Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: The 2-4-6 study

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Background: Numerous dietary restrictions and endoscopies limit the implementation of empiric elimination diets in patients with eosinophilic esophagitis (EoE). Milk and wheat/gluten are the most common food triggers.

Objective: We sought to assess the effectiveness of a step-up dietary strategy for EoE.

Methods: We performed a prospective study conducted in 14 centers. Patients underwent a 6-week 2-food-group elimination diet (TFGED; milk and gluten-containing cereals). Remission was defined by symptom improvement and less than 15 eosinophils/high-power field. Nonresponders were gradually offered a 4-food-group elimination diet (FFGED; TFGED plus egg and legumes) and a 6-food-group elimination diet (SFGED; FFGED plus nuts and fish/seafood). In responders eliminated food groups were reintroduced individually, followed by endoscopy.

Results: One hundred thirty patients (25 pediatric patients) were enrolled, with 97 completing all phases of the study. A TFGED achieved EoE remission in 56 (43%) patients, with no differences between ages. Food triggers in TFGED responders were milk (52%), gluten-containing grains (16%), and both (28%). EoE induced only by milk was present in 18% and 33% of adults and children, respectively. Remission rates with FFGEDs and SFGEDs were 60% and 79%, with increasing food triggers, especially after an SFGED. Overall, 55 (91.6%) of 60 of the TFGED/FFGED responders had 1 or 2 food triggers. Compared with the initial SFGED, a step-up strategy reduced endoscopic procedures and diagnostic process time by 20%.

Conclusions: A TFGED diet achieves EoE remission in 43% of children and adults. A step-up approach results in early identification of a majority of responders to an empiric diet with few food triggers, avoiding unnecessary dietary restrictions, saving endoscopies, and shortening the diagnostic process. (J Allergy Clin Immunol 2018;141:1365-72.)

Key words: *Eosinophilic esophagitis, diet, milk, wheat, six-food elimination*

Eosinophilic esophagitis (EoE) is a chronic immune/antigen-mediated disease isolated to the esophagus and characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.[1] Since its initial description in the early 1990s,[2,3] EoE has become the leading cause of dysphagia in children and young adults living in westernized countries.[4] The first study, which was published in 1995, showed complete reversal of refractory EoE attributed to gastroesophageal reflux disease after exclusive feeding with an amino acid–based formula (elemental diet) for at least 6 weeks.[5] This seminal report first established the etiologic role of food in patients with EoE, which is currently known to be an allergic condition triggered predominantly by food antigens. Unlike conventional IgE-mediated food allergy, EoE has been demonstrated to be a distinct form of food allergy that is largely dependent on non-IgE, delayed, cell-mediated hypersensitivity.[6]

Despite dietary therapy being the only treatment targeting the cause of the disease instead of its inflammatory consequences, pharmacologic therapy (proton pump inhibitor [PPI] or topical steroid therapy) has become more popular. Among the 3 major modalities of dietary therapy for EoE, an elemental diet remains

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Abbreviations used
DSS: Dysphagia Symptom Score
EoE: Eosinophilic esophagitis
FFGED: Four-food-group elimination diet
hpf: High-power field
IQR: Interquartile range
PPI: Proton pump inhibitor
SFGED: Six-food-group elimination diet
TFGED: Two-food-group elimination diet

the most effective intervention in children and adults,[7] but it is hampered by multiple disadvantages, including complete avoidance of food, poor palatability, socialization impairment, and lack of reimbursement. Results for food allergy testing–guided elimination have been consistently low in adults[8-11] and variable in children.[6] An empiric elimination diet was first tested in 2006.[12] This diet, termed a 6-food-group elimination diet (SFGED), consisted of eliminating the 6 food groups most commonly associated with food allergy in the pediatric population in Chicago (cow's milk protein, wheat, egg, soy, peanut/tree nuts, fish, and seafood) for 6 weeks. An SFGED led to clinicohistologic remission in three quarters of children,[12] and consistent results have been obtained in adults from the United States,[11,13] Spain,[14,15] and Australia.[16] The effectiveness and wide reproducibility of SFGEDs are counteracted by the large number of endoscopies required after individual food reintroduction. Currently, food groups to be avoided in the long term for each responder to an SFGED can only be identified through individual food reintroduction, followed by histologic re-evaluation.

It is of note that up to three quarters of responders to an SFGED have been found to have just 1 or 2 food triggers after individual food reintroduction.[17] The most common causative foods identified after a response to an SFGED were cow's milk, wheat, egg, and, to a lesser extent, soy/legumes. In light of these data, a 4-food-group elimination diet (FFGED) was developed. A first prospective multicenter study in adult Spanish patients showed a 54% remission, with half of responders having cow's milk, gluten-containing grains, or both as food triggers.[18] Therefore the aim of this study was to determine the effectiveness and resource saving of a step-up strategy for empiric elimination diet in pediatric and adult patients with EoE by means of starting with elimination of the 2 most common food triggers (milk and gluten) and then stepping up to an FFGED and eventually to an SFGED in nonresponders.

METHODS

Patient selection and eligibility

This was a multicenter, prospective, quasiexperimental study conducted in 13 Spanish and 1 Italian centers between September 2014 and November 2016. Informed consent was obtained from all patients included in the study. Ethical approval was granted by the institutional review board in all participating centers. Consecutive children older than 2 years and adults with a diagnosis of EoE defined by consensus guidelines (symptoms of esophageal dysfunction, ≥15 eosinophils per high power field [hpf]) and lack of histologic response (≥15 eosinophils/hpf) after an 8-week trial of PPI therapy were eligible for enrollment.[1] Patients were recruited from outpatient gastroenterology clinics or endoscopy units. All eligible patients were naive for topical steroid or dietary therapy. Exclusion criteria included previous diagnosis of an eosinophilic gastrointestinal disorder, any potential cause for esophageal eosinophilia different from EoE (achalasia, caustic or radiation esophagitis, parasites, inflammatory bowel disease, neoplasm, and drugs), food-associated anaphylaxis to milk or wheat, inability to adhere to an elimination diet, or inability to take biopsy specimens because of the presence of esophageal varices or active anticoagulant therapy. Patients with severe fibrostricturing EoE, either with strictures or a narrow-caliber esophagus, were also excluded.

Assessment of clinical, endoscopic, and histologic data

Physical examinations, clinical data records, and baseline endoscopies with esophageal biopsies during PPI therapy at both the distal and proximal esophagi were recorded. Dysphagia in older children and adults was assessed by using the Dysphagia Symptom Score (DSS), a nonvalidated instrument used in previous adult studies on EoE.[13,18] This score assigns points for the frequency, intensity, duration of symptoms, and presence of lifestyle changes, with a range from 1 to 18, with greater intensity of dysphagia reflected by higher scores. All patients or their parents were asked whether they believed symptoms had been resolved after each dietary intervention.

All endoscopic procedures were performed with either topical pharyngeal anesthesia or propofol-based sedation, according to patient preference, by board-certified gastroenterologists and pediatricians. By using conventional grasping forceps, at least 4 biopsy specimens were taken from both the distal and proximal esophagi. Endoscopic abnormalities suggestive of EoE were recorded after a standardized classification.[19] Mucosal biopsy specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin for histologic examination. They were reviewed by senior gastrointestinal pathologists with expertise in EoE at each center. Peak eosinophil count was determined in the area of highest eosinophil density, and esophageal eosinophilia was defined based on the presence of 15 or more eosinophils/hpf in at least 1 field.[1]

Definition of clinical and histologic remission

A decrease of more than 50% in baseline DSS after dietary therapy was considered clinical remission in older children and adults. Subjective symptom improvement reported by either children or parents was considered for younger children. Histologic remission was defined as an eosinophil peak count of less than 15 eosinophils/hpf at both the distal and proximal esophagi. Response to any dietary intervention was defined by a combination of clinical and histologic remission.

Two-food-group elimination diet

A 2-food-group elimination diet (TFGED) with elimination of cow's milk and wheat was instituted in all patients for 6 weeks. Because of potential cross-reactivity between food allergens[20] and in accordance with our previous experience with a FFGED,[18] we decided to eliminate all dairy products (either goat's or sheep's milk can cross-react with cow's milk) and all gluten-containing grains (cross-reactive with wheat, including barley, rye, and oats). Concomitant PPI therapy was allowed if gastroesophageal reflux disease symptoms were present. Treatment with oral, nasal, airway, or swallowed steroids was not allowed from 8 weeks before enrollment until the end of the study. In case of exacerbated rhinitis or asthma during the study period, H_1-antihistamines, inhaled β_2-agonists, and anticholinergic bronchodilator drugs were allowed.

Food allergens known to cause oral allergy syndrome symptoms were avoided already by patients before enrollment. Over the study period with a TFGED, patients were allowed to eat rice and corn, eggs, all kind of legumes, and vegetables, meat, fish/seafood, fruits, and nuts. Gluten-free products were also permitted, provided they did not contain milk. They could also drink coffee, tea and herbal infusions, soy/rice/almond/hazelnut milk, soft drinks, and alcoholic beverages, although beer or whiskey consumption was not allowed because of gluten content. Written instructions for adequate reading of food labeling were given to patients to avoid foods containing potential hidden names for milk (casein and caseinates, lactalbumin, hydrolysates,

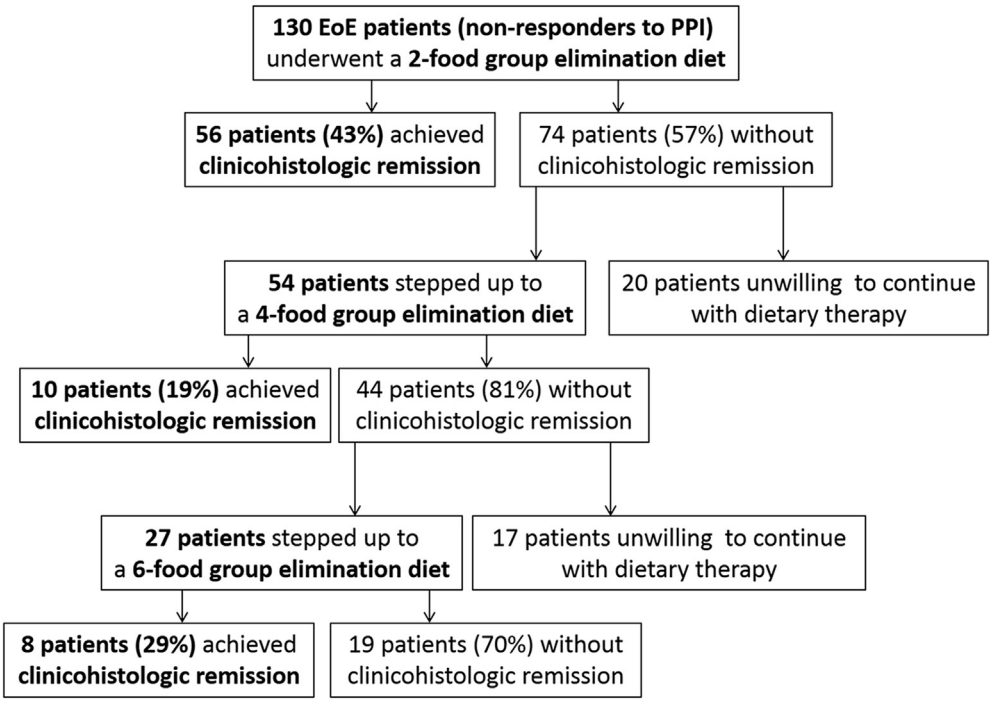

FIG 1. Flowchart of patients during the study.

whey, custard, animal protein, cream, and flavoring) and wheat (farina, flour, starch, vegetable protein, glutamate, dextrin, maltodextrin, seitan, semolina, couscous, kamut, spelt, triticale, and triticum) on food labels. Patients were also advised to avoid processed foods because of the high likelihood of containing wheat or milk traces, including processed meats (eg, sausages and hamburgers), soups, sauces, pizza, mashed potato, and instant rice. A thorough list of foods and sample menus allowed and to be avoided was also provided to patients (see Supplementary Material E1 in this article's Online Repository at www.jacionline.org in English and see http://www.aegastro.es/sites/default/files/archivos/documento-grupo/esofagitis_eosinofilica_0.pdf for material in Spanish). No registered dietitian or nutrition specialist was involved in the study. A telephone number and e-mail address were also provided to patients in case of further doubts regarding the TFGED.

Step-up dietary therapy

Nonresponders to a TFGED were offered to step up to an FFGED (TFGED plus elimination of egg and legumes, including soy, lentils, chickpeas, peas, beans, and peanuts) over 6 weeks. Patients were instructed to read carefully gluten-free product labels because milk, egg, and legume flour were not allowed. Nonresponders to an FFGED were offered rescue dietary therapy with an SFGED (FFGED plus additional exclusion of all kind of nuts, fish, and seafood) for an additional 6-week period. Response to an FFGED or SFGED was also defined by clinicohistologic remission. Nonresponders to a step-up dietary approach or those unwilling to increase dietary restrictions after TFGED or FFGED were offered treatment with swallowed topical steroids (viscous oral budesonide, 2 mg twice daily in adults and 1 mg twice daily in children, or swallowed fluticasone, 800 μg twice daily) for 8 weeks, with further histologic re-evaluation.

Food reintroduction in responders to empiric diets

Patients achieving clinicopathologic remission on any empiric diet underwent individual food reintroduction of eliminated food groups to identify foods triggering EoE. Gluten, especially white bread, was suggested to be the first food to be reintroduced, but the order of food reintroduction was set according to patient preference. Daily consumption of foods from each food group was encouraged for a 6-week period, with endoscopic re-evaluation after each reintroduced food group. If the peak eosinophil count was less than 15 eosinophils/hpf after a single-food challenge, this food was considered well tolerated and maintained in the diet. In contrast, if inflammation (≥15 eosinophils/hpf) recurred, that food was considered an EoE trigger and removed from the diet indefinitely. There was no washout period after inflammation recurrence with a food challenge.

Study end points

The primary study end points were clinicohistologic remission rates after a first-line TFGED in patients with EoE, as well as after stepping up to FFGED and SFEGD rescue therapies. Secondary end points included identifying the frequency and number of food triggers through systematic reintroduction of individual food groups and determining savings regarding endoscopic procedures and diagnostic process time when starting with a TFGED compared with beginning dietary therapy with an FFGED or SFGED.

Statistical analysis

The SPSS (version 21.0; SPSS, Chicago, Ill) statistical analysis package was used. Categorical variables were described with frequencies and percentages, and continuous variables were described with means (SDs) or medians (interquartile ranges [IQRs]), as appropriate. Associations between categorical variables were tested with the χ^2 test (with Fisher correction when necessary), and continuous data were assessed with the 2-sample *t* test or the Mann-Whitney *U* test for parametric and nonparametric data, respectively. A Wilcoxon signed-rank test was used to assess differences in eosinophil counts and symptom scores before and after empiric diet treatment and after reintroduction of the trigger food.

Effectiveness of each of the dietary approaches was measured per protocol as the number of patients who responded to a particular diet divided by the total number of patients who effectively underwent that diet. Missing data from patients who abandoned the step-up protocol before starting an FFGED or SFGED were managed with data imputation techniques (by imputing response rates assuming patients who discontinued from the step-up protocol had the same response rate as those who completed the

TABLE I. Baseline characteristics of patients included in the study

	Overall (n = 130)	Adults (n = 105)	Children (n = 25)	*P* value
Age (y), mean (range)	29 (5-59)	32 (14-59)	11 (5-13)	<.001
Male sex, no. (%)	94 (72)	77 (73)	17 (68)	.5
Smoking habit, no. (%)	14 (11)	14 (13)	—	—
Family history of EoE, no. (%)	6 (5)	5 (5)	1 (4)	.8
Family history of atopy, no. (%)	66 (51)	49 (47)	17 (68)	.004
Atopic disorders, no. (%)	115 (88)	94 (89)	21 (84)	.7
Rhinoconjunctivitis	80 (61)	67 (64)	13 (52)	.09
Asthma	59 (45)	48 (46)	11 (44)	.8
Food allergy/oral allergy syndrome	27 (21)	17 (16)	10 (40)	.006
Atopic dermatitis	23 (18)	14 (13)	9 (36)	<.001
Angioedema	13 (10)	9 (8)	4 (16)	.4
Symptoms, no. (%)				
Dysphagia	110 (85)	101 (96)	9 (36)	<.001
Food bolus impaction	71 (55)	69 (66)	2 (8)	<.001
Heartburn/regurgitation	58 (45)	47 (45)	11 (44)	.8
Epigastralgia/abdominal pain	19 (15)	4 (4)	15 (60)	<.001
Chest pain	14 (11)	14 (13)	—	—
Nausea/vomiting	11 (8)	1 (1)	10 (40)	<.001
DSS, points	9.6	9.8	5.5	<.001
Endoscopic findings, no. (%)				
Normal endoscopic appearance	16 (12)	13 (12)	3 (12)	.6
Rings	76 (58)	74 (70)	2 (8)	<.001
Longitudinal furrows	88 (68)	68 (65)	20 (80)	.1
Edema	111 (85)	89 (85)	22 (88)	.7
Whitish exudates	45 (35)	35 (33)	10 (40)	.3
Reflux esophagitis	13 (10)	12 (11)	1 (4)	.008
Crepe paper esophagus	10 (8)	8 (8)	2 (8)	.8
Esophageal eosinophilia (eosinophils/hpf)				
Proximal esophagus	45 (0-300)	47 (0-300)	41 (0-60)	.6
Distal esophagus	42 (0-157)	42 (0-157)	37 (16-90)	.4

Comparisons were made between adult and pediatric patients.

step-up protocol). A *P* value of less than .05 was considered statistically significant. In line with previous studies and meta-analyses,[7,14,18] a prespecified sample size of 100 patients was considered, with 1 child included for every 4 adult patients.

RESULTS

Baseline characteristics of patients

Over the recruitment period, 227 consecutive patients with EoE and documented lack of histologic response to PPI therapy were eligible for enrollment. Seven patients were excluded because of severe fibrostenotic EoE, and 90 refused dietary interventions. Finally, 130 patients (25 pediatric patients <14 years old) were included. Among children, 13 patients were between 5 and 9 years old, and 12 were between 10 and 13 years old. Sixty-two (48%) patients continued to receive concomitant PPI therapy during the TFGED. The flow of patients during the study is exhibited in Fig 1.

Before enrollment, all patients regularly consumed foods within the 2 food groups excluded in the TFGED. Additional food avoidance at baseline was observed in 11 patients with IgE-mediated egg, legumes, nuts, and fish allergy, and 15 patients had oral allergy syndrome to some nuts and fruits.

Baseline characteristics of patients included in the study are presented in Table I. Children had a higher rate of food allergy and symptoms, such as epigastric pain, abdominal pain, and nausea or vomiting, whereas adult patients were more likely to have dysphagia/food impaction and show rings or reflux esophagitis on endoscopy.

Effectiveness of the TFGED

Regarding dysphagia symptoms, the median baseline DSS in the whole series was 10 (IQR, 4), which significantly decreased after a TFGED to 4 (IQR, 7). Overall, 75.4% of patients achieved clinical response criteria (reduction ≥50% of baseline DSS). The decrease in DSSs was greater among patients who achieved a histologic response (3 [IQR, 4]; $P < .001$) than in those who did not (6 [IQR, 9]; $P = .02$; Fig 2). Symptom improvement after a TFGED was reported in a similar proportion of older children and adults (73% vs 91%, $P = .28$).

As for histopathologic remission, 56 (43%) patients achieved histologic remission on a TFGED (all of them having achieved clinical remission). There were no differences in histologic remission rates for a TFGED when comparing adult and pediatric patients (46 [44%] of 105 vs 10 [40%] of 25, $P = .6$), concomitant use of PPI therapy (PPIs: 28 [45%] of 62 vs no PPIs: 28 [41%] of 68, $P = .5$), or implementation of the diet within the pollen season, which lasts from March to August in Spain (during pollen season: 22 [43%] of 51 vs out of pollen season: 34 [43%] of 79, $P = .8$). Demographic and clinical characteristics of patients, as well as personal or family atopic background, did not predict response to any dietary therapy (data not shown). The effectiveness of the different dietary interventions evaluated in the study is summarized in Fig 3.

Effectiveness of step-up FFGEDs and SFEGDs

Dysphagia regarding the baseline DSS remained unchanged when increasing the level of dietary restriction to either an FFGED (5 [IQR, 8.75]; $P = .01$) or SFGED (6.5 [IQR, 8.25];

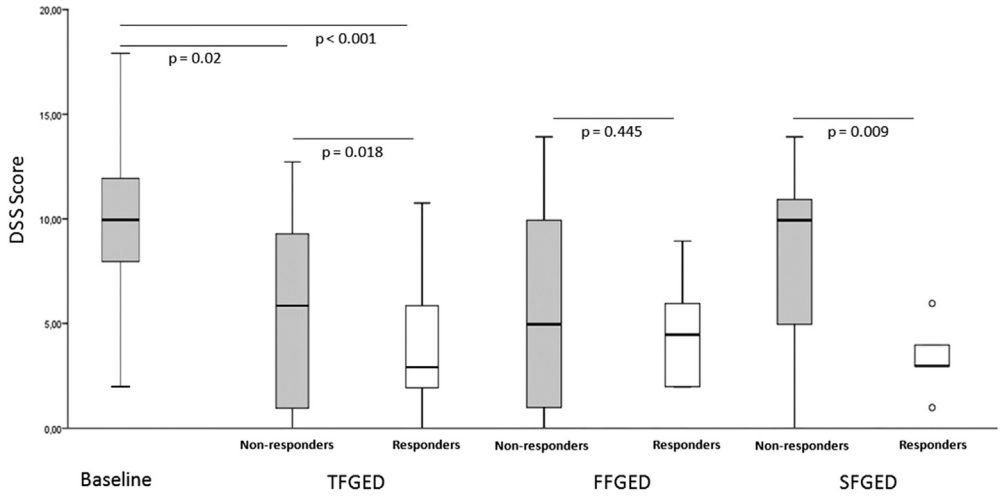

FIG 2. DSSs (medians ± IQRs) in included patients with EoE at baseline and after any dietary intervention, irrespective of remitted or persistent esophageal eosinophilia.

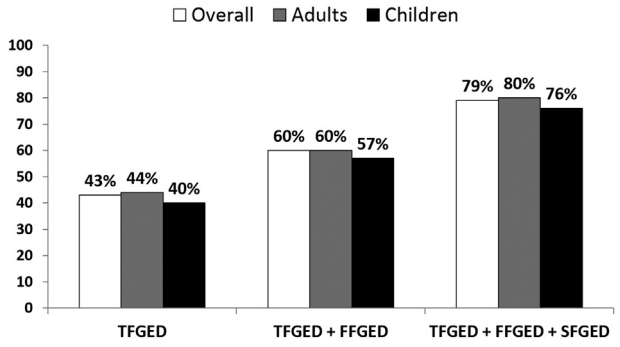

FIG 3. Per-protocol remission rates on a TFGED (56 patients) and after a step-up intervention with an FFGED (10 patients) and an SFGED (7 patients).

$P = .011$). Of note, no differences were observed in DSSs among responders and nonresponders to an FFGED. However, symptom scores were significantly reduced after an SFGED among those patients who experienced histologic remission (3 [IQR, 3] in responders vs 10 [IQR, 8] in nonresponders, $P = .009$; Fig 2).

Among 74 nonresponders to a TFGED, 54 (72%) patients accepted stepping up to an FFGED. Ten (18%) of 54 achieved histologic remission on an FFGED. Remission rates in adults and children were 9 (20%) of 45 and 1 (11%) of 9 ($P = .2$), respectively. Among 44 patients who achieved no histologic remission on TFGEDs and FFGEDs, 27 (61%) patients decided to step up to an SFGED. Eight (29%) of 27 achieved histologic remission on an SFGED (6 [28%] of 21 pediatric patients vs 2 [33%] of 6 adult patients). Cumulative per-protocol clinicohistologic remission rates after TFGEDs, FFGEDs, and SFGEDs were 43%, 60%, and 79%, respectively, and are summarized in Fig 3. For the whole recruited series and having assumed no patient dropout, data imputation analysis provided remission rates after TFGEDs, FFGEDs, and SFGEDs of 43%, 54%, and 68%, respectively (see Table E1 in this article's Online Repository at www.jacionline.org).

Identification of food triggers through individual food group reintroduction

Individual food reintroduction was completed in 50 (89%) of 56 TFGED responders, 10 (100%) of 10 FFGED responders, and 4 (50%) of 8 SFGED responders. The most common food triggers were milk (52/64 [81%]), gluten (28/64 [43%]), egg (10/64 [15%]), and legumes (6/64 [9%]). Food triggers identified in responders to each dietary intervention are shown in Table II. Twenty-six patients (19 adults and 7 children) were found to have milk as the only food trigger. Therefore milk-induced EoE was present in 19 (18.4%) of 103 and 7 (33.3%) of 21 adult and pediatric patients in our study, respectively. It is of note that 55 (91.6%) of 60 responders to TFGEDs/FFGEDs were found to have 1 or 2 food triggers identified after individual food reintroduction. The number of food triggers increased notably with increasing dietary restrictions, especially with SFGEDs, as shown in Fig 4.

Endoscopic and diagnostic process time with a step-up dietary strategy

Assuming histologic remission rates of 40% (TFGED), 60% (FFGED), and 70% (SFGED) and a 6-week period before endoscopy for either elimination diet or food reintroduction, we compared the number of endoscopies and time on dietary restriction necessary to complete the diagnostic process for different top-down and step-up strategies in 10 patients with EoE unresponsive to PPI therapy. The results are shown in Table III. Compared with the initial SFGED, step-up 2-4-6 or 2-4 strategies might save 20% and 30% of endoscopic procedures and diagnostic process time, respectively.

Effectiveness of rescue topical steroid therapy

From 130 included patients, 73 were responsive to some dietary intervention. Thirty-seven patients refused to further increase dietary restrictions on a step-up basis (20 after TFGEDs and 17 after FFGEDs), whereas 20 patients did not respond to TFGEDs, FFGEDs, and SFGEDs. Among these 57 patients (13 children), 24 (9 children and 15 adults) accepted rescue therapy with swallowed topical steroids for 8 weeks, 19 (79%) of whom achieved histologic remission.

TABLE II. Food triggers identified after individual food reintroduction followed by endoscopy in each dietary intervention

TFGED responders (50/56)		
One food trigger	34/50	68%
Milk	26/50	52%
Gluten	8/50	16%
Two food triggers	14/50	28%
Milk and gluten	14/50	28%
No food trigger	2/50	4%
FFGED responders (10/10)		
One food trigger	1/10	10%
Egg	1/10	10%
Two food triggers	6/10	60%
Milk and legumes	3/10	30%
Milk and egg	3/10	30%
Three food triggers	3/10	30%
Milk, gluten, and egg	2/10	20%
Milk, gluten, and legumes	1/10	10%
SFGED responders (4/7)		
Three food triggers	1/4	25%
Milk, egg, and fish/seafood	1/4	25%
Four food triggers	1/4	25%
Gluten, egg, legumes, and fish/seafood	1/4	25%
Five food triggers	2/4	50%
Milk, gluten, egg, nuts, and fish/seafood	1/4	25%
Milk, gluten, egg, legumes, and fish/seafood	1/4	25%

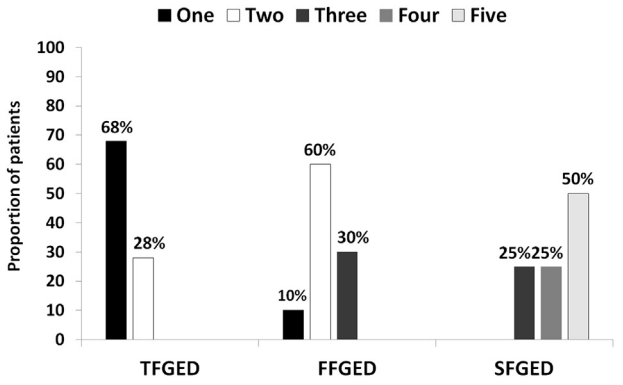

FIG 4. Proportion of responders to each dietary intervention and corresponding number of food triggers identified after individual food reintroduction.

DISCUSSION

In the present study a TFGED achieved 43% efficacy and obtained similar results to those previously reported[13-18] when patients were stepped up to an FFGED (60%) or SFGED (79%). This step-up strategy, starting with a TFGED, exhibits a relevant number of advantages over beginning with highly restrictive diets (top-down dietary strategies).

To begin with, it allows early identification of two thirds of responders to any empiric elimination diet with the performance of a single endoscopic procedure.

Second, we showed that a single food trigger (either animal milk or gluten-containing cereals) was present in up to 70% of TFGED responders, with the remaining patients having both. Additionally, 70% of responders to an FFGED were also found to have 1 or 2 food triggers. As such, a step-up combination of TFGED and FFGED is capable of detecting the vast majority of those potential SFGED responders who had just 1 or 2 food triggers after 6 food challenges, followed by 6 endoscopies.[17] Undoubtedly, these patients with 1 or 2 food triggers are the best candidates for maintenance dietary therapy through long-term avoidance of these few food triggers.

Third, a TFGED can be undertaken easily without need for a dietician. Allergists and pediatric and adult gastroenterologists are familiar with gluten-free, lactose-free, and/or cow's milk protein–free diets, which are usually prescribed for common conditions, such as celiac disease, wheat allergy, irritable bowel syndrome, or food protein–induced enterocolitis.

Fourth, specific referral to an allergist for food allergy testing can be avoided with a TFGED, resulting in improved resource management and avoidance of confusion from positive results on food allergy testing.

Fifth, a TFGED allows egg and legume intake, which might be difficult to avoid, especially in gluten-free products.

Sixth, a TFGED or FFGED can save a relevant proportion of endoscopic procedures and time on unnecessary dietary restrictions.

Last but not least, patient uptake for dietary therapy might notably increase with less restrictive diets, and a step-up strategy might boost the patient's willingness to try dietary therapy.

Milk was found to be the only food triggering the disease in half of the TFGED responders. Overall, milk-induced EoE was present in 18% and 33% of adult and pediatric patients, respectively. Our results are consistent with those of our previous sub-analysis from the first FFGED study[18] but discrepant with previous pediatric studies reporting 65% and 61% cure rates with a cow's milk elimination diet.[21,22] Concerns about methodological flaws hang over these studies, including selection bias (exclusive inclusion of patients with IgE-mediated cow's milk food allergy resolved after cow's milk oral desensitization)[21] and concomitant use of PPIs and dietary therapy.[22] The effectiveness of a milk elimination diet should be evaluated in well-designed, rigorous, multicenter studies in children and adults. In line with previous studies on SFGED,[12-17] we obtained similar results in children and adults with every evaluated dietary intervention.

Interestingly, egg has been reported as the third most common food trigger for EoE, with gluten as the second most common food trigger.[17] Milk, gluten-containing grains, and eggs are staple foods worldwide. In contrast, legumes seem to be common food triggers only in Spanish studies (including the present study),[14,15,18] with a minor role reported in studies conducted in the United States[12,13] and Australia.[16] In these countries soybean seems to be the only relevant legume related to EoE. These discrepant findings might reflect merely distinct patterns of food consumption among different geographic areas. Legumes, such as lentils, chickpeas, beans, and peas, are regularly consumed in Mediterranean countries. Because of these data, the effectiveness of a 3-food elimination diet (milk, gluten-containing grains, and egg) warrants further research in specific settings where legumes, including soy and peanuts, are not elements of a regular diet. In our country we firmly believe that a TFGED and an FFGED should be used in all patients with EoE willing to undergo dietary therapy, whereas stepping up to an SFGED can be reserved for highly motivated patients who wish to identify potential causative foods and are willing to remove several food groups from their diets indefinitely.

TABLE III. Calculations on the number of endoscopic procedures and correlative diagnostic process time required for empiric dietary interventions in 10 patients with EoE

	Initial endoscopy after an SFGED	Food reintroduction in SFGED responders (n = 7)					Total no. of endoscopies	Total weeks on dietary restrictions
6	10	7 × 6 = 42					52	312
	Initial endoscopy after a FFGED	Food reintroduction in FFGED responders (n = 6)	Step-up SFGED	Food reintroduction in SFGED responders (n = 1)				
4-6	10	6 × 4 = 24	4	1 × 6 = 6			44	264
	Initial endoscopy after a TFGED	Food reintroduction in TFGED responders (n = 4)	Step-up FFGED	Food reintroduction in FFGED responders (n = 2)	Step-up SFGED	Food reintroduction in SFGED responders (n = 1)		
2-4-6	10	4 × 2 = 8	6	2 × 4 = 8	4	1 × 6 = 6	42	252

Histologic remission rates of 40% (TFGED), 60% (FFGED), and 70% (SFGED) and a 6-week period before each endoscopy for either elimination diet of food reintroduction were assumed.

In accordance with our previous research with FFGEDs,[18] concomitant PPI therapy or implementing the diet out of the pollen season did not increase the efficacy of a TFGED. Likewise, we found 2 responders to a TFGED who achieved sustained remission despite reintroduction of both milk and wheat. The significance of this intriguing phenomenon, which has been described in other studies,[16,18,23] remains unknown. Sampling error in esophageal biopsy specimens, misdiagnosed responders to PPI therapy, cross-reactivity with airborne allergens, or disease activity fluctuations might be potential explanations. We also replicated typical clinicohistologic dissociation after therapeutic interventions in patients with EoE, with higher clinical response over histologic remission after a TFGED but no clinic improvement despite histologic remission with FFGEDs or SFGEDs. This finding might be related to a high degree of motivation at the first step of this multistage process, which can decrease and then alter symptom perception when more restrictive diets are accomplished.

Our study has several strengths, such as being the first multicenter prospective study on a step-up dietary strategy, the first study coupling children and adults, and the study with the largest sample size reported thus far. No differences were observed between children and adults in the present study, confirming previous reports of similar remission rates for an SFGED, regardless of patient age.[7] On account of recent homogeneous cure rates also reported for PPI[24] and topic steroid[25] therapy between pediatric and adult patients, our findings confirm that EoE is likely a continuum of the same disease in children and adults. However, several limitations should be acknowledged in this study, namely the absence of a control group and use of a nonvalidated questionnaire to assess symptoms in patients with EoE. The more recent EoE Activity Index instrument, which was validated only in adult patients,[26] has not been validated yet to be used in the Spanish language. Nevertheless, esophageal symptoms alone, measured through the EoE Activity Index instrument, have recently showed a modest predictive capacity for estimating the presence of either histologic and endoscopic remission in adult patients with EoE.[27] No validated[28] or nonvalidated[29] symptom scores were used for younger children with dysphagia. The Pediatric Eosinophilic Esophagitis Symptom Score has shown a good correlation with clinical and histologic outcomes after therapy.[30] Of note, a 28% dropout rate among the initially enrolled patients should be acknowledged, which could lead mistakenly to a sense of overestimation of the success rate of the diet. However, the design of the present study allows only a per-protocol analysis in patients who were assessed before and after the dietary intervention. All previous studies and meta-analyses published on dietary therapy have also followed this methodology. Indeed, efficacy rates calculated by means of data imputation were slightly lower for an FFGED and SFGED. In either case the observed per-protocol response rates paralleled those of all previously published data, and therefore the effect of a possible selection bias would have been quite limited. Compliance with dietary recommendations was not assessed structurally, and lack of a dietitian might have underrated weight loss or growth failure. Although the need for a washout period between endoscopies after disease relapse during food reintroduction remains unproven, its lack in the present study might have led to misleading results. However, our findings are quite similar to those described in previous literature.[14-18,23] Finally, our results might be transferable to settings with similar staple diets and food consumption habits. Therefore generalization should not be made until further validation is made in other geographic areas with different food consumption habits.

In conclusion, the present study prospectively demonstrates that a TFGED achieves remission in 43% of patients with EoE, with no differences between children and adults. After a rescue FFGED, 92% of responders to either a TFGED or an FFGED were found to have 1 or 2 food triggers identified after individual food reintroduction. Compared with an initial SFGED, an initial TFGED allows early recognition of two thirds of responders to any empiric elimination diet, whereas stepping up to an FFGED identified all patients with one of 2 food triggers, the best candidates for maintenance dietary therapy. Whether an exclusive milk elimination diet is suitable as a first-line therapy for pediatric populations with remission rates close to 30% in our study should be evaluated in large, prospective, well-conducted studies. We also replicated previous data on the effectiveness of FFGEDs and SFGEDs, although the number of identified food triggers

increased notably, especially after an SFGED. These findings provide useful and realistic information for patients undertaking empiric elimination diets. We believe that this multistage step-up approach might be recommended to simplify dietary management of EoE, avoid unnecessary dietary restrictions, reduce the number of endoscopic procedures, and shorten the diagnostic process time. All these advantages can help engage both patients with EoE and physicians with dietary therapy.

Clinical implications: A step-up empiric elimination diet (2-4-6) allows early identification of a majority of patients with EoE who respond to empiric diets with few food triggers, saving endoscopic procedures, shortening the diagnostic process, and avoiding unnecessary dietary restrictions.

REFERENCES

1. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3-20.
2. Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993;38:109-16.
3. Straumann A, Spichtin HP, Bernoulli R, Loosli J, Vögtlin J. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings [in German with English abstract]. Schweiz Med Wochenschr 1994;24:1419-29.
4. Arias Á, Pérez-Martínez I, Tenías JM, Lucendo AJ. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther 2016;43:3-15.
5. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology 1995;109:1503-12.
6. Simon D, Cianferoni A, Spergel JM, Aceves S, Holbreich M, Venter C, et al. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. Allergy 2016;71:611-20.
7. Arias A, Gonzalez-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. Gastroenterology 2014;146:1639-48.
8. Molina-Infante J, Martin-Noguerol E, Alvarado-Arenas M, Porcel-Carreño SL, Jimenez-Timon S, Hernandez-Arbeiza FJ. Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis. J Allergy Clin Immunol 2012;130:1200-2.
9. van Rhijn BD, Vlieg-Boerstra BJ, Versteeg SA, Akkerdaas JH, van Ree R, Terreehorst I, et al. Evaluation of allergen-microarray-guided dietary intervention as treatment of eosinophilic esophagitis. J Allergy Clin Immunol 2015;136:1095-7.
10. Wolf WA, Jerath MR, Sperry SL, Shaheen NJ, Dellon ES. Dietary elimination therapy is an effective option for adults with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2014;12:1272-9.
11. Philpott H, Nandurkar S, Royce SG, Thien F, Gibson PR. Allergy tests do not predict food triggers in adult patients with eosinophilic oesophagitis. A comprehensive prospective study using five modalities. Aliment Pharmacol Ther 2016;44:223-33.
12. Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol 2006;4:1097-102.
13. Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012;142:1451-5.
14. Lucendo AJ, Arias A, Gonzalez-Cervera J, Yagüe-Compadre JL, Guagnozzi D, Angueira T, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. J Allergy Clin Immunol 2013;131:797-804.
15. Rodríguez-Sánchez J, Gómez Torrijos E, López Viedma B, de la Santa Belda E, Martín Dávila F, García Rodríguez C, et al. Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic oesophagitis. Allergy 2014;69:936-42.
16. Philpott H, Nandurkar S, Royce SG, Thien F, Gibson PR. A prospective open clinical trial of a proton pump inhibitor, elimination diet and/or budesonide for eosinophilic oesophagitis. Aliment Pharmacol Ther 2016;43:985-93.
17. Molina-Infante J, Lucendo AJ. Letter: dietary therapy in eosinophilic oesophagitis—do not test, just eliminate and reintroduce the most common food triggers. Aliment Pharmacol Ther 2016;44:904-5.
18. Molina-Infante J, Arias A, Barrio J, Rodríguez-Sánchez J, Sanchez-Cazalilla M, Lucendo AJ. Four-food group elimination diet for adult eosinophilic esophagitis: a prospective multicenter study. J Allergy Clin Immunol 2014;134:1093-9.e1.
19. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62:489-95.
20. Kliewer KL, Venter C, Cassin AM, Abonia JP, Aceves SS, Bonis PA, et al. Should wheat, barley, rye, and/or gluten be avoided in a 6-food elimination diet? J Allergy Clin Immunol 2016;137:1011-4.
21. Kagalwalla AF, Amsden K, Shah A, Ritz S, Manuel-Rubio M, Dunne K, et al. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2012;55:711-6.
22. Kruszewski PG, Russo JM, Franciosi JP, Varni JW, Platts-Mills TA, Erwin EA, et al. Prospective, comparative effectiveness trial of cow's milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis. Dis Esophagus 2016;29:377-84.
23. Kagalwalla AF, Shah A, Li BU, Sentongo TA, Ritz S, Manuel-Rubio M, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. J Pediatr Gastroenterol Nutr 2011;53:145-9.
24. Lucendo AJ, Arias A, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histological remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016;14:13-22.e1.
25. Murali AR, Gupta A, Attar BM, Ravi V, Koduru P. Topical steroids in eosinophilic esophagitis: Systematic review and meta-analysis of placebo-controlled randomized clinical trials. J Gastroenterol Hepatol 2016;31:1111-9.
26. Schoepfer AM, Straumann A, Panczak R, Coslovsky M, Kuehni CE, Maurer E, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology 2014;147:1255-66.
27. Safroneeva E, Straumann A, Coslovsky M, Zwahlen M, Kuehni CE, Panczak R, et al. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. Gastroenterology 2016;150:581-90.
28. Franciosi JP, Hommel KA, DeBrosse CW, Greenberg AB, Greenler AJ, Abonia JP, et al. Development of a validated patient-reported symptom metric for pediatric eosinophilic esophagitis: qualitative methods. BMC Gastroenterol 2011;11:126.
29. Aceves SS, Newbury RO, Dohil MA, Bastian JF, Dohil R. A symptom scoring tool for identifying pediatric patients with eosinophilic esophagitis and correlating symptoms with inflammation. Ann Allergy Asthma Immunol 2009;103:401-6.
30. Martin LJ, Franciosi JP, Collins MH, Abonia JP, Lee JJ, Hommel KA, et al. Pediatric Eosinophilic Esophagitis Symptom Scores (PEESS v2.0) identify histologic and molecular correlates of the key clinical features of disease. J Allergy Clin Immunol 2015;135:1519-28.