

Allergy-test-driven elimination diet is useful in children with eosinophilic esophagitis, regardless of the severity of symptoms

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Abstract

Background: A combination of PPIs and corticosteroids is the pharmacotherapy mostly used to treat eosinophilic esophagitis (EoE), while dietetic manipulations consist also an efficient option. The aim of this study was to compare the efficacy of allergy-test-driven elimination diet in children with mild symptoms of EoE to a group of children with moderate/severe symptoms.

Methods: Thirty-five children, aged 7 months to 12 yr, with EoE were enrolled in the study. They had a clinical history of GERD-like (21 children, Group A) or more severe symptoms (14 children, Group B). The diagnosis had been confirmed after two preliminary months of therapy with PPIs and an esophagogastroduodenoscopy. Soon after diagnosis, they were allergy-tested, using IgE detection (SPT and serum-specific IgE) and atopy patch tests (APTs). A 12-month tailor-made diet was prescribed according to the tests. Patients of Group B continued PPIs for two more months, while swallowed topical steroids were also prescribed to them for the first 5 months after diagnosis, followed by an 'as-needed' use of them for the rest of the study. Endoscopy was repeated at the end of the study.

Results: Milk and egg were the most common APT-positive allergens. Thirty-two patients were instructed to follow an elimination diet, which was completed by 15/18 of Group A and 12/14 of Group B. An improvement of symptoms was reported by 26/27 patients that completed the study. The use of swallowed corticosteroids was noticeably decreased during the as-needed period, in Group B. A remarkable reduce of eosinophils was noticed in biopsies; from 42.84 ± 18.08 , they decreased to 6.41 ± 3.20 , a year after.

Conclusion: All children with EoE and mild symptoms had resolution of symptoms and normal eosinophils in the esophageal mucosa a year after an allergy-driven elimination diet. Patients with moderate/severe EoE symptoms had the same improvement, indicating that an elimination diet is an efficient complementary treatment to corticosteroids.

Eosinophilic esophagitis (EoE) is an immune-mediated disorder with symptoms of esophageal dysfunction that can affect all ages (1). Esophageal eosinophilia is a more general term describing the pathologic finding of increased esophageal epithelial infiltration by eosinophils, seen in EoE as well as in other diseases of the digestive system (2). The presence of intra-epithelial eosinophils, unaffected by antacid therapy with proton pump inhibitors, is crucial for the diagnosis of EoE (1).

The prevalence of EoE has increased during last decade. The increase of newly diagnosed cases has fueled skepticism on whether this is due to improved diagnostic yields and/or heightened awareness by medical professionals. Studies have shown that the increase is true and it is presumably associated with the increase of other immunological diseases, like allergy (3, 4). The majority of patients with EoE present concomitant allergic rhinitis, asthma, food allergy, and eczema, confirmed with allergy *in vitro* and *in vivo* tests (5, 6).

Treatment of EoE consists of pharmacologic management, diet, and—in the presence of esophageal stenosis and severe persistent symptoms—of endoscopic dilatation (7). Diet is an important option. Food allergen-driven dietary manipulations are effective in approximately 70–80% of pediatric patients (6, 8–12). The effectiveness of elimination diets is confirmed by disease's recrudescence upon reintroduction of the culprit foods (12). However, whether food allergen elimination is more successful when based on empiric standards, rather than it is when allergy tests directed, is a subject of much debate (11).

Differentiating EoE from gastroesophageal reflux disease (GERD) is often a challenge for the clinician, as they have some common symptoms (regurgitation, vomiting, heartburn) and eosinophils may be present in both diseases (2, 3, 13, 14). Diagnosis appears even more complicated when proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE) is encountered; biopsies show an increased esophageal infiltration by eosinophils that decline after PPI therapy (2).

Severity of symptoms ranges from mild (GERD-like symptoms) to serious (food impaction and dysphagia). Dietary manipulations have been shown to be useful in cases of EoE with different clinical profiles, but it is unclear whether the expected effectiveness is the same in mild and in moderate/severe clinical cases.

The aim of the following prospective study was to investigate the culprit allergens in cases of EoE and assess the effect of tailor-made allergy-test-driven dietary manipulations in pediatric EoE patients of different severity.

Patients and methods

Patients

Thirty-five children with EoE, aged 7 months to 12 yr (median age 81 months), were enrolled in the study. Their clinical profiles were classified from mild to severe. Patients were divided into two groups, according to their medical history: Group A (21 children) presenting with mild symptomatology, usually GERD-like symptoms, and Group B (14 children) with more severe symptomatology. In infants, the most common presentations comprised of irritability, feeding difficulties, vomiting, and abdominal pain. These symptoms were considered mild. On the contrary, infants with a history of choking and gagging, serious food refusal causing weight loss, or hemorrhage were considered of moderate/severe symptomatology. In older children, vomiting and heartburn with intense retrosternal pain were considered mild symptoms, while dysphagia and food impaction were considered moderate/severe.

Twenty, age- and gender-matched, apparently healthy infants and children were studied for atopy patch testing, as controls, to exclude false-positive results.

Diagnosis of EoE

The clinical symptoms leading to the diagnosis of EoE were vomiting, regurgitation, food refusal, irritability, abdominal

pain, food impaction, and/or dysphagia. Esophagogastroduodenoscopy (EGD) was performed in all children, after informed consent, and at least two biopsies were obtained from the proximal, mid and distal esophagus, stomach, and duodenum. The biopsies were evaluated under $\times 40$ high-powered microscopic field (HPF). The diagnosis of EoE was confirmed when more than 15 eosinophils in the most densely involved HPF of the esophagus were found.

Patients with more than 15 eosinophils/HPF were prescribed proton pump inhibitors (PPIs), for eight weeks, upon their first endoscopy and were then reevaluated. The definitive diagnosis of EoE was given to the cases that were clinically and histologically (confirmed with a second endoscopy) unresponsive to an 8-wk-long treatment with PPIs, excluding 'eosinophilia secondary to GERD' and PPI-responsive esophageal eosinophilia ('PPI-REE'). Repeated biopsies were routinely obtained after the first one only to children with confirmed EoE (Fig. 1).

Allergy tests

Following confirmation of EoE, all children were subjected to detection of IgE-mediated food allergy, with specific IgE (sIgE), skin tests, and atopy patch tests (APT) for the detection of cell-mediated food allergy. The tested foods were cow's milk, egg, wheat, rice, corn, potato, peanut, soy, chicken, beef, pork, and fish.

The ImmunoCAP System (Phadia, Uppsala, Sweden) was used for the *in vitro* detection of sIgE. The skin prick test (SPT) and the prick-to-prick methods were both used for skin testing. SPTs were performed using commercial extracts for cow's milk, potato, peanut, pork, chicken (ALK Diagnostics, Hørsholm, Denmark), fish (Leti, Spain), egg white, egg yolk, wheat, rice, corn and soy (Alyostal, Stallergens, France), and beef (Allergopharma, Germany). Prick-to-prick tests were performed using the same preparations made for the APTs. Skin tests were carried out on the volar surface of the right (SPT to commercial extracts) and the left (prick-to-prick to fresh preparations) forearm. Negative (50% glycerinated HAS-saline) and positive (histamine dihydrochloride, 10 mg/ml) controls were used.

Patients with a sIgE level > 0.35 kU/l (ImmunoCAP detection limit, Pharmacia, Uppsala, Sweden) were considered sensitized to the relative allergen. Skin tests were considered positive when the wheal's diameter was larger than 3 mm compared to the negative controls. A patient resulting positive to both sIgE and SPT or to either of them was considered IgE-sensitized, taking into consideration that sensitized is not synonymous to allergic.

APTs to all the above-mentioned allergens were performed using fresh foods; one drop of fresh cow's milk containing 3.5% fat, whisked hen's egg (white and yolk), wheat flour, rice flour, corn flour, potato flour, soy flour (all flours were pure), crude chicken, crude beef, crude pork, crude fish, and well-smashed peanut were dissolved in NaCl 0.9% (1 g food/10 ml). The mixtures were then placed in 12-mm aluminum cups (Finn

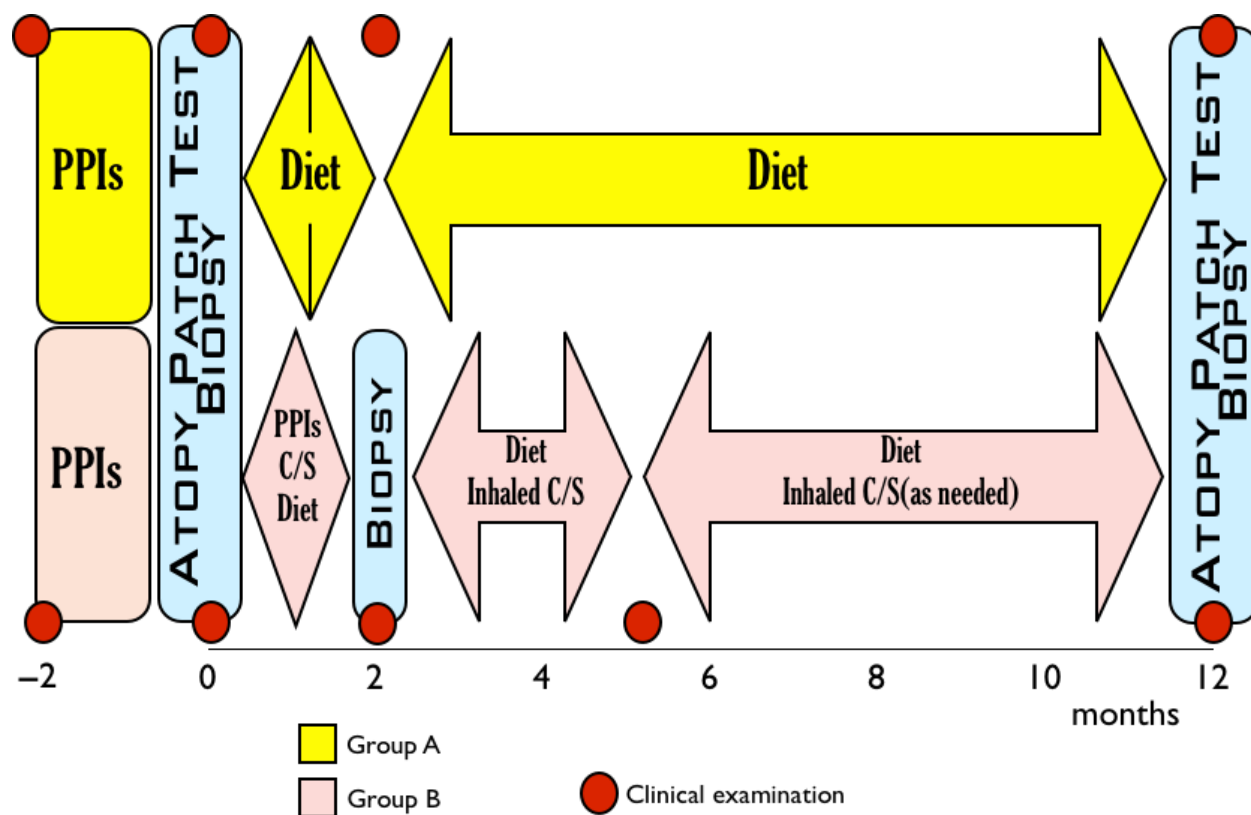


Figure 1 Protocol of the study.

Chambers on Scanpore, Tuusula, Finland) on uninvolved areas of the patient's back. The patch test occlusion time and its readings followed the revised European Task Force on Atopic Dermatitis recommendations; a reaction is considered positive when at least erythema, infiltration, and possible discrete papules are present (15). A first reading was taken 20 min after the application of the allergens so as to exclude an immediate skin reaction. The occlusion time was 48 h, and then, we had a first evaluation, 20 min after removing the apparatus. The final APT evaluation was at 72 h.

Clinical follow-up

After the initial evaluation and confirmation of EoE following an 8-wk treatment with PPIs, all children with positive allergy tests were advised to follow an elimination (allergen free) diet avoiding completely the foods that resulted positive to APTs or to sIgE and/or SPT. It was considered necessary to follow different protocol for each group, as patients of Group B had more severe clinical problems, rather impossible to be cured with diet only.

Children of Group B continued the treatment with PPIs, while corticosteroids were also prescribed (Fig 1); twelve of them received swallowed topical steroids, while the remaining two were treated with prezonon *per os* (1 mg/kg/day), until the 8-wk reevaluation. EGD with biopsies was repeated 8 wk after

the diagnosis of EoE, to evaluate histological changes following pharmaceutical treatment and diet.

Group A patients were clinically reexamined 2 and 12 months after the confirmation of EoE, following only an elimination diet, and instructed to contact our department in case of symptoms' relapse. Group B patients were reevaluated 2, 5, and 12 months after their diagnosis of EoE (Fig. 1). In Group B, PPIs were stopped after the second endoscopy performed for reevaluation (2 months after confirmation of diagnosis) and swallowed topical steroids were stopped after the fifth month's clinical reevaluation, with the instruction to use them 'as needed', if no clinical improvement was achieved.

Clinical improvement was defined as the resolution, or the significant reduction of symptoms. In infants, the aforementioned symptoms were evaluated: weight gain, resolution of choking and hemorrhage, decrease of irritability, feeding problems, vomiting, and food refusal. In older children, the improvement was more subjective in cases of heartburn, retrosternal pain, and dysphagia and more objective when vomiting and food impaction were evaluated.

A biopsy was not repeated in all patients of Group B, after the two-month diet, mainly due to parental refusal of consent. All children with improved symptoms were instructed to continue the exclusion diet. Additional medical treatment was decided individually.

Statistical analysis

The nonparametric Mann–Whitney *U*-test was used to compare the results of APTs and of IgE detection (negative or positive) between the two groups. The level of significance was $p = 0.05$. Wilcoxon nonparametric test was used to compare the number of eosinophils in the initial (month 0) and final (month 12) biopsies.

Results

Allergy test results

Thirty-two patients had at least one positive allergy test (APTs, sIgE/SPT detection or both), while 24/35 of our patients were atopic. This term was used to describe a patient with a) history of an atopic disease and/or a relative family history, and b) the presence of sIgE antibodies in serum or by a positive skin prick test.

IgE detection was considered positive when either or both sIgE and SPT resulted positive and negative when both were negative. SPTs were not performed in 3/21 cases of Group A and 1/14 cases of Group B, due to lack of cooperation or skin problems (a case of solar burn), so in these cases, only sIgE was evaluated. Overall, IgE detection was positive in 12/21 cases in Group A and in 12/14 cases of Group B. In cases with positive sIgE, its level was >0.7 kU/l. There was no significant difference in the presence of positive sIgE and/or SPT between the two groups ($\chi^2 = 3.18$, $p = 0.07$).

Atopy patch testing was positive in 30/35 patients with EoE: 17/21 in Group A and 13/14 in Group B. Five were monosensitive (with positive APTs to only one food allergen), 3/30 to two allergens, and the remaining 22/30 to three or more allergens. Egg and soy were the commonest APT-positive allergens in Group A (8/17), followed by milk, beef, and chicken (7/17). Milk was the most common allergen in APTs in Group B (7/13), followed by egg (5/13).

Regarding our control group, 14/20 were atopic with positive SPT and/or sIgE, to aeroallergens. All APTs were negative or doubtful in control group.

Three patients had negative allergy detection (negative in both APTs and IgE detection test), so no specific diet was advised. Two patients with negative APTs had positive IgE detection; one of them was fish allergic, with a relative history of anaphylaxis, while the other one had multiple sensitizations.

Dietary outcomes

An elimination diet was prescribed in 32 patients with positive allergy tests: 18 of Group A and 14 of Group B (11 with failure to thrive, 5 with food impaction, and 3 with hemorrhage). The child with fish allergy (Group A), presenting a positive IgE detection and negative APTs, had already been following a fish-free diet ever since anaphylaxis, so the diet was unaltered. An elimination diet was also proposed to a child with food impaction of Group B, with positive IgE detection and negative APTs.

Elimination diets were tailored-made, according to the positive APTs, while the results of SPT and sIgE tests were individually taken into consideration, upon clinical history; a patient with weak (<3 mm) SPT and sIgE <0.7 kU/l to a food was instructed to eliminate only others with clearly positive tests. Our patient with +SPT/+sIgE to fish was already avoiding it, while a diet according to the positive findings was instructed to our patient with multiple IgE sensitizations and negative APTs. Instructions were clearly given to parents so as to avoid completely the discriminated food(s).

As mentioned in methodology, rice, corn, and wheat were examined separately and resulted positive in different patients, leading to the conclusion that there is no cross-reaction. As far as beef is concerned, it was found positive in 8 cases with a coexisting milk sensitization and in 5 cases without sensitivity to milk. No cross-reactivity was observed between egg and chicken.

Upon the 12th-month reexamination, an improvement in the symptoms of EoE was reported by 15 patients of Group A and by 11 patients of Group B. There were six dropouts in Group A and two dropouts in Group B (Table 1).

In Group B, there was a patient who followed the 12-month elimination diet without clinical improvement; this was the case of a twelve-year-old atopic patient with a history of dysphagia and food impaction, with positive APTs to egg, rice, and chicken, receiving swallowed topical fluticasone (500 mcg/daily), throughout the egg/rice/chicken elimination diet. No other patient has used corticosteroids during the 'as-needed' period.

In conclusion, among patients that completed the protocol, APT-driven diet resulted in clinical improvement in all patients of Group A and in 11/12 in Group B, at 12-month reevaluation.

Biopsy outcomes

Complete biopsies' data were collected from fifteen patients of Group A and twelve of Group B (Fig. 2). The clinical

Table 1 Data according to allergy tests, elimination diet, and biopsy outcome

	Group A	Group B
Number of participants	21	14
Positive allergy tests		
Total	18	14
APT +	17	13
SPT/sIgE +	12	12
Elimination diet		
Prescribed	18	14
Completed	15	12
Clinical improvement	15	11
Biopsy outcomes		
Month 0	42.1 $\pm$ 16.9	44.1 $\pm$ 18.6
Month 2	–	12.3 $\pm$ 4.8
Month 12	6.9 $\pm$ 3.4	6.3 $\pm$ 2.8

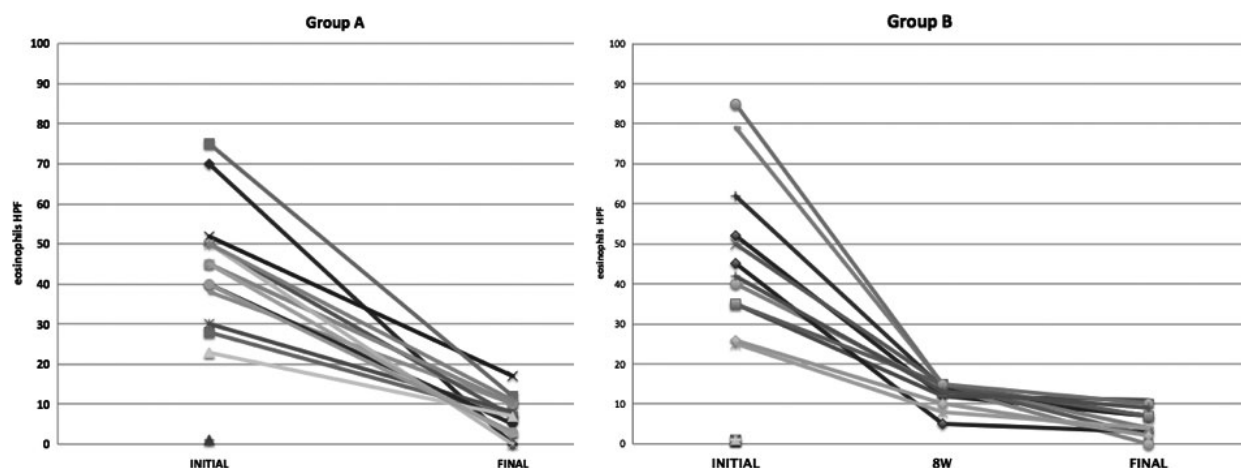


Figure 2 Number of eosinophils before, 2, and 12 months after intervention. There was no statistically significant difference among the two groups regarding initial (42.1 ± 16.9 in A and 44.1 ± 18.6 in B) or final (6.9 ± 3.4 for A and 6.3 ± 2.8 for B) number of eosinophils. In Group B, a drop in eosinophils (12.3 ± 4.8) was noticed since the 8th week, after pharmacotherapy.

improvement was followed by an outstanding, statistically significant ($p < 0.01$), decrease of eosinophils in our patients' biopsies; from 42.84 ± 18.08 HPF in the initial biopsies, they decreased to 6.41 ± 3.20 HPF in the final biopsies.

Discussion

Our study confirms that most children with EoE have multiple sensitizations to APTs; however, milk (15/30) and egg (13/30) were observed as the most common allergens. The high frequency of egg sensitization is not described by other authors (10, 11), and it might be due to different dietary habits of our population or due to the inclusion of more severe cases in our study.

There is no known different pathophysiologic basis differentiating mild-to-moderate/severe clinical presentation of EoE. However, we decided to separate patients in two groups because those with moderate/severe symptoms urgently needed pharmaceutical treatment additionally to the dietetic one. On the contrary, patients with EoE and mild symptoms allowed a dietetic intervention without additional pharmaceutical treatment, giving a clear message whether allergy-test-driven elimination diet could have an effect on resolution of both symptoms and histological abnormalities. The present study showed that in such a group of patients, diet according to APTs could be the first option, avoiding therefore unnecessary diets or steroids. Additionally, in most severe cases, elimination diet according to allergy tests could prevent relapse after steroid withdrawal.

The effect of specific allergy-test-driven diet on EoE is debatable, since recent studies have shown that an empiric elimination diet can also be effective (11). The beneficial response to elimination diets, that has been reported even in patients without food sensitization, suggests a more general anti-inflammatory effect (16, 17). Such an anti-inflammatory effect has also been hypothesized to be useful in non-allergic

gastrointestinal disorders such as Crohn's disease (16), but their positive impact has not been confirmed (18). Our team has also shown the positive effect of an allergen-test-driven diet in cases of chronic constipation, unresponsive to laxatives (19).

Treatment with steroids was prescribed in Group B during the first 5 months. Although swallowed topical steroids definitely had a positive impact on the clinical improvement, the fact that only one child used them during the 'as-needed' interval of months 5–12 enforced the evidence that dietary manipulations were possibly effective, helping to prevent symptoms' relapse.

It was recently shown that the daily administration of a high dose (1760 mcg) of fluticasone propionate induces histological remission in 65–77% of patients with EoE, after a treatment of 3 months (20). Diet is regarded as a supplementary treatment to the use of inhaled steroids; however, the course of our patients was much more promising, showing its great impact in the treatment of EoE.

Depending on the effects of the diet, the swallowed topical steroids were reintroduced in children that had symptoms' relapse upon their withdraw. The decision for them was individual, and the duration of this combined approach (diet and pharmacotherapy) was taken during follow-up. Topical swallowed steroids (or systemic in severe cases) should be considered for all patients so as to avoid symptoms' recurrence (1, 21). Achieving tolerance of foods after a dietary manipulation in children with EoE is rare (8%), but is more promising than medical therapy alone, that is not leading to clinical resolution (6). No spontaneous remission is expected in children with EoE, if therapeutic manipulations are not followed. In adults, treatment improves the clinical history, but histological findings are usually irreversible, so symptoms of EoE are recurrent (22).

The decision to use one of the dietary approaches (elemental, empiric, or targeted elimination) should rather be tailored

according to the individual patient needs and depends on the age, severity, and of course on the clinician's experience (2). Elemental diets are generally unpalatable, with poor compliance by young children. Additionally, their cost is high, having an impact on the quality of life in an already stressed life (23, 24).

A suggested empiric six-food diet includes the elimination of milk, eggs, wheat, soy, seafood (fish and shellfish), and nuts (peanuts and tree nuts) (7). Such a diet is reported to have very high (81–95%) symptomatic response and to be as effective as the allergy-test-driven ones (9, 25, 26). Allergen-reintroducing studies, regarding six-food elimination diet, have shown milk, egg, soy, and wheat to be the most common triggers of EoE (10, 24). The downside, however, is the elimination of food groups that the patient may tolerate and which are potentially 'innocent' and unrelated to the underlying diagnosis in EoE.

Besides milk and egg, the most common foods identified by allergy tests were rice, beef, and chicken. Seafood and nuts are uncommon EoE triggers and our results confirmed this (11). Soy was not a common food in our patients' diet, so it was the easiest food to exclude in our 10 patients testing positive, all of them being multisensitive. Soy has IgE cross-reacting proteins with milk that can explain sensitization to both allergens in milk-allergic patients (27); however, in our study, as far as APTs are regarded, only 3 patients were positive to both milk and soy and 7 soy-sensitive patients were not milk sensitive.

Although the number of patients is low and safe conclusions cannot be extracted, according to our data in EoE, cross-reactivity was not noticed among grains or between soy and milk, so rules of cross-reactivity do not apply, like in the IgE-mediated food allergy. However, a case report of a patient with EoE caused by flour, cross-reacting with buckwheat and quinoa, has been reported (28).

The advantage of using tailored-made allergy-driven diet is the fact that offers our patients better alternatives. For example, rice, corn, and wheat that can be examined separately and do not cross-react are grains that can be individually introduced in a diet, avoiding only the ones that result APT positive. The same applies of course to all other foods. We also

believe that a six-food empiric diet should be tried only after the failure of a tailored-made diet.

A long-term and potentially lifelong diet is per se stressful and restricts patient's quality of life. It is much easier to offer the chance of a specific elimination diet to a monosensitive, or a few-sensitizations patient. It also should be taken into consideration that the 'blind' elimination of multiple potential allergens places the child at risk of essential nutrient depletion (24).

A very interesting approach of dietary elimination for EoE patients has been proposed by Spegel et al., based on the observations that milk testing has a high false-negative predictive value and that milk is the most common EoE trigger they removed milk and positive foods on SPTs and APTs (11). The success of this diet was identical to the one of an empiric diet eliminating milk, soy, egg, wheat, chicken, turkey, pork, and beef. Vegan diets can be a useful suggestion but have a success rate of 48% and can be potentially dangerous for young, developing children (11).

The role of a dietitian in individual counseling is important, and nutritional implications of an elimination diet on the nutritional status of the developing child should be always evaluated and taken into consideration (29). In order to avoid the relapsing and remitting course of symptoms and to improve patient compliance, patients, gastroenterologists, and allergologists should collaborate to identify the culprit food allergens and design a 'tailor-made' elimination diet, ideally approved by a dietitian.

In conclusion, in the present study, children with EoE and mild symptoms responded clinically and histologically to allergen-driven diet without need of pharmaceutical treatment, while in severe cases, diet possibly contributes to resolution of symptoms, histological improvement, or prevention of relapse after cessation of steroids. Therefore, allergen-driven diets are useful in EoE patients, regardless of the severity of their symptoms. They prevent unnecessary exclusion of foods that would otherwise be well tolerated, a factor of paramount importance in the growing child. A regular clinical follow-up of the patient is, however, the cornerstone of the best management of EoE.

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