts advised securing an intravenous line before starting OFC.[19] Hence, the FPIES OFC procedures may require considerable health care resources, highlighting the need for a more efficient approach that balances safety with resource use.

To date, no systematic review of FPIES OFC procedures has been conducted; therefore, this review aims to summarize the published FPIES OFC protocols for children and adults with acute FPIES, assess clinical outcomes, and identify protocol features associated with safer and more accurate clinical outcomes.

METHODS

The systematic review protocol was registered with the International Prospective Register of Systematic Reviews.[20]

Search strategy

Table E1 (in this article's Online Repository at www.jaci-inpractice.org) shows the search strategy developed for Medline OVID. T.I. and L.A. searched databases, including the Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Cochrane Methodology Register), MEDLINE, Embase, CINAHL, AMED, CAB, Global Health, PsycINFO, ISI Web of Science, and TRIP Database for publications from January 1978 to February 2024. Reference lists were manually reviewed, and the first authors were contacted for additional information when appropriate.

Inclusion criteria

We included studies on children and adults with a diagnosis of acute FPIES or suspected of having it (population) that described OFCs used to assess FPIES diagnosis or resolution (intervention). The primary outcome was OFC protocol designs, and the secondary outcome was the clinical outcomes linked to these protocols. We excluded case reports, case series with fewer than five participants, animal studies, non-English articles, and studies focused solely on chronic FPIES.

Screening

The search results were uploaded into an EndNote library. T.I. and L.A. screened titles, abstracts, and full texts against the inclusion criteria. Discrepancies were resolved through discussion or, when necessary, arbitration by a third party (U.N. or M.V.-O.).

Data extraction, analysis, and synthesis

T.I., L.A., and S.I. independently extracted the data of eligible studies into a customized spreadsheet. Disagreements were resolved by arbitration by a third party (U.N. or M.V.-O.).

Quality assessment

T.I., L.A., and S.I. independently assessed the methodological quality of each study using the Effective Public Health Practice Project.[21] Each study was rated as strong, moderate, or weak based on selection bias, study design, confounders, blinding, data collection, and participant withdrawals or dropouts.

RESULTS

Search results

The search yielded 1,140 records, of which 52 articles were included in this review after screening (see Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram in Figure 1).

Included studies and participants' characteristics

Most studies were conducted in Spain (n = 15), followed by the United States (n = 11), Italy (n = 9), Korea and Japan (n = 3 each), Turkey, Greece, Australia, Israel, and France (n = 2 each), and Austria (n = 1) (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Regarding the study design, 27 were retrospective cohorts, 16 were prospective cohorts, four were ambispective, two were case series, and one was a case-control study.

Table E3 (in this article's Online Repository at www.jaci-inpractice.org) lists participants' characteristics; 88% of studies included only children (2,429 patients; 43.7% were female). Five studies included adults (226 patients; 86% were female). One study included children and adults (n = 160). A total of 3,556 OFCs were conducted (3,466 in children and 90 in adults). Diagnostic OFCs were conducted in 64.7% of studies; among those reporting this, 23.6% of patients (72 of 305) underwent diagnostic OFCs.

Quality assessment

Critical appraisal using the Effective Public Health Practice Project rated 35 (67.4%) as strong, 10 (19.6%) as moderate, and seven (13%) as weak (Table E2).

Outcomes

All studies reported the primary outcome of this systematic review (the OFC design), but the secondary outcome reporting was incomplete. Three studies did not report the number of positive OFCs. Definitions of positive OFC and severity grading were provided in 23 and 13 studies, respectively. Nineteen studies reported severity grading. The OFC reaction symptoms were documented in 634 OFCs.

Primary outcome

Design of OFC protocols. There was great heterogeneity in cumulative doses and dosing schedules across the studies, with 28 different protocols reported (Table I).

Cumulative dose. The most common cumulative doses were 0.06 to 0.6 g food protein/kg, used in 14 studies,[4,8,9,22,23,30,32,34,42,43,51,53,54,61] and 0.3 g protein/kg in eight studies,[33,35,37,45,49,58,67,68] with a maximum dose of 3 g protein. Furthermore, if no reaction occurred 4 to 6 hours after administering this dose, an additional dose of an age-appropriate portion (AAP) was administered in eight studies.[28,42,45,49,58,67,68] Eighteen studies used AAP to calculate the cumulative dose.[15,24,28,36,39,41,44,47,52,55-57,59,60,62-64,68] Comparatively lower cumulative doses were used; four studies used 0.15 g protein/kg,[10,25,26,29] two used 0.03 to 0.05 g protein/kg,[10,26] and one used 0.12 to 0.18 g protein/kg.[50] Finally, in two studies on FPIES solely to cow's

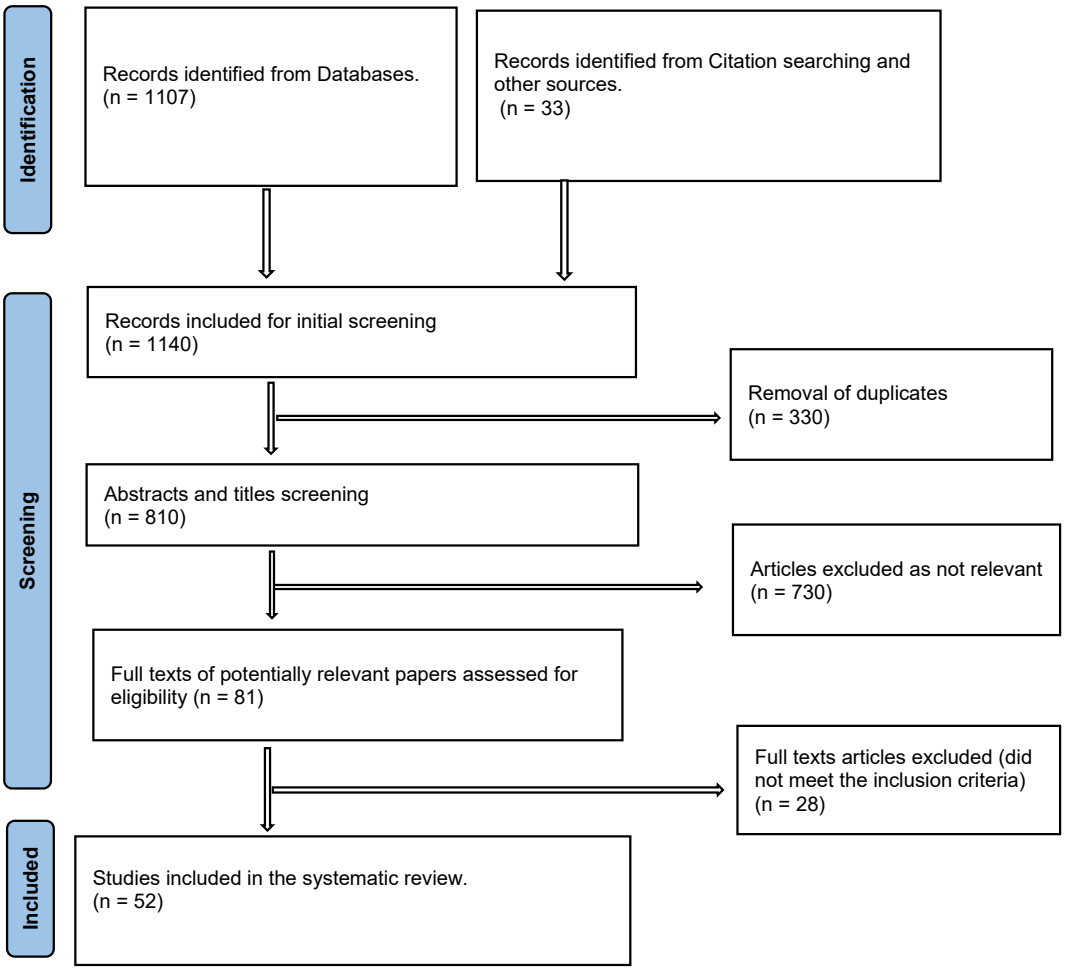


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses Flow Diagram of the systematic search and included studies.

milk, a cumulative protein dose of 11.55 g was used by Katz et al,[27] and 1.3 g by Faitelson et al.[66]

Dosing schedule. Eleven studies administered the cumulative dose as a single dose.[10,22,26,32,36,37,46,56,59,64,67] Fifteen studies used divided doses that differed in size and interval.

The cumulative dose of 0.06 to 0.6 g protein/kg was administered as an unspecified number of increasing doses over 45 to 60 minutes[4,8] and over 4 hours.[23] This dose was also administered in three equal doses over 30,[51,61] 45,[9,34,54] and 60 minutes.[30]

The cumulative dose of 0.3 g protein/kg was administered in three equal doses separated by 30,[45] 45,[49,58,68] and 90 minutes.[35]

In patients who received an additional AAP after incremental doses, the interval between the previous dose and the final AAP varied from 2[45] to 2 to 3[67] and 3 to 4 hours.[28,42,43,49,53,58,68]

When an AAP was used, it was divided into three doses (12.5%, 25%, and 50%), followed by an AAP[24] or the remaining dose up to a full AAP,[41] all given at 30-minute intervals.

Another approach was administering 25% of the AAP, followed by 75% of AAP after 4[47,52,57] or 2 hours.[60] Sopo et al[28] used three different OFC protocols: one involved administering 50% of the AAP and then the full AAP 2 hours later (ie, the cumulative dose was 150% of the AAP).

Argiz et al[49,68] used 10% of an AAP, followed by 30% and 60%, every 45 minutes. Ortega et al[58] used the same dosing, with an interval of 45 minutes between the first and second doses and 2 hours between the second and third doses.

In three studies, OFC was performed over more than 1 day, with 25% of the AAP administered on day 1 and an AAP 48 hours later.[15,39,55] Infante et al[41] performed an OFC administering 25%, 50%, and 100% of the AAP every 48 hours.

Sopo et al,[28] in a different protocol, administered 25% and 50% of AAP 4 hours apart on day 1 and an AAP after 24 hours. Garcia Paz et al[62] administered 30% of the AAP on day 1, followed by an AAP after 24 hours.

Nishimura et al[65] performed the OFC over 4 consecutive days, administering one-50th, one-tenth, one-half, and then full AAP, one dose per day. Argiz et al,[68] in a different protocol reported in the same study, performed an OFC by administering 25% of AAP on day 1, followed by a full AAP on day 2.

In another OFC performed over days by Fogg et al,[25] an initial dose was administered in the hospital (0.05-0.15 g protein in two increasing doses over 30 minutes) followed by further doses at

TABLE I. Published food protein-induced enterocolitis syndrome oral food challenge protocols

First author, year, country	Food tested	Cumulative dose*	Administration	Interval between doses	Observation time after last dose, h	Individualization based on clinical characteristics
Burks et al, 1994, United States[22]	CM, soy	0.6 g protein/kg body weight	Single dose	NA	24	Lower dose if history of severe reaction
Sicherer et al, 1998, United States[4]	CM, grains, soy	0.6 g protein/kg body weight	Increasing doses†	Over 45-60 min	6-8	Lower dose (0.15-0.3 g protein/kg body weight) if history of severe reaction
Chung et al, 2002, Korea[23]	NR	0.6 g protein /kg body weight	Increasing doses†	Over 4 h	24	Lower dose (0.15-0.3 g protein/kg) if history of severe reaction
Nowak-Wegrzyn et al, 2003, United States[8]	CM, soy, grains, meat/poultry	0.6 g of protein/kg body weight	Increasing doses†	Over 45-60 min	6-8	NR
Zapatero et al, 2005, Spain[24]	Fish	Age-appropriate portion‡	4 doses: one-eighth of portion, one-quarter, one-half, then full AAP	30 min	3	NR
Fogg et al, 2006, United States[25]	CM, egg, soy, grains	Hospital phase: 0.05-0.15 g protein/kg body weight	2 increasing doses†	Over 30 min	4	NR
		Home phase: Days 1-3: 0.05-0.15 g/kg protein/d Days 4-6: 0.1-0.3 g/kg protein/d Days 7-9: 0.15-0.45 g/kg protein/d	Single dose increased every 3 d	24 h		
Hwang et al, 2008, Korea[26]	CM	0.15 g protein/kg body weight (about 50-100 mL)	Single dose	Gradually over 1 h	4 in fasting state, then12 h	NR
Hwang et al, 2009, Korea[10]	CM, soy	Initial OFC for CM: 0.15 g protein/kg body weight Follow-up OFC: 0.03-0.05 g protein/kg body weight	Single dose	NA	NR	NR
Katz et al, 2011, Israel[27]	CM	11.55 g CM protein	6 doses: 0.15, 0.6, 0.9, 1.8, 3.6, and 4.5 g	10 min between first 2 doses. 20 min between next 2 doses and then 45 min between remaining doses	3	NR
Sopo et al, 2012, Italy[28]	CM, egg, soy, grains	Rome‡: 150% of age-appropriate portion	2 doses: 50% of age-appropriate portion, and 100% serving size	2 h	4	NR

		Benevento: 0.4 g protein/kg plus age-appropriate portion	0.4 g protein/kg divided into 3 equal doses over 3 h, followed by whole meal	3 doses in 3 h; wait 4 h, then final dose	2	
		Florence: full age-appropriate portion and 75% of age-appropriate portion	3 doses: Day 1: 25% and 50% of AAP Day 2:100% of AAP	Doses 1 and 2: 4 h Doses 2 and 3: 24 h	4	
Järvinen et al, 2012, United States[29]	CM, grains, soy	0.15-0.6 g protein/kg body weight	3 equal doses	Over 45 min		NR
Caubet et al, 2014, United States[9]	CM, grains, egg, fish, soy, fruits, vegetables, meat/poultry	0.06 g to ≤0.6 g protein/kg body weight, with maximum of 3 g protein	3 equal doses	Over 45 min	4-8	IgE-mediated allergy protocols if positive allergy test
		For rice and oats, age-appropriate portion‡				
Konstantinou et al, 2014, USA[30]	CM	0.06-0.6 g protein/kg body weight	3 equal doses	Over 1 h	4	NR
Kimura et al, 2016, Japan[31]	CM	8.58 g milk (260 mL)	3 doses: Day 1: 1 mL/kg (up to 10 mL) once Day 2: 5 mL/kg (up to 50 mL) once Day 3: normal volume for child (up to 200 mL)	24 h	24	NR
Sopo et al, 2016, Italy[32]	Soy, grains, legumes, meat/poultry	0.06-0.6 g protein /kg of each food	Single dose of food mixture	NA	4	NR
Gonzalez-Delgado et al, 2016, Spain[33]	Fish	0.3 g protein/kg body weight	2 doses: First: 25% of total amount Second:75% of amount	2 h	4	NR
Pena et al, 2017, United States[34]	CM, grains, soy	0.06-0.6 g protein/kg body weight	3 equal portions	Over 45 min	3	NR
Vazquez-Ortiz et al, 2017, Spain[35]	CM, egg, fish, grains	0.3 g protein/kg, maximum 3 g protein	Divided into 3 equal doses (7 for CM)	90 min	24	NR
Lee et al, 2017, Australia[36]	Rice, CM, egg, other grains, fish, soy, fruits, chicken, peanut	Age-appropriate portion (at least 3 g food protein except for rice [at least 1 g])	Single dose	NA	4	Graded challenge if positive allergy test
Sopo et al, 2017, Italy/Australia[37]	CM, fish, shellfish, nuts, egg, grains	At least 3 g food protein Rice 1-2 g protein	Single dose	NA	6	NR

(continued)

TABLE I. *(Continued)*

First author, year, country	Food tested	Cumulative dose*	Administration	Interval between doses	Observation time after last dose, h	Individualization based on clinical characteristics
Shimomura et al, 2018, Japan[38]	CM	8.58 g milk (260 mL)	3 doses: Day 1: 1 mL/kg (up to 10 mL) once Day 2: 5 mL/kg (up to 50 mL) once Day 3: up to 200 mL once	24 h	24	NR
Infante et al, 2018, Spain[39]	Fish	140% age-appropriate portion‡	2 doses: Day 1: 25% to 40% of AAP Day 3: age-appropriate portion	48 h	4	Challenge was performed in 3 d in case of history of severe reaction
Sopo¶ et al, 2019, Italy[40]	Egg	Variable doses§: half an egg, whole egg, teaspoonful of egg	Variable dosing: 3 doses over 30 min Single dose 1/10th of egg, with remainder of egg 1 h later	Variable	NR	IgE-mediated allergy protocol in case of positive allergy test
Infante et al, 2019, Spain[41]	Fish	Method 1‡: age-appropriate portion	4 doses: 1/8th, 1/4th, and 1/2 of AAP, then remainder of meal	30 min	2	In case of mild reactions or if an alternative fish (other than the FPIES trigger) was tested, OFC was performed within 2 d: day 1: 40% of AAP; day 2: AAP
		Method 2‡: age-appropriate portion	3 doses: Day 1: 25% of AAP Day 3: 50% of AAP Day 5: full AAP	48 h	4	
Douros et al, 2019, Greece[42]	CM, fish, egg, grains, meat/poultry	0.06-0.6 g protein/kg body weight plus age-appropriate portion‡	4 doses: 0.06-0.6 g of protein divided into 3 equal doses, then age-appropriate portion	3 doses over 45 min; observed 3-4 h before last dose	4	IgE-mediated allergy protocol, if positive allergy test
Gonzalez-Delgado et al, 2019, Spain[43]	Fish and shellfish	0.6 g protein/kg body weight maximum, 3 g plus AAP‡	4 doses: 0.06-0.6 g of protein divided into 3 equal doses, then age-appropriate portion	3 doses over 45 min, observed 4 h before last dose	Several hours	NR
Wang et al, 2019, United States[44]	CM, fish, soy, grains, nuts, fruits, vegetables, meat/poultry	Hospital phase§: one-third age-appropriate portion	Day 1: 1 dose equal to 1/3 of AAP	24 h	4	NR
		Home phase: equivalent to two or more age-appropriate portions	Home phase: Once-daily dose, to increase by 1/3 every 3 d over 9-12 d			

Xepapadaki et al, 2019, Greece[45]	CM, fish, egg, grains, meat/poultry	0.1-0.3 g protein/kg plus age-appropriate portion‡	4 doses: 0.1-0.3 g protein divided in 3 equal doses, then full age-appropriate portion	30 min between first 3 doses, then 2 h	4-6	IgE-mediated allergy protocol in case of positive allergy test
Mehr et al, 2019, Australia[46]	CM, fish, egg, grains, fruits, soy, meat/poultry	4 g food protein except for rice, 1 g food protein	Single dose	NA	4	NR
Barni et al, 2019, Italy[47]	CM, fish, egg, grains	Full age-appropriate portion	2 doses: 25% of AAP (0.3 g protein/kg body weight), then 75% of AAP	4 h	4	Lower dose (0.06 g protein/kg body weight) if history of severe reaction
Alonso et al, 2019, Spain[48]	CM, fish, egg	Milk: 6.6 g (200 mL) Egg: 60 g food Fish: 35 g food	3 doses: Milk: 20, 60, and 120 mL Egg: 5, 20, and 35 g Fish: 5, 15, and 25 g	45 min between first and second doses; 2 h between second and third doses	4	NR
Argiz et al, 2020, Spain/ Italy[49]	CM, fish, egg, fruits, nuts, vegetables, grains, meat/poultry	Protocol A§: maximum of 3 g protein/kg body weight maximum plus age-appropriate portion	4 doses: 3 doses of 0.1 g protein/kg body weight, then full age-appropriate portion	45 min between first 3 doses, observed 4 h, then last dose	4	NR
		Protocol B§: full age-appropriate portion	3 doses: 10%, 30%, and 60% of full age-appropriate portion	45 min	4	
Le et al, 2020, France[50]	CM, fish, vegetables	For CM: 0.12-0.18 g protein/kg body weight	2 doses: First: 0.03-0.06 g protein/ kg body weight Second: 0.09-0.12 g/kg body weight	2 h	4-6	NR
		For solid food: age-appropriate portion‡	2 doses: 20% followed by 80% of AAP			
Ocak et al, 2020, Turkey[51]	CM, fish, egg, grains, fruits, nuts, vegetables, meat/poultry	0.06-0.6 g protein/kg body weight, maximum 3 g protein	3 equal doses	Over 30 min	4-6	NR
Barni et al, 2020, Italy[52]	CM, fish, egg, fruits, grains, vegetables, soy, legumes, meat/poultry	Full age-appropriate portion	2 doses: 25% of AAP (0.3 g protein/kg body weight), then 75% of AAP	4 h	4	NR
Guenther et al, 2020, United States[53]	CM, soy, grains	Method 1‡: 0.06-0.6 g protein/kg body weight, maximum 3 g protein plus appropriate portion	4 doses: 0.06-0.6 g protein/kg divided into 3 equal doses, then, age-appropriate portion	First 3 doses over 30 min, observe 3 hours, then last dose	4	Lower dose (0.06 g protein/kg) in case of history of severe reaction
		Method 2: 0.06-0.6 g food protein/kg body weight, maximum 3 g protein	3 equal doses			
Ocak et al, 2021, Turkey[54]	CM, fish, egg, grains, nuts, meat/poultry	0.06-0.6 g food protein/kg body weight, maximum 10 g protein	3 equal doses	Over 45 min	4	NR

(continued)

TABLE I. *(Continued)*

First author, year, country	Food tested	Cumulative dose*	Administration	Interval between doses	Observation time after last dose, h	Individualization based on clinical characteristics
Crespo et al, 2021, Spain[15]	Shellfish	Age-appropriate portion‡	2 doses: Day 1: 25% of AAP Day 3: full AAP	48 h	4	NR
Infante et al, 2021, Spain[55]	Fish	Age-appropriate portion‡	2 doses: Day 1: 25% of AAP Day 3: 50% to 100% of AAP	48 h	4	NR
Sopo et al, 2021, Italy[56]	CM, fish, egg, shellfish, grains, legumes, meat/poultry	Age-appropriate portion§	Single dose	NA	NR	NR
Ballini et al, 2021, Italy[57]	CM, fish, egg, fruits, legumes, grains, shellfish, meat/poultry	Age-appropriate portion	2 doses: 25% of AAP (0.3 g protein/kg body weight), then 75% of AAP	4 h	4	NR
Ortega‖ et al, 2021, Spain[58]	CM, egg, fish	Method 1: 0.3 g protein/kg, maximum 3 g plus age-appropriate portion	4 doses: 3 doses, each equal to 0.1 g protein/kg masked with puree, then age-appropriate portion without masking	45 min between first 3 doses and wait 4 h before last dose	4	NR
		Method 2‡: full age-appropriate portion	3 doses: 10%, then 30% and 60% of full age-appropriate portion	45 min between first and second doses; 2 h between second and third doses		
Lemoine et al, 2022, France[59]	Cow's milk, egg, fruits, fish, grains, legumes, vegetables	Age-appropriate portion	Single portion	NA	4	Timing and interval were modified depending on history of severe reaction and type of food
			2-3 equal doses	Over 30 min		
Gonzalez-Delgado et al, 2022, Spain[60]	Fish, cephalopods, crustacean, vegetables, egg, CM	Full age-appropriate portion‡	2 doses: 25% of AAP, then rest of dose	2 h	4	NR
Wong et al, 2022, Austria[61]	CM, soy, egg, grains, meat/poultry	0.06-0.60 g food protein/kg body weight, maximum 3 g food protein	3 equal doses	Over 30 min	4	NR
García et al, 2022, Spain[62]	Fish, seafood	Full age-appropriate portion‡	2 doses: Day 1: 30% of AAP Day 2: complete portion	24 h	4	NR
Crespo et al, 2022, Spain[63]	Shellfish, fish, vegetables, egg	Full age-appropriate portion‡	2 doses: Day 1: 25% of AAP Day 3:100% of AAP	48 h	NR	NR

Sopo et al, 2022, Italy[64]	Cow's milk, egg, chicken, fruit, fish, shellfish, grains	Full age-appropriate portion	Single dose	NA	4	NR
Nishimura et al, 2022, Japan[65]	Soy, cow's milk, egg yolk, egg white, wheat, rice, fish	Full age-appropriate portion (0.3 g protein/kg, maximum 3 g protein)	4 doses: Day 1: 1/50th of AAP Day 2: 1/10th of AAP Day 3: 1/2 of AAP Day 4: Full AAP	24 h	4	Lower cumulative dose (0.06 g protein /kg) if history of severe reaction. If IgE-mediated food allergy was suspected, OFC was administered in three divided doses every 40 min
Faitelson et al, 2023, Israel[66]	Cow's milk (baked)	1.3 g protein	3 equal doses	20 min	4	NR
Patel et al, 2023, United States[67]	Milk, wheat, soy, rice, oat, egg, peanut	0.3 g protein/kg, maximum 3 g food protein ± full age-appropriate portion‡ (in OFC before 2018)	Single dose	2-3 h (if second full AAP was served)	4	NR
Argiz et al, 2024, Spain/Italy[68]	Cow's milk, egg, fruit, vegetables, meat, fish, shellfish	Age-appropriate portion	2 doses: 10% of AAP 90% of AAP	2 h	4	NR
		Age-appropriate portion§	3 doses: 10%, then 30% and 60% of AAP	45 min between doses 1 and 2, and 120 min between doses 2 and 3		
		0.3 g protein/kg body weight (maximum, 3 g) plus age-appropriate portion	3 equal portions (0.1 g protein/kg each) at 45 min, then final dose	45 min between first 3 doses, then 4 h wait before last dose		
		Age-appropriate portion	2 doses: Day 1: 25% of AAP Day 2: full age-appropriate portion as single dose	24 h		

AAP, age-appropriate portion; *CM*, cow's milk; *NA*, not applicable; *NR*, not reported; *OFC*, oral food challenge.
*In case of OFC protocols over days, the cumulative dose is reported as the maximum dose in a single day.
†Size and number of doses not specified.
‡Reference to serving size dose calculation not mentioned.
§Provided the serving size for age dose measurement.
¶The variable OFC approach and dosing in this study are due to the primary outcome of testing whether the cooking technique affects the development of tolerance in egg food protein-induced enterocolitis syndrome and measuring the relation between the dose ingested and the severity of the reaction.
‖OFC details were obtained from the author.

home, including an equivalent dose administered for 3 days, then 0.1 to 0.3 protein/kg for 3 days followed by 0.15 to 0.45 g protein/kg for another 3 days. Wang et al[44] performed a hospital OFC by administering one-third of an AAP, followed by a home dose increment of one-third every 3 days over 9 to 12 days.

Other individual protocols are listed in Table I.

Further characteristics of the OFC protocol design (observation time and protocol individualization) are described the Supplemental Text (in this article's Online Repository at www.jaci-inpractice.org).

Secondary outcomes

Positive OFC. Of the 3,556 OFCs conducted (3,466 in children and 90 in adults), 35.5% (1,264 of 3,556) were assessed as positive by the authors. Of the included studies, 42% used predefined criteria to define challenge positivity and 25% used predefined criteria for reaction severity (Table II). Severe reactions were documented in 11% (142 of 1,264) of the positive OFCs, with 35% (50 of 142) involving hypotension.

In children, symptoms of positive OFC were documented in 643 OFCs. Vomiting was the most common symptom (94%), followed by lethargy (40%), pallor (28%), abdominal pain or distension (16%), and diarrhea (10%). Less common symptoms included dehydration (2.7%), fever (1.2%), hypothermia (1.2%), cyanosis (0.9%), and floppiness (0.9%) (Table II).

In adults, positive OFC symptoms were available for 52 OFCs. Abdominal pain was the most common symptom (98%), followed by diarrhea (71%) and vomiting (40%). Other less-reported symptoms were lethargy (13%), nausea (9.6%), abdominal distension (9.6%), hypothermia (9.6%), weakness (7.6%), and chills (5.7%) (Table II).

For children and adults, treatment was reported for 668 positive OFCs. The intravenous fluid treatment was the most frequently used (45.6%), followed by ondansetron (42.9%), corticosteroids (28.7%), paracetamol (1.7%), antiemetics (1.3%), and analgesics (0.7%). Oral hydration was administered to 6.4% of patients, whereas 11.5% required no treatment (Table II).

Eliciting dose. There was heterogeneity and deficiency in reporting the eliciting doses (Table II). In single-dose OFCs, reactions were triggered by doses ranging from 0.03 to 0.05 g protein/kg[10] to 0.15 g protein/kg,[10,26] 0.6 g protein/kg,[22] 3 g protein,[37] 4 g protein,[46] one-third of the AAP,[44] and a full AAP.[36,41,56]

Different triggering doses have been reported in the OFC using incremental or fractioned doses (Table II). Notably, four studies used a single 25% of an AAP dose, followed by 4 hours of observation. This method triggered reactions in 100% (19 of 19) of reactive OFCs performed by Barni et al,[47] 100% (10 of 10) by Argiz et al,[68] 91.7% (11 of 12 adults) by Crespo et al,[63] and 81.35% (26 of 32) by Infante et al.[41]

Impact of OFC protocol on reaction severity. Owing to the heterogeneity of OFC protocols and outcome reporting, we could not analyze the data to identify safer protocols. Only two studies examined the potential impact of protocols on reaction severity.

Infante et al[41] compared the outcome of two OFC methods. The first was conducted in 1 day by giving patients four doses every 30 minutes (12.5%, 25%, and 50% of AAP, and then the rest of the meal). In the second OFC method, patients received 25%, 50%, and 100% of the AAP dose 48 hours apart. Of the failed OFCs after the first approach, 95.3% had to receive up to the full dose before they experienced a reaction, and 81.3% of reactions (35 of 43) were moderate to severe. After the second OFC method, 25% of the AAP was the triggering dose in 81.35% of cases, and symptoms were mild in 68.8% ($P < .001$).

Argiz et al[68] reported the clinical outcomes of an OFC protocol involving a single dose of 25% of an AAP administered on day 1 followed by full AAP on day 2. This was compared with the outcome of protocols involving multiple (generally larger) doses in a single day. The former triggered symptoms in 100% of patients (10 of 10) within the first day (90% [nine of 10] with mild to moderate symptoms and 10% [one of 10] with severe symptoms). Regression analysis showed that the 2-day OFC protocol was associated with reduced odds of a severe reaction compared with administering multiple doses in a single day. Cumulative dose, food, age, sex, and previous reaction severity were not independently associated with the outcome. However, the regression model explained only 16% of the variance, leading the authors to suggest that severe reactions at OFC were largely unpredictable.

Time of symptom onset. Six studies (11.5%) reported the time between the first dose and reaction onset, which ranged between 120 and 390 minutes (Table II).

The time from the last dose to reaction onset was reported by 42% of studies. The shortest latency was 30 to 35 minutes,[9,24,27,67] whereas 76% of the studies (16 of 21) reported reactions between 60 and 180 minutes. Vomiting, lethargy, and pallor presented early compared with diarrhea, which occurred after 300 to 900 minutes (Table II).

No difference in reaction onset was observed between single-dose and multidose OFCs (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Post-OFC observation and follow-up. Approximately half of the studies reported where the extended observation was required; 11% (74 of 660) of symptomatic patients required extended observation in emergency departments, intensive care units, or inpatient units (Table II). Only 15.63% of studies reported assessing late symptoms beyond the OFC observation period or after re-exposure following negative OFCs (see Table E5 in this article's Online Repository at www.jaci-inpractice.org).

Oral food challenge setting. Almost all OFCs were conducted in hospital settings: 24 in hospital wards or admission, four in hospital day units, and four in outpatient clinics. The setting was unspecified in 17 studies (13 noted as Allergy Center and four as under direct physician/medical supervision) (see Table E6 in this article's Online Repository at www.jaci-inpractice.org).

Hwang et al[10] performed the initial OFC in an inpatient setting and the follow-up OFC in the outpatient clinic. Fogg et al[25] and Wang et al[44] started the OFC in the outpatient clinic and in-hospital day unit, respectively, and completed the procedure at home.

Further outcomes are described in the Supplementary Text (food allergy testing, securing an intravenous line before OFC, the timing of OFC, and blood tests before and after OFC).

TABLE II. Reported OFC outcomes

First author, year, country	Positive OFC (%) (n/total n OFCs)	Eliciting dose (%) (n/total n positive OFCs)	Time from last dose to reaction, min	Time from first dose to reaction, min	Symptoms of positive reaction (%) (n/total n positive OFCs)	Severity of reactions (%) (n/total n positive OFCs)	Food caused severe reaction	Treatment of positive challenge (%) (n/total n positive OFCs)	Patients requiring further observation (%) (n/total n positive OFCs)	OFC reaction severity grading assessment criteria	Criteria of positive challenge
Burks et al, 1994, United States[22]	28.6% (37/129)	0.6 g protein/kg	NR	NR	V or D: 81% (30/37)	NR	NA	NR	NR	NR	Predefined criteria*
Sicherer et al, 1998, United States[4]	42.3% (11/26)	NR	NR	NR	V2†	Mild: 36.3% (4/11) Moderate: 63.6% (7/11)	NA	IV fluids: 63.6% (7/11) Corticosteroids:63.6% (7/11)	NA	NR	NR
Chung et al, 2002, Korea[23]	Total n OFCs: 26	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nowak-Wegrzyn et al, 2003, United States[8]	100% (8/8)	NR	120	NR	NR	NR	NA	IV fluid and corticosteroids: 62.5% (5/8)	NR	NR	NR
Zapatero et al, 2005, Spain[24]	100% (9/9)	1/8 piece: 22% (2/9)	30	NR	V: 88.8% (8/9) L: 22% (2/9) D:11% (1/9)	NR	NA	IV fluids: 33% (3/9) Corticosteroids: 33% (3/9) Oral hydration: 66.6% (6/9)	ED: 33% (3/9) Hospitalization: 11% (1/9)	NR	NR
		1/4 piece: 22% (2/9)	120, 180								
		1/2 piece: 11% (1/9)	120								
		Full piece: 44.4% (4/9)	90, 180, 300								
Fogg et al, 2006, United States[25]	48.4% (16/33)	0.15 g protein/kg	R: 120-240	NR	V: 93.7% (15/16) D:62.5% (10/16)	Severe: 18.7% (3/16)	CM, rice, soy	IV fluids: 18.7% (3/16)	18.7% (3/16)	NR	Predefined criteria*
Hwang et al, 2008, Korea[26]	94.1% (16/17)	0.15 g protein/kg	V, L:R: 60-180. BS:R: 360-600	NR	V: 87.5% (14/16) L: 62.5% (10/16) BS: 43.8% (7/16)	NR	NA	NR	NR	NR	Predefined criteria*
Hwang et al, 2009, Korea[10]	37.5% (27/72)	0.15 g protein/kg body weight 0.03-0.05 g protein/kg body weight	V: R: 66-264 L: R: 72-282 CY:R: 66-264 HN: R: 60-240 D:R:360-960	NR	V: 100% (27/27) L: 100% (27/27) D:33% (9/27) HN: 11% (3/27) CY: 22% (6/27)	Severe: 33% (9/27)	Milk, soy	NR	NR	NR	Predefined criteria*
Katz et al, 2011, Israel[27]	100% (24/24)	1.65 g (in 12.5%; 3/24) 3.45 g (in 12.5%; 3/24) 6.3 g (in 4%; 1/24) 7 g (in 16.6%; 4/24) 11.55 g (in 54.1%; 13/24)	M: 120 R: 30-180	M: 230	V: 100% (24/24) L: 79% (19/24) P: 25% (6/24) D: 20.8% (5/24)	Mild: 100% (24/24)	NA	Oral hydration: 100% (24/24)	0	NR	NR
Sopo et al, 2012, Italy[28]	41% (16/39)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Järvinen et al, 2012, United States[29]	42% (16/38)	NR	NR	M:150 R: 120-372	V: 100% (16/16) L: 6.25% (1/16) D: 6.25% (1/16) HN: 6.25% (1/16)	NR	NA	NR	NR	NR	NR

(continued)

TABLE II. *(Continued)*

First author, year, country	Positive OFC (%) (n/total n OFCs)	Eliciting dose (%) (n/total n positive OFCs)	Time from last dose to reaction, min	Time from first dose to reaction, min	Symptoms of positive reaction (%) (n/total n positive OFCs)	Severity of reactions (%) (n/total n positive OFCs)	Food caused severe reaction	Treatment of positive challenge (%) (n/total n positive OFCs)	Patients requiring further observation (%) (n/total n positive OFCs)	OFC reaction severity grading assessment criteria	Criteria of positive challenge
Caubet et al, 2014, United States[9]	41% (74/180)	NR	M:120 R: 5-320	M:150 R: 35-370	V: 96% (70/74) AP: 80% (59/74) HN: 19% (14/74) L: 7% (5/74) D:7%(5/74)	Not severe: 81% (60/74) Severe: 19% (14/74)	Milk, soy, grains	IV fluids: 96% (70/74) Corticosteroids: 94% (69/74) No treatment: 4% (3/74)	0	Predefined criteria*	Modified Powell's criteria‡
Konstantinou et al, 2014, United States[30]	83.8% (26/31)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kimura et al, 2016, Japan[31]	100% (18/18)	NR	M: 120 (in 6.6%; 8/18), within 240 (in 72.2%; 13/18)	NR	V: 66.7% (12/18) D: 55.6% (10/18) F: 33.3% (6/18)	NR	NA	NR	NR	NR	NR
Sopo et al, 2016, Italy[32]	0 (0/14)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gonzalez-Delgado et al, 2016, Spain[33]	Total OFCs: 23	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pena et al, 2017, United States[34]	33% (13/39)	NR	NR	NR	V: 85% (11/13) HN:0 D[2] L. DH.	NR	NA	IV fluids plus IV corticosteroids: 23% (3/13) Oral treatment (ondansetron, diphenhydramine, and oral hydration): 77% (10/13)	0	Likert scale‡	NR
Vazquez-Ortiz et al, 2017, Spain[35]	40.7% (33/81)	0.2 g (in 36.4%; 12/33) 0.3 g (in 51.5%; 17/33) 0.16 g (in 33.3%; 1/33) 0.2 g (in 9%; 3/33)	M: 300 (SD, 64.8)	NR	V: 90.9% (30/33) L: 48.5% (23/33) P: 27.3% (9/33) D: 15.2% (5/33) HN: 0	NR	NA	IV fluids: 57.6% (19/33)	0	Predefined criteria*	Powell's modified by Sicherer[72]
Lee et al, 2017, Australia[36]	25% (20/81)	Full age-appropriate portion	M: 150; IQR: 120-180	NR	V: 100% (20/20) P: 25% (5/20) Floppiness: 30% (6/20) D: 10% (2/20) HN: 5% (1/20)	NR	NA	IV fluids: 20% (6/20) Ondansetron: 65% (13/20)	Overnight admission: 5% (1/20)	NR	Predefined criteria*
Sopo et al, 2017, Italy/Australia[37]	100% (66/66)	3 g protein	NR	NR	V: 100% (66/66) P: 45% (30/66) L: 37.8% (25/66) D:7.5% (5/66)	NR	NR	IV fluids and corticosteroids: 21.2% (14/66) Ondansetron: 56% (37/66) No treatment: 22.7% (15/66)	Admitted to hospital: 21% (14/66)	NR	Predefined criteria*
Shimomura et al, 2018, Japan[38]	75% (6/8)	NR	NR	NR	V: 66.7% (4/6) D: 66.7% (4/6) BS: 16.7% (1/6)	NR	NR	NR	NR	NR	NR
Infante et al, 2018, Spain[39]	49% (85/173)	NR	NR	NR	NR	NR	NR	NR	NR	NR	

Sopo et al, 2019, Italy[40]	15% (9/61)	Whole egg: 55.6% (5/9) Half egg: 22.2% (2/9) Teaspoon of egg: 22.2% (2/9)	126	NR	V: 100% (9/9) HN: 22.2% (2/9) HT: 22.2% (2/9)	Mild: 22.2% (2/9) Moderate: 55.6% (5/9) Severe: 22.2% (2/9)	Egg	IV fluids and corticosteroids: 77.7% (7/9) Ondansetron: 11.1% (1/9) No treatment: 22.2% (2/9)	NR	NR	Predefined criteria*
Infante et al, 2019, Spain[41]	Total 39.6% (75/189) Method 1: 57.3% (43/75)	Method 1: full AAP: 95.3% (41/43)	NR	NR	V[2] L HN CY	Method 1: Mild: 18.6% (8/43) Moderate: 41.9% (18/43) Severe: 39.5% (17/43)	Fish	NR	Method 1: Transferred to ED: 34.9% (15/43) Hospitalization:7% (3/43)	IC criteria (1)	NR
	Method 2: 42.7% (32/75)	Method 2: 25% of AAP: 81.35% (26/32) Full AAP: 18.75% (6/32)				Method 2: Mild: 68.8% (22/32) Moderate: 18.8% (6/32) Severe: 12.5% (4/32)			Method 2: Transferred to ED: 18.8% (6/32) Hospitalization: 6.25% (2/32)		
Douros et al, 2019, Greece[42]	61.6% (61/99)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gonzalez-Delgado et al, 2019, Spain[43]	54.5% (6/11)	NR	NR	NR	AP: 100% (6/6) HT: 83.3 (5/6) V: 66.6% (4/6) D: 66.6% (4/6)	NR	NR	NR	NR	NR	Predefined criteria*
Wang et al, 2019, United States[44]	18% (30/169) 10% (17/169) during OFC in hospital	1/3 AAP	M: 85 R: 85-120 (for hospital OFC)	NR	V: 100% (17/17) D: 18% (3/17) HN: 5.8% (1/17)	Severe: 29.4% (5/17) during hospital OFC)	CM, oat, Turkey	IV fluids: 7.1% (14/169) Ondansetron: 6.1% (12/169) (IV in 11 and 1 oral) Oral hydration: 1.7% (3/169)	Transferred to ED: 5/5 Hospitalization: 3/5 ICU: 1/5	NR	IC
	7.7% (13/169) at home	NR	NR		V: 23% (3/13) D (in most)	Mild: 100% (13/13)	NA	NR	ED: 7.6% (1/13)		
Xepapadaki et al, 2019, Greece[45]	40.9% (25/69)	Full AAP 65% (16/25)	M: 156 (in diagnostic OFC) M:123 (in OFC to check resolution)	NR	V: 100% (25/25) L: 88% (22/25) P:44% (11/25) HN: 40% (10/25) D: 4% (1/25)	Severe: 40% (10/25)	NR	NR	NR	NR	Predefined criteria*
Mehr et al, 2019, Australia[46]	27.7% (10/36)	4 g food protein	NR	NR	V†	NR	NR	Ondansetron:90% (9/10)	NR	NR	NR
Barni et al, 2019, Italy[47]	35.2% (19/54)	0.3 g protein/kg body weight (25% of AAP) in 100% (19/19)	M:136 Median: 120; interquartile range, 105-165; R:60-230	M:136 Median, 120; interquartile range, 105-165; R: 60-230	NR	Mild: 21% (4/19) Moderate: 32% (6/19) Severe: 47% (9/19)	NR	Ondansetron: 78.9% (15/19)Cortico steroids: 73.7% (14/19) IV fluids: 57.9% (11/19) No treatment: 10.5% (2/19)	0	IC Criteria (1)	IC Criteria (1)
Alonso et al, 2019, Spain[48]	100% (6/6)	NR	V:M: 60-240 D:M: 300-600	NR	V: 100% (6/6) L: 100% (6/6) P: 100% (6/6) D: 33.3% (2/6)	NR	NA	IV fluids: 83.3% (5/6) Ondansetron: 83.3% (5/6) No treatment: 16.67% (1/6)	0	IC Criteria (1)	IC Criteria (1)
Argiz et al, 2020, Spain/Italy[49]	41.5% (47/113)	NR	NR	NR	NR	NR	NR	NR	NR	NR	IC Criteria (1)

(continued)

TABLE II. *(Continued)*

First author, year, country	Positive OFC (%) (n/total n OFCs)	Eliciting dose (%) (n/total n positive OFCs)	Time from last dose to reaction, min	Time from first dose to reaction, min	Symptoms of positive reaction (%) (n/total n positive OFCs)	Severity of reactions (%) (n/total n positive OFCs)	Food caused severe reaction	Treatment of positive challenge (%) (n/total n positive OFCs)	Patients requiring further observation (%) (n/total n positive OFCs)	OFC reaction severity grading assessment criteria	Criteria of positive challenge
Le et al, 2020, France[50]	100% (7/7)	For CM: (0.63, 1.6, 6.4, and 6.6 g). For mushroom: 2.6 g Salmon: 16.8 g Codfish: 18 g	NR	CM: 120, 210, 180,100. Mushroom: 300. Salmon: 390 codfish: 240	V: 100% (7/7) L: 14.2% (1/7) P: 28.5% (2/7)	NR	NR	IV fluids: 28.5% (2/7) Ondansetron: 100% (7/7) Ooral in 7 and IV in 2)	0	NR	NR
Ocak et al, 2020, Turkey[51]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Barni et al, 2020, Italy[52]	3.3% (6/183)	NR	NR	NR	NR	Mild: 66.66% (4/6) Moderate: 16.66% (1/6) Severe:16.66% (1/6)	Banana	No treatment:50% (3/6) Ondansetron:33.33% (2/6)Cortico steroids: 33.33% (2/6) IV fluids: 16.66% (1/6)	Transferred to ED: 16.66% (1/6)	IC Criteria (1)	NR
Guenther et al, 2020, United States[53]	11% (10/88)	0.35 g protein/kg (R: 0.2-0.6 g protein/kg)	NR	M: 120-180	NR	NR	NR	Ondansetron: 90% (9/10) IV fluids: 10% (1/10) No treatment: 10% (1/10)	0	IC Criteria (1)	NR
Ocak et al, 2021, Turkey[54]	41.3% (66/160)	3 parts of whole portion (in patient who was admitted to ICU)	M:120 R:120-180	NR	V: 100% (66/66) L: 63.6% (42/66) P: 54.5% (36/66) DH: 22.7% (15/66) AP: 10.6% (7/66) D: 7.6% (5/66) HN:7.6% (5/66) Shock:7.6% (5/66) HT: 4.5% (3/66)	Mild:18.2% (12/66) Moderate: 27.3% (18/66) Severe: 54.5% (36/66)	24 with fish, 10 with eggs, 2 CM	IV fluids: 83.3% (55/66) Ondansetron: 72.7% (48/66)Cortico steroids: 66.7% (44/66)	Admitted to hospital: 13.8% (9/66) ICU: 1.5% (1/66) (egg challenge)	IC Criteria (1)	NR
Crespo et al, 2021, Spain[15]	50% (1/2)	25% of AAP	180	NR	D: 100% (1/1) AP: 100% (1/1)	NR	NR	NR	NR	NR	Predefined criteria*
Infante et al, 2021, Spain[55]	40% (28/70)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sopo et al, 2021, Italy[56]	21.6% (48/222)	Full AAP	M: 129 ± 35 R: 60-180	NR	V* AP	Mild: 45.8% (22/48) Moderate: 45.8% (22/48) Severe: 8.3% (4/48)	CM, egg	Ondansetron: 47.91% (23/48) Corticosteroids: 18.75% (9/48) No treatment: 33.3% (16/48) IV fluids:14.6% (2/48)	0	IC Criteria (1)	Predefined criteria*
Ballini et al, 2021, Italy[57]	9.5% (14/148)	NR	NR	NR	V: 100% (14/14) L: 57.2% (8/14) D: 42.8% (6/14) P: 42.8% (6/14)	Mild: 42.8% (6/14) Moderate: 21.4% (2/14) Severe: 35.7% (5/14)	2 with fish, 2 with CM, and 1 with egg	IV fluids: 47% (8/14) Antiemetics: 42.8% (6/14) Corticosteroids: 28.5% (4/14) No treatment: 35.7% (5/14)	ED: 1	IC Criteria (1)	IC Criteria (1)
Ortega et al, 2021, Spain[58]	50% (19/38)	NR	NR	NR	V: 100% (19/19) Hyporeactivity: 39.3% D: 24.2% P: 12.1% HT: 3%	NR	NA	IV fluids: 45.5%, Ondansetron: 39.4%	NR	NR	NR
Lemoine et al, 2022, France[59]	27.3% (58/212)	NR	NR	NR	NR	NR	NR	NR	NR	NR	Leonard criteria[73]

González-Delgado et al, 2022, Spain[60]	67.3% (33/49)	NR	NR	NR	AP: 100% (33/33) D: 69.7% (23/33) V: 51.5% (17/33) HN: 12.1% (4/33) Weakness: 12.1% (4/33) L: 12.1% (4/33)	Mild: 66.7% (22/33)	NA	No treatment: 66.7% (22/33) IV fluids: 21.20% (7/33) Ondansetron: 12.10% (4/33)	NR	NR	Predefined criteria*
Wong et al, 2022, Austria[61]	12.5% (3/24)	NR	NR	NR	NR	NR	NA	Ondansetron: 66.6% (2/3) IV fluids: 33.3% (1/3) No treatment: 33.3% (1/3)	Hospital admission: 33.3% (1/3)	NR	NR
Garcia et al, 2022, Spain[62]	100% (7/7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Crespo et al, 2022, Spain[63]	57.1% (12/21)	25% of AAP (in 91.7%; 11/12)	367.8 R: 60-1,440	NR	AP: 91.7% (11/12) D: 75% (9/12) Nausea: 5/12 (41.6%) AN: 33.3% (5/12) Chills: 25% (3/12) L: 25% (3/12)	Mild to moderate: 100% (12/12)	NA	IV fluids: 33.3% (4/12) Analgesics: 41.6% (5/12) Antiemetics: 41.6% (5/12) Metoclopramide: 33.3% (4/12) Ondansetron: 8.3% (1/12) Paracetamol: 41.6% (5/12)	NR	NR	NR
Sopo et al, 2022, Italy[64]	34.3% (22/64)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nishimura et al, 2022, Japan[65]	35% (8/23)	1/50 of AAP (0.006-0.008 g protein/kg) in 75% (6/8) 0.03 g protein/kg in 12.5% (1/8) 0.3 g protein/kg in 12.5% (1/8)	Mean: 202 (120-480)	NR	V: 100% (8/8) L: 37.5% (3/8) Abdominal pain: 25% (2/8) D: 12.5% (1/8)	Mild: 25% (2/8) Moderate: 75% (6/8) Severe: 0	NA	IV fluids: 62.5% (5/8) Corticosteroids: 25% (2/8) No treatment: 37.5% (3/8)	0	IC Criteria (1)	Predefined criteria*
Faitelson et al, 2023, Israel[66]	27.2% (3/11)	NR	NR	NR	V: 100% (3/3)	Mild: 100% (3/3)	NA	Ondansetron: 66.6% (2/3) No treatment: 33.3% (1/3)	0	NR	IC
Patel et al, 2023, United States[67]	15.6% (29/185)	NR	30 min in 3.4% (1/29) 90 min in 3.4% (1/29)	NR	NR	NR	NA	Ondansetron: 86.2% (25/29) IV fluids: 20.6% (6/29) No treatment: 6.8% (2/29) Antihistamine: 6.8% (2/29)	0	NR	NR
Argiz et al, 2024, Spain/Italy[68]	Total 81% (81/100) Protocols 1-3 (1-d protocol): 88% (71/81)	Median: 5.1 g; p25-p75: (2.9-8.4)	Median 120 min p25-p75: (70-150)	NR	V: 100% (81/81) P: 93% (75/81) L: 81% (66/81) HN: 16% (13/81) D: 14% (11/81) HT: 4% (3/81) DH:4% (3/81) F: 2.4%(2/81) AP: 43% (35/81)	Mild: 8% (6/71) Moderate: 60% (43/71) Severe: 30% (22/71)	NR	Ondansetron: 81% (66/81) IV fluids: 57% (46/81) Corticosteroids: 11% (9/81) Paracetamol: 9% (7/81)	3% (3/81) admitted to hospital	IC criteria (1)	IC criteria (1)
	Protocol 4: 12% (10/81)					Mild: 30% (3/10) Moderate: 60% (6/10) Severe: 4% (1/10)					

AAP, age-appropriate portion; *AN*, abdominal distension; *AP*, abdominal pain; *BS*, bloody stool, *CM*, cow's milk; *CY*, cyanosis; *D*, diarrhea; *DH*, dehydration; *ED*, emergency department; *F*, fever; *IC Criteria*, food protein-induced enterocolitis syndrome international consensus criteria; *ICU*, intensive care unit; *IV*, intravenous; *HN*, hypotension; *HT*, hypothermia; *L*, lethargy; *M*, Mean, *NA*, not applicable; *NR*, not reported; *OFC*, oral food challenge; *P*, pallor; *R*, range; *V*, vomiting.

*Predefined criteria for positive reaction definition, severity and treatment authors' own or local criteria.

†Frequency and percentage are not clear or not specified.

‡Likert scale in which mild indicates either V or D; moderate, having both V and D; and severe, any patient with L, DH, or clinically significant HT.

DISCUSSION

To our knowledge, this systematic review is the first comprehensive investigation of OFC approaches in FPIES, encompassing OFC protocols, clinical outcomes, and characteristics associated with safer and more accurate outcomes.

All included studies employed observational designs. There was notable heterogeneity in the OFC protocols, with 28 different protocols reported. These varied in cumulative doses (from 0.05 g protein/kg to AAP), initial doses (12.5% to 100% of an AAP), number of doses (one to seven), intervals between doses (15 minutes to 48 hours) and observation time after the last dose (2-24 hours).

Whether OFC protocols using cumulative doses below an AAP reliably detect all patients with ongoing FPIES remains unclear, raising concerns about diagnostic accuracy. Most studies did not document subsequent tolerance to AAP at home after a negative OFC, which would have helped clarify this issue.

Since 1978, modifications to OFC protocols have been developed. Using an AAP to calculate the cumulative dose has become more common, in addition to using a single low dose and incremental doses at variable intervals. Home OFC has also been reported.

Many studies followed OFC practice recommendations from the recent consensus, although these are not validated.[1]

Significant heterogeneity was observed in outcome reporting; many publications did not providing criteria for a positive OFC or severity assessment. Of the 33 studies published after April 2017, three applied consensus criteria for a positive OFC, and six for reaction severity grading; four used both (Table II). Further use of standardized assessment approaches should aid future comparisons of OFC protocols. Vomiting was present in 94% of children and only in 40% of adults whose OFC was considered positive by the supervising clinician. On the one hand, this may raise concerns about the reliability of the outcome reported because the major criterion is not met. On the other hand, this reinforces the need to adapt adult-specific criteria for FPIES diagnosis and OFC outcome assessment, as highlighted by Gonzalez-Delgado et al.[69]

Increased neutrophils were noted in most positive OFC cases in the studies assessing this, although this seems more prominent several hours after the reaction has started.[68] From mechanistic studies, it is not fully clear whether the increase in neutrophils is central to FPIES pathophysiology (eg, via T_H17 activation) or results from cortisol secretion via the hypothalamus−pituitary−adrenal axis in the context of stress caused by vomiting or treatment with corticosteroids.[70] Further studies should address whether routine neutrophil measurement in FPIES OFCs could enhance diagnostic accuracy.

Few studies reported reaction severity; only 11% of reactions were classified as severe. However, over 95% of patients with positive OFC received medical treatment, often intravenously, which suggests that health care providers judged such interventions appropriate. Whether these treatments reduced reaction severity requires further investigation, especially because robust evidence on the effectiveness of ondansetron in FPIES management is limited and that of corticosteroids is lacking.[50] Owing to the observational design of the studies reviewed and the paucity of data, the impact of treatment on clinical outcomes could not be assessed.

Given the reported treatment use and severity rates, a conservative approach to OFC in FPIES, including close in-hospital supervision and prompt intravenous access, seems appropriate despite being resource-intensive. However, it remains unclear whether routinely securing intravenous access before starting the OFC contributed to the high rate of intravenous treatments.

Optimizing OFC safety is crucial in food allergies, particularly in FPIES, because of the absence of biomarkers to predict outcomes. There is insufficient evidence on key elements that would help inform the best OFC approach in FPIES, including reactivity thresholds, whether the dose impacts the severity, and how severity evolves over time.

Because of data heterogeneity and paucity in some areas, we could not analyze factors associated with safer outcomes. Nevertheless, four studies with small sample sizes highlighted that over three-quarters of children and adults reacted to only 25% of an AAP when administered as a single starting dose with at least 4 hours of observation.[41,47,63,68] This OFC method (compared with giving multiple larger doses in a single day) was associated with milder reactions.[41,68] Argiz et al[68] identified this as the only protective factor against severe reactions.

In single-dose protocols, most patients reacted after at least 2 hours. These observations question the appropriateness and safety of the widely accepted OFC protocol of administering 0.3 g protein/kg (maximum of 3 g) in three equal doses over 30 minutes. An OFC protocol with a starting dose of 25% of an AAP followed by 2 to 4 hours of observation may be more appropriate. For most foods involved in FPIES (cow's milk, egg, soy, grains, fruit, vegetables, tree nuts, and some legumes, excluding high-protein foods such as seafood, peanut, and meat), administering 25% of an AAP involves a smaller dose than the cumulative protein dose of 3 g recommended for children weighing over 10 kg in current consensus guidelines. This strategy may reduce reaction severity, as seen in IgE-mediated peanut allergy, where administering doses after reaching the individual's threshold dose increases the severity.[71] However, these findings are based on small, heterogeneous observational studies, and further evidence is needed before guideline changes can be recommended. Additional research is required to understand better factors influencing FPIES reaction severity and evaluate the impact of different OFC strategies on clinical outcomes through experimental designs. Harmonizing clinical data and OFC outcome reporting is essential to allow comparisons in future studies.

Strengths and limitations

Strengths of this systematic review include the comprehensiveness of the search and its high methodologic rigor. International experts were consulted to enhance the search strategy. We scrutinized all OFC approaches in FPIES to assess their impact on patient safety and diagnostic accuracy. However, this study had limitations, including the heterogeneity in OFC methodologies, variability in outcome reporting across studies, and the lack of data on some OFC outcomes, which precluded meta-analysis.

CONCLUSIONS

This systematic review highlights the heterogeneity in OFC procedures and outcome reporting worldwide, which hinders comparisons to identify the safest and most accurate approach. Harmonizing clinical data and OFC outcome reporting is essential to allow comparisons in future studies. Although the recent publications tend to follow consensus guidance, our

review suggests limitations in this, such as the usefulness of the OFC outcome assessment criteria in adults and the appropriateness of the recommended dosing protocol. Four studies with a small sample size suggested that a single dose of 25% of an AAP was sufficient to trigger symptoms in most patients with FPIES, and two studies suggested that this may be a safer approach than giving multiple (larger) doses in a single day. Further studies should validate these findings. Future research should focus on critical knowledge gaps potentially affecting OFC procedure safety, including reactivity thresholds, the relationship between dose and severity, severity trends over time, as well as head-to-head comparisons of standardized OFC protocols. Research on diagnostic and prognostic biomarkers for FPIES is also needed to avoid the risks and limitations associated with OFC.

Acknowledgments

U. Nurmatov and M. Vazquez-Ortiz conceived the idea of the study and contributed to the study protocol with T. Ibrahim and S. Arasi. T. Ibrahim and L. Argiz completed the literature search; T. Ibrahim, L. Argiz, and S. Infante contributed to data extraction and critical appraisal of the studies; and T. Ibrahim and M. Vazquez-Ortiz led the data interpretations and drafted the manuscript. All the authors contributed to the final manuscript. Thanks to the Imperial College Medicine Library support group for their advice on literature search methodology.

REFERENCES

1. Nowak-Wegrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive Summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy. Asthma & Immunology. J Allergy Clin Immunol 2017;139:1111-1126.e4.
2. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. J Pediatr 1978;93:553-60.
3. Powell GK. Food protein-induced enterocolitis of infancy: differential diagnosis and management. Compr Ther 1986;12:28-37.
4. Sicherer SHEP, Sampson HA. Clinical features of food protein—induced enterocolitis syndrome. J Pediatr 1998;133:214-9.
5. Leonard SA, Nowak-Wegrzyn A. Clinical diagnosis and management of food protein-induced enterocolitis syndrome. Curr Opin Pediatr 2012;24:739-45.
6. Miceli Sopo S, Greco M, Monaco S, Tripodi S, Calvani M. Food protein-induced enterocolitis syndrome, from practice to theory. Expert Rev Clin Immunol 2013;9:707-15.
7. Leonard SA, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome. Pediatr Clin North Am 2015;62:1463-77.
8. Nowak-Wegrzyn ASH, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food protein. Pediatrics 2003;111(4 part 1):829-35.
9. Caubet JC, Ford LS, Sickles L, Jarvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol 2014;134:382-9.
10. Hwang JB, Sohn SM, Kim AS. Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome. Arch Dis Child 2009;94:425-8.
11. Vazquez-Ortiz M, Khaleva E, Mukherjee S, Infante S, Meyer J, LeFew A, et al. Challenges and unmet needs in FPIES from the parents and adult patients' perspective - an international survey. J Allergy Clin Immunol Pract 2023;11:1306-1309.e2.
12. Stiefel G, Alviani C, Afzal NA, Byrne A, du Toit G, DunnGalvin A, et al. Food protein-induced enterocolitis syndrome in the British Isles. Arch Dis Child 2022;107:123-7.
13. Mehr S, Frith K, Barnes EH, Campbell DE, Group FS. Food protein-induced enterocolitis syndrome in Australia: a population-based study, 2012-2014. J Allergy Clin Immunol 2017;140:1323-30.
14. Argiz L, Infante S, Machinena A, Bracamonte T, Echeverria L, Prieto A, et al. Children with acute food protein-induced enterocolitis syndrome from Spain and Italy usually tolerate all other food groups. Clin Exp Allergy 2021;51:1238-41.
15. Crespo J, Skrabski F, Perez-Pallise ME, De Castro-Martinez FJ, Zubeldia JM, Infante S. Relevant features of adult-onset food protein-induced enterocolitis syndrome. J Allergy Clin Immunol Pract 2021;9:1759-17560.e1.
16. Anvari S, Ruffner MA. Adult food protein-induced enterocolitis syndrome. Front Allergy 2022;3:889879.
17. Bird JA, Barni S, Brown-Whitehorn TF, du Toit G, Infante S, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome oral food challenge: time for a change? Ann Allergy Asthma Immunol 2021;126:506-15.
18. Nicolaides R, Bird JA, Cianferoni A, Brown-Whitehorn T, Nowak-Wegrzyn A. Oral food challenge for FPIES in practice-a survey: report from the Work Group on FPIES Within the Adverse Reactions to Foods Committee, FAED IS, AAAAI. J Allergy Clin Immunol Pract 2021;9:3608-36014.e1.
19. Ford LS, Konstantinou GN, Caubet JC. PRO: Peripheral intravenous access should always be secured before initiating food protein-induced enterocolitis syndrome oral food challenge. Ann Allergy Asthma Immunol 2021;126:460-1.
20. National Institute for Health Care and Research, Oral food challenge (OFC) approaches in food-protein induced enterocolitis syndrome (FPIES): a systematic review. Accessed April 1, 2024. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022298955
21. Effective Public Health Practice Project. Quality assessment tool for quantitative studies. Accessed January 1, 2024. https://www.ephpp.ca/quality-assessment-tool-for-quantitative-studies/
22. Burks AWCH, Fiedorek SC, Williams LW, Pumphrey CL. Prospective oral food challenge study of two soybean protein isolates in patients with possible. Pediatr Allergy Immunol 1994;5:40-5.
23. Chung HL, Hwang JB, Park JJ, Kim SG. Expression of transforming growth factor beta1, transforming growth factor type I and II receptors, and TNF-alpha in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome. J Allergy Clin Immunol 2002;109:150-4.
24. Remón Zapatero, Alonso Lebrero E, Martín Fernández E, Martínez Molero MI. Food protein-induced enterocolitis syndrome caused by fish. Allergol Immunopathol (Madr) 2005;33:312-6.
25. Fogg MI, Brown-Whitehorn TA, Pawlowski NA, Spergel JM. Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol 2006;17:351-5.
26. Hwang JB, Song JY, Kang YN, Kim SP, Suh SI, Kam S, et al. The significance of gastric juice analysis for a positive challenge by a standard oral challenge test in typical cow's milk protein-induced enterocolitis. J Korean Med Sci 2008;23:251-5.
27. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. J Allergy Clin Immunol 2011;127:647-653.e1-3.
28. Sopo SM, Giorgio V, Dello Iacono I, Novembre E, Mori F, Onesimo R. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. Clin Exp Allergy 2012;42:1257-65.
29. Jarvinen KM, Caubet JC, Sickles L, Ford LS, Sampson HA, Nowak-Wegrzyn A. Poor utility of atopy patch test in predicting tolerance development in food protein-induced enterocolitis syndrome. Ann Allergy Asthma Immunol 2012;109:221-2.
30. Konstantinou GN, Bencharitiwong R, Grishin A, Caubet JC, Bardina L, Sicherer SH, et al. The role of casein-specific IgA and TGF-beta in children with food protein-induced enterocolitis syndrome to milk. Pediatr Allergy Immunol 2014;25:651-6.
31. Kimura M, Ito Y, Tokunaga F, Meguro T, Shimomura M, Morishita H, et al. Increased C-reactive protein and fever in Japanese infants with food protein-induced enterocolitis syndrome. Pediatr Int 2016;58:826-30.
32. Miceli Sopo S, Bersani G, Cerchiara G, Monaco S. Oral food challenge with a mixture of 'at risk' foods in children with FPIES. Pediatr Allergy Immunol 2016;27:872-4.
33. Gonzalez-Delgado P, Caparros E, Moreno MV, Clemente F, Flores E, Velasquez L, et al. Clinical and immunological characteristics of a pediatric population with food protein-induced enterocolitis syndrome (FPIES) to fish. Pediatr Allergy Immunol 2016;27:269-75.
34. Pena LE, Guffey D, Minard CG, Anvari S, Davis CM. The role of intravenous access during oral food challenges in food protein-induced enterocolitis syndrome. Allergy Asthma Proc 2017;38:467-73.
35. Vazquez-Ortiz M, Machinena A, Dominguez O, Alvaro M, Calvo-Campoverde K, Giner MT, et al. Food protein-induced enterocolitis syndrome to fish and egg usually resolves by age 5 years in Spanish children. J Allergy Clin Immunol Pract 2017;5:512-515.e1.
36. Lee E, Campbell DE, Barnes EH, Mehr SS. Resolution of acute food protein-induced enterocolitis syndrome in children. J Allergy Clin Immunol Pract 2017;5:486-488.e1.

37. Miceli Sopo S, Bersani G, Monaco S, Cerchiara G, Lee E, Campbell D, Mehr S. Ondansetron in acute food protein-induced enterocolitis syndrome, a retrospective case-control study. Allergy 2017;72:545-51.
38. Shimomura M, Ito Y, Tanaka H, Meguro T, Kimura M. Increased serum cortisol on oral food challenge in infants with food protein-induced enterocolitis syndrome. Pediatr Int 2018;60:13-8.
39. Infante S, Marco-Martin G, Sanchez-Dominguez M, Rodriguez-Fernandez A, Fuentes-Aparicio V, Alvarez-Perea A, et al. Food protein-induced enterocolitis syndrome by fish: not necessarily a restricted diet. Allergy 2018;73:728-32.
40. Miceli Sopo S, Romano A, Bersani G, Fantacci C, Badina L, Longo G, et al. Cooking influence in tolerance acquisition in egg-induced acute food protein enterocolitis syndrome. Allergol Immunopathol (Madr) 2019;47:221-6.
41. Infante S, Marco-Martin G, Zubeldia JM, Fuentes-Aparicio V, Alvarez-Perea A, Cabrera-Freitag P, et al. Oral food challenge in food protein-induced enterocolitis syndrome by fish: is there any room for improvement? Int Arch Allergy Immunol 2019;179:215-20.
42. Douros K, Tsabouri S, Feketea G, Grammeniatis V, Koliofoti EG, Papadopoulos M, et al. Retrospective study identified fish and milk as the main culprits in cases of food protein-induced enterocolitis syndrome. Acta Paediatr 2019;108:1901-4.
43. Gonzalez-Delgado P, Caparros E, Moreno MV, Cueva B, Fernandez J. Food protein-induced enterocolitis-like syndrome in a population of adolescents and adults caused by seafood. J Allergy Clin Immunol Pract 2019;7:670-2.
44. Wang KY, Lee J, Cianferoni A, Ruffner MA, Dean A, Molleston JM, et al. Food protein-induced enterocolitis syndrome food challenges: experience from a large referral center. J Allergy Clin Immunol Pract 2019;7:444-50.
45. Xepapadaki P, Kitsioulis NA, Manousakis E, Manolaraki I, Douladiris N, Papadopoulos NG. Remission patterns of food protein-induced enterocolitis syndrome in a Greek pediatric population. Int Arch Allergy Immunol 2019;180:113-9.
46. Mehr S, Lee E, Hsu P, Anderson D, de Jong E, Bosco A, et al. Innate immune activation occurs in acute food protein-induced enterocolitis syndrome reactions. J Allergy Clin Immunol 2019;144:600-602.e2.
47. Barni S, Sarti L, Mori F, Liotti L, Pucci N, Novembre E. A modified oral food challenge in children with food protein-induced enterocolitis syndrome. Clin Exp Allergy 2019;49:1633-6.
48. Alonso SB, Ezquiaga JG, Berzal PT, Tardon SD, San Jose MM, Lopez PA, et al. Food protein-induced enterocolitis syndrome: Increased prevalence of this great unknown-results of the PREVALE study. J Allergy Clin Immunol 2019;143:430-3.
49. Argiz L, Infante S, Machinena A, Pascal M, Echeverria L, Barni S, et al. Reactions on re-exposure following negative and inconclusive follow-up food challenges in children with acute FPIES. J Allergy Clin Immunol Pract 2020;8:3228-3231.e3.
50. Le S, de Boissieu D, Garcelon N, Lageix F, Bodilis H, Branellec A, et al. Efficacy of oral ondansetron in acute FPIES: a case series of 6 patients. Allergy 2020;75:2949-51.
51. Ocak M, Akarsu A, Sahiner UM, Soyer O, Sekerel BE. Phenotypes and natural history of food protein-induced enterocolitis syndrome in the east Mediterranean region. Allergy Asthma Proc 2020;41:420-7.
52. Barni S, Liotti L, Mori F, Liccioli G, Pucci N, Novembre E. Are oral food challenges for introduction of high-risk foods in children with food protein-induced enterocolitis syndrome needed? Pediatr Allergy Immunol 2020;31:326-9.
53. Guenther MW, Crain M, Parrish CP, Bird JA. An observed serving dose may not be necessary following a standard divided-dose FPIES oral food challenge. J Allergy Clin Immunol Pract 2020;8:1462-4.
54. Ocak M, Akarsu A, Sahiner UM, Soyer O, Sekerel BE. Food protein-induced enterocolitis syndrome: current practices in oral food challenge. Allergy Asthma Proc 2021;42:343-9.
55. Infante S, Perez-Pallise E, Skrabski F, Cabrera-Freitag P, Morales-Cabeza C, Fuentes-Aparicio V, et al. Poor prognosis of food protein-induced enterocolitis syndrome to fish. Pediatr Allergy Immunol 2021;32:560-5.
56. Miceli Sopo S, Sinatti D, Gelsomino M. Retrospective analysis of 222 oral food challenges with a single dose in acute food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol 2021;32:1066-72.
57. Ballini G, Gavagni C, Guidotti C, Ciolini G, Liccioli G, Giovannini M, et al. Frequency of positive oral food challenges and their outcomes in the allergy unit of a tertiary-care pediatric hospital. Allergol Immunopathol (Madr) 2021;49:120-30.
58. Ortega SE, Vega MG, Fernández AI, Martínez BB, Fernández SF, Teruel SJ, et al. Food protein-induced enterocolitis syndrome (FPIES), a rare disease with common symptoms. A retrospective study from 2011 to 2020. J Pediatr Gastroenterol Nutr 6th World Congress of PGHAN: Abstracts 2021;72:1-1313.
59. Lemoine A, Colas AS, Le S, Delacourt C, Tounian P, Lezmi G. Food protein-induced enterocolitis syndrome: a large French multicentric experience. Clin Transl Allergy 2022;12:e12112.
60. Gonzalez-Delgado P, Muriel J, Jimenez T, Cameo JI, Palazon-Bru A, Fernandez J. Food protein-induced enterocolitis syndrome in adulthood: clinical characteristics, prognosis, and risk factors. J Allergy Clin Immunol Pract 2022;10:2397-403.
61. Wong S, Duan L, Galper A, Atkinson A, Upton J, Eiwegger T. Food protein-induced enterocolitis syndrome in a tertiary pediatric center: safety of guideline-conforming food challenges. Allergy Asthma Clin Immunol 2022;18:54.
62. Garcia Paz V, Carballeira Anca I, Romero Sanchez L, Otero Alonso A, Gonzalez Torres L, Vila Sexto L. Food protein-induced enterocolitis syndrome in an adult population from Spain. J Investig Allergol Clin Immunol 2023;33:136-8.
63. Crespo J, Perez-Pallise ME, Skrabski F, Zambrano G, Rojas-Perez-Ezquerra P, Noguerado-Mellado B, et al. The natural course of adult-onset food protein-induced enterocolitis syndrome. J Allergy Clin Immunol Pract 2022;10:2986-92.
64. Sopo SM, Sinatti D, Sodero G, Gelsomino M, Mastellone F. Adherence to dietary prescriptions in patients with acute food protein-induced enterocolitis syndrome. Pediatr Investig 2022;6:207-10.
65. Nishimura K, Yamamoto-Hanada K, Sato M, Toyokuni K, Ogita H, Kiguchi T, et al. Remission of acute food protein-induced enterocolitis syndrome confirmed by oral food challenges in Japan. Nutrients 2022;14:4158.
66. Faitelson Y, Yoffe S, Segal N, Marcus N, Greenbaum E, Shahar-Nissan K, et al. Tolerability of baked milk consumption in children with food protein-induced enterocolitis syndrome. J Allergy Clin Immunol Pract 2023;11:329-31.
67. Patel G, Crain M, Bird JA, Parrish CP. Intravenous access is rarely necessary in food protein-induced enterocolitis syndrome oral food challenges. J Allergy Clin Immunol Pract 2023;11:3792-3794.e1.
68. Argiz L, Valsami-Fokianos M, Arasi S, Barni S, Boscia S, Bracaglia G, et al. Clinical-hematological changes and predictors of severity in acute food protein-induced enterocolitis syndrome reactions at oral food challenge: a multicenter observational study. J Allergy Clin Immunol Pract 2024;12:2454-2467.e8.
69. Gonzalez-Delgado P, Anvari S, Entrala A, Infante S. Medical algorithm: diagnosis and management of adult food protein-induced enterocolitis syndrome. Allergy 2024;79:2881-4.
70. Berin MC. Advances in understanding immune mechanisms of food protein-induced enterocolitis syndrome. Ann Allergy Asthma Immunol 2021;126:478-81.
71. Wainstein BK, Studdert J, Ziegler M, Ziegler JB. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. Pediatr Allergy Immunol 2010;21(4 part 1):603-11.
72. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. J Allergy Clin Immunol 2005;115:149-56.
73. Leonard SA, Pecora V, Fiocchi AG, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome: a review of the new guidelines. World Allergy Organ J 2018;11:4.