ORIGINAL ARTICLE

Allergy Assessment in Children with Eosinophilic Esophagitis

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Abstract

Background: Eosinophilic esophagitis (EoE) is of growing interest for pediatricians and allergists. There is no general agreement about diagnostic and clinical management procedures. The objective of this prospective, observational study was to evaluate the efficacy of a protocol for the etiologic diagnosis and accurate treatment of EoE in the pediatric population.
Patients and Methods: Starting in 2001, patients aged 0 to 14 years with a diagnosis of EoE were consecutively included in a protocol which included an allergy study. Depending on the results, an avoidance or elemental diet was established. Topical corticosteroids were prescribed to patients who rejected the diet. Clinical, endoscopic, and histological evaluation was performed to assess response. In the case of disease remission, challenge tests were performed to identify the offending food.
Results: Seventeen patients were included. Most of them were male (14/17) and a high percentage (88%) had a history of allergy as well as a history of atopy in parents. Fifteen patients were sensitized to 1 or more foods. With this protocol and the subsequent treatment, 9 out of 17 patients were cured (1 out of 4 with swallowed corticosteroids, 3 out of 3 with an elemental diet, and 5 out of 12 with an avoidance diet). The offending food was identified in 8/17 patients. Milk and eggs were the most common foods implicated.
Conclusions: The allergy study was a useful diagnostic tool but it was not sufficient to identify the offending food. An elemental diet should be attempted before food is excluded as the cause of the disease.

Key words: Elemental diet. Eosinophilic esophagitis. Food allergy. Milk allergy.

Resumen

Justificación: La esofagitis eosinofílica (EoE) está despertando un interés creciente en pediatras y alergólogos. No hay consenso sobre el diagnóstico ni abordaje. El objetivo del estudio, prospectivo observacional, fue evaluar la eficacia de un protocolo diagnóstico etiológico y un tratamiento preciso de la EoE población pediátrica
Pacientes y métodos: Desde 2001 se incluyeron pacientes de 0 a 14 años que cumplían el diagnóstico de EoE en un protocolo que incluía una evaluación alergológica. Dependiendo de los resultados se establecía una dieta de eliminación o una dieta elemental. Cuando el paciente rehusaba la dieta, se prescribían corticoides deglutidos. Se realizó un seguimiento clínico, endoscópico e histológico. Si se lograba la resolución de la EoE se realizaban test de provocación hasta la identificación del alimento implicado.
Resultados: Diecisiete pacientes fueron incluidos, con predominio de varones (14/17). Un alto porcentaje (88%) tenían historia personal y familiar de alergia. Quince pacientes estaban sensibilizados frente a uno o más alimentos. Con este protocolo y el subsiguiente tratamiento, en 9 de 17 pacientes se resolvió la esofagitis (1 de 4 con corticoides tópicos, los tres pacientes tratados con dieta elemental y 5 de los 12 tratados con dieta de exclusión). Se identificó el alimento implicado en 8 de los 17 pacientes, principalmente la leche y el huevo.
Conclusiones: El estudio alergológico fue una herramienta útil, pero no lo suficiente como para identificar el alérgeno alimentario implicado. Estos resultados sugieren la conveniencia de probar una dieta elemental antes de excluir los alimentos como causa de esta entidad.

Palabras clave: Dieta elemental. Esofagitis eosinofílica. Alergia alimentaria. Alergia a leche.

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Introduction

Eosinophilic esophagitis (EoE) is a relatively new entity; it was first described in the 1970s but it was not until 1993 that it was well delineated [1]. There is a growing interest in EoE, as shown by the increasing number of publications on the topic in recent years. While relatively recent population studies have shown the real incidence and magnitude of EoE in some countries [2,3], there is still a shortage of data on etiology, diagnostic approaches, and clinical management.

The aims of the present study were to apply a preliminary protocol designed for the diagnosis, treatment, and follow-up patients with EoE, to define the role of food in this condition, and to establish safe treatment.

Material and Methods

We performed a prospective, observational pilot study to evaluate a protocol for the diagnosis and treatment of EoE. The patients, all with a diagnosis of EoE confirmed by histology (>20 eosinophils/high-power field [HPF]), were recruited in the Pediatric Gastroenterology Clinic at Hospital Ramon y Cajal in Madrid, Spain from 2001 to 2009. The diagnostic protocol is described below and summarized in Figure 1.

– The patients treated under the protocol were asked about their clinical history of gastrointestinal symptoms, food restriction diets, and diagnoses of food allergy. The history also included a detailed description of symptoms caused by food and data about personal and family history of atopy.

– Laboratory tests included blood count and determination of serum immunoglobulin (Ig) A, IgG, IgM, IgE, IgG, and IgA antigliadin and IgA antitransglutaminase antibodies.

– Oral endoscopies and biopsies of esophageal mucosa, from at least two locations, and biopsy of gastric and duodenal mucosa were performed. Nasal and oral mucosa smears were obtained in all patients to evaluate the presence and number of eosinophils in these locations. Histological evaluation was performed by the same pathologist in all cases. In short, EoE was defined by histological findings of esophagitis and the presence of more than 20 eosinophils per HPF.

– The allergy study was performed in the allergy department. All patients underwent skin prick and patch tests for a standard series of food allergens, including milk and its fractions, beef, egg and its fractions, chicken, fish (oily and white), legumes, and nuts. Aeroallergens tested included pollens (grass, olive tree, and tree pollens), domestic dust mites, and cat and dog dander, and fungi (*Alternaria* species). Total IgE was evaluated and when an allergen was identified, specific IgE was also measured by the CAP method (Pharmacia, Uppsala, Sweden). Patients with an immediate reaction and positive tests for immediate hypersensitivity (skin prick or specific IgE) to a particular food were diagnosed with IgE-mediated allergy.

To facilitate the study and analysis of the data collected, foods were grouped in 7 categories, as shown in Table 1.

Treatment and Follow-up

An avoidance diet was prescribed after diagnosis in patients whose clinical history and/or skin tests identified 1 or 2 foods included in the daily diet. In cases where the suspicious foods belonged to more than 2 groups or where no allergens were identified, an elemental diet was recommended. Swallowed corticosteroids (Fluticasone metered-dose inhaler without a spacer, 250 µcg/puff, 2 puffs once or twice daily) were administered as first-line therapy in patients who were unable to tolerate any diet

Patients were monitored and sequential biopsies performed after each of the 3 treatment modalities was started. Asymptomatic patients with histological remission (<10 eosinophils/HPF) were considered responders. In responders on an elemental or avoidance diet, foods were reintroduced sequentially to establish which triggered symptoms or eosinophilic infiltrate in the esophagus. In patients on an elemental diet, the food introduction sequence was defined according to the consensus recommendations in the medical literature [4].

Clinical evaluation was carried out every 4 weeks and endoscopy and biopsy after 8 weeks of treatment.

In nonresponders on any of the 3 treatments, the approach was to change to either of the 2 therapeutic procedures not previously attempted.

Results

Epidemiologic Characteristics

From 2001 to 2009, 17 patients were diagnosed with EoE; 14 of the diagnoses had been made in the previous 5 years. The mean age at the time of diagnosis was 9 years (range, 2 years and 8 months to 14 years and 5 months) and the mean follow-up period was 1 year and 11 months (range, 2 months to 5 years); there was a clear predominance of boys over girls (14 vs 3).

A family history of atopy was found in 76% of the patients and concomitant allergic disease in 88% (Table 2).

Six patients diagnosed previously with IgE-mediated allergy, with oral syndrome, urticaria, or immediate digestive symptoms were already on an avoidance diet. These patients are discussed in more detail below.

Other digestive disorders were celiac disease in 5 children (29%), chronic gastritis (including 2 cases associated with *Helicobacter pylori*) in 4 children (23%), and gastroesophageal reflux disease in 1 child (5%).

Clinical Characteristics

Thirteen patients presented with symptoms at the time of diagnosis. The most frequent symptoms were esophageal food impaction and/or dysphagia (n=10), vomiting (n=6), and abdominal pain (n=2). Four patients (23%) did not have EoE-related symptoms and their condition was detected during an endoscopy performed for exploratory purposes or during follow-up testing in celiac patients.

The median time between the onset of symptoms and diagnosis was 24 months (range, 1-72 months).

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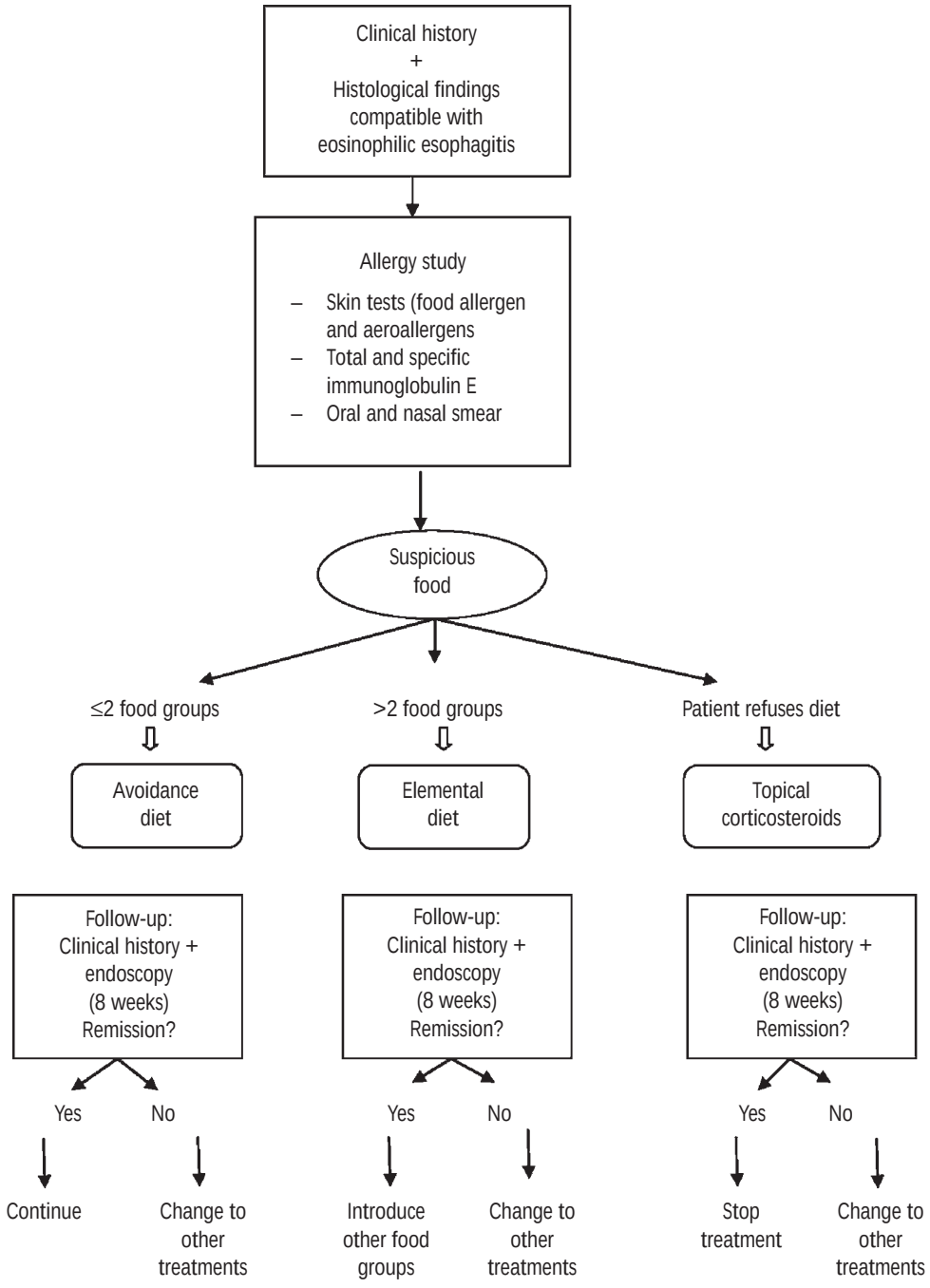

Figure 1. Decision Diagram

Diagnostic Work-up

Allergy Study

Fourteen patients (82%) had positive skin prick tests. Three were positive for aeroallergens only, 5 were positive for food allergens only, and 6 were positive for both.

Patch tests were positive in 2 patients, both of whom tested positive for cow milk proteins (the corresponding skin prick test had been negative).

Specific IgE for the suspicious food was positive (>0.35 kU/L) in 15 patients, 2 of whom showed positivity for more than 1 food category. The median total IgE was 231 kU/L (12-1655 kU/L)

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Table 1. Food Categories Employed in the Study

Group 1: Cow milk and dairy products, beef
Group 2: Eggs and chicken
Group 3: Fruits and vegetables
Group 4: Legumes and soya
Group 5: Seafood, fish, cephalopods
Group 6: Nuts
Group 7: Cereals

Table 2. Allergies in Patients With Eosinophilic Esophagitis (n=17)

	No. of Patients (%)
Rhinoconjunctivitis	7 (49)
Atopic dermatitis	9 (47)
Asthma	10 (58)
Aeroallergen allergy	5 (29)
Immunoglobulin E-mediated food allergy	6 (35)

Table 3 shows the distribution by food categories of immediate and delayed hypersensitivity test results for patients previously diagnosed with IgE-mediated food allergy and patients with food sensitization diagnosed de novo.

Six patients with previously diagnosed IgE-mediated food allergy were already avoiding the offending food. Consequently, a causal relationship between these foods and EoE could be ruled out with reasonable confidence. Three of the patients were allergic to 1 food group, 1 was allergic to 2 groups, and 2 were allergic to 3 or more groups. In 5 patients, we detected sensitization to new food groups that were generally well tolerated.

Of the patients diagnosed with new food sensitizations, 5 had positive tests for 1 food group, 6 for 2 groups, and 2 for 3 or more groups (Table 1). None of the patients developed an immediate reaction on eating the corresponding foods.

The most frequently implicated food was cow milk (n=8), eggs (6), wheat and fish (n=4), and nuts (n=3).

Endoscopic Findings

In order to evaluate response to treatment, 34 endoscopies were performed in 14 children. The median number of esophageal biopsy specimens was 4.3 (taken from the upper and/or middle and lower third of the esophagus). Whitish mucosal patches were observed in the esophagus of 4 asymptomatic children diagnosed with EoE. Among the group of symptomatic patients, 3 had normal esophageal mucosa and 10 had whitish mucosal patches, associated with lineal fissuring (5 cases), vertical furrowing or felinization (4 cases), friability (3 cases), or stenosis (2 cases) (Table 4).

Histological Study

The histological study showed a dense eosinophilic infiltrate (>20 eosinophils/HPF), characteristic of EoE; eosinophilic microabscesses were found in 4 cases. In 7 cases (4 at the time of the diagnosis and 3 during follow-up), the

Table 3. Allergy Test Results by Food Groups

Food Categories (See Table 1)	De novo[a] Food Sensitizations, No. (n=15)			Previous IgE-Mediated Food Allergy (n=6)
	SPT/sIgE[b]	PT	Total	SPT/sIgE[b]
Group 1: Cow milk and dairy products, beef	6	2	8	2
Group 2: Eggs and chicken	4	0	4	1
Group 3: Fruits and vegetables	2	0	2	1
Group 4: Legumes and soya	1	0	1	0
Group 5: Seafood, fish, cephalopods	3	0	3	4
Group 6: Nuts	3	0	3	2
Group 7: Cereals	2	0	2	1

Abbreviations: Ig, immunoglobulin; PT, patch test; sIgE, specific immunoglobulin E
[a]Food sensitization without immediate symptoms
[b]CAP Pharmacia, Uppsala, Sweden

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Table 4. Endoscopic Findings in Patients With Eosinophilic Esophagitis (n=17)

	Diagnosis	Follow-up
White plaques	14	5
Vertical lines	5	6
Furrowing	4	2
Edema/Friability	3	4
Rings and strictures	2	2
Normal esophagus	3	11

eosinophilic infiltration was patchy with normal fragments alternating with infiltrated mucosal fragments.

There was no eosinophilic infiltration of the oral, gastric, or duodenal mucosa. Nasal mucosa smears showed eosinophilia in 7 patients, all of whom had been previously diagnosed with allergic disease (rhinoconjunctivitis or atopic dermatitis).

Treatment and Response

Following the previously described protocol, 12 patients were treated with the avoidance diet protocol after the allergy study. Five responded, 6 did not, and 1 was lost to follow-up. Among the nonresponders, clinical, endoscopic, and histological remission was achieved with an elemental diet in 1 patient; another was treated unsuccessfully with swallowed fluticasone, and the other 4 patients are still under clinical management (Figure 2). Two patients without food sensitization successfully responded to the elemental diet. The sequential introduction of foods enabled the identification of the allergens in both cases: milk in the first patient and cow milk proteins, eggs, and chicken proteins in the second patient. This allowed us to subsequently prescribe an appropriate avoidance diet, with good results.

Three patients who rejected the option of an elemental or avoidance diet were treated with swallowed fluticasone. Only 1 responded and none had side effects.

In short, 9 patients improved with treatment (1/4 with swallowed steroids, 3/3 with an elemental diet, and 5/12 with an avoidance diet). The offending food was identified in 8 patients (47%). Table 5 summarizes the treatment results.

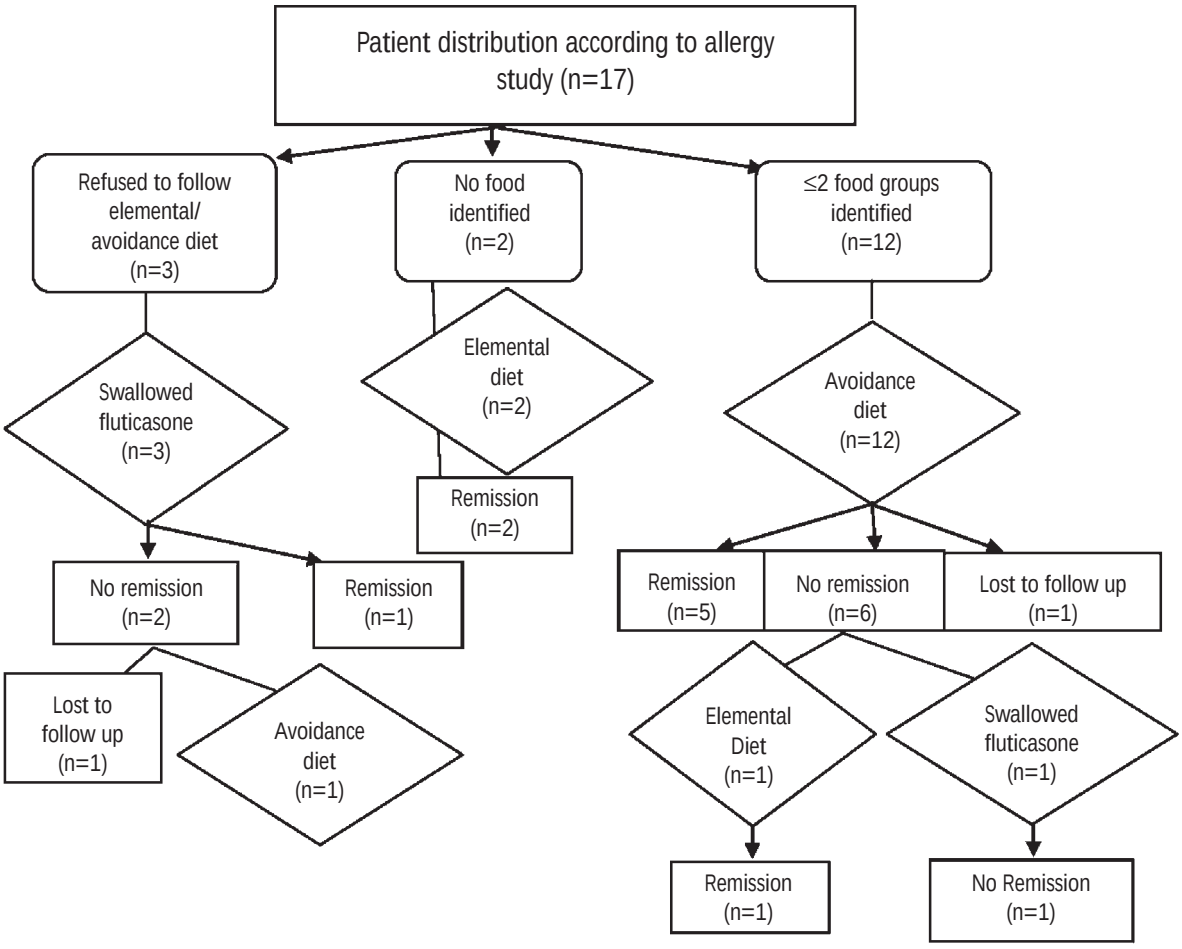

Figure 2. Patient distribution according to allergy study.

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Table 5. Relation Between Treatment, Remission, and Implicated Foods

Treatment	Remission	Implicated Foods
Swallowed steroids	1	Unknown
Elemental diet	3	Milk
		Milk, beef (or cow), eggs and chicken
		Patient stopped diet during reintroduction stage
Avoidance diet	5	Milk Milk, beef, eggs and nuts Milk Milk, beef Milk

Discussion

EoE is an intriguing condition that is growing in prevalence and whose pathophysiology has not yet been elucidated. There is a lack of agreement on the definition of the disease although diagnostic criteria have recently been proposed [5]. Moreover, there are no noninvasive methods, such as the use of serum markers or radiological studies, for diagnosis or follow-up. These evaluations are currently based on the findings of endoscopy and biopsy of the esophageal mucosa.

An eosinophilic infiltrate of >20 eosinophils/HPF is currently widely accepted as characteristic of EoE. However, esophageal lesions can be patchy, as was the case in 7 of the patients in our series. For this reason, multiple biopsies, taken from different levels of the esophagus, are recommended. Some authors recommend the collection of 5 specimens from 3 levels of the esophagus [6]. This practice is strongly recommended in patients without visible lesions in the endoscopy, as occurred with 3 of our patients.

All the patients in the present series had biopsies of the gastric and duodenal mucosa as well as cytological smears of the oral mucosa. None of them showed eosinophilic infiltration in these tissues. These findings, not previously described, support the exclusive involvement of the esophagus in this disease and raise questions about its pathogenic mechanisms. Nasal smears have shown eosinophilia in some children but more in relation to the underlying atopic condition than to EoE [7].

Previous studies have demonstrated that EoE is closely related to atopy [8,9], illustrated by the high prevalence of atopy and allergic disease in patients and relatives. Eighty-eight percent of the patients in our series had another type of allergic disease and 35% had an IgE-mediated food allergy and were following a diet without the known food allergen.

EoE is very probably caused by allergy, at least in a large number of patients [10], and children in particular [11]. Indeed, we observed very good clinical and histological response in patients who avoided offending food allergens. However, the allergic response to food in EoE is complex and depends on immunologic mechanisms that have not yet been fully elucidated. EoE is now considered to be an allergic disease to food allergens with a mixed mechanism involving immediate- and late-response phenomena [12]. The absence of validation of diagnostic tools such as tests for immediate hypersensitivity (prick tests and serum levels of specific IgE) as well as the lack of standardization of delayed hypersensitivity tests makes it difficult to establish an etiologic diagnosis.

In 13 of the 17 patients included in the study, allergic tests demonstrated a previously unknown sensitization to food. In most of the cases, this sensitization was demonstrated by prick testing and/or by the measurement of specific IgE, and in 2 cases, it was demonstrated by patch testing. Multiple food sensitizations were found in our study but not all of the foods were implicated in EoE. The avoidance protocol and subsequent introduction of foods demonstrated the implication of only 2 food groups: milk/beef (or cow) and eggs/chicken. These preliminary results suggest the need for an extensive study of allergens to identify offending foods and thereby correctly guide the sequence of the food avoidance challenge. Some authors who, like us, followed a strict protocol [13], also found that the number of truly implicated foods was very low and that milk and eggs were predominant [14]. Our study has certain limitations and as we have only preliminary data, we cannot yet propose removing the most frequently implicated foods as a first option. Allergy studies need to be continued until supportive data from a sufficient number of patients have been collected.

With the avoidance of the foods identified in the allergy studies, 9 of the patients in our series were cured. The absence of response to treatment in the other patients could be attributed to an unidentified food or to the fact that the 8-week avoidance diet was insufficient. These children might be candidates for the elemental diet.

In 2 patients, the allergy study did not suggest the existence of food sensitization but the elemental diet cured the EoE. The subsequent introduction of several food categories allowed the identification of the offending food and the challenge test confirmed its implication in the esophageal lesion. Our results strongly suggest that a food allergen cannot be excluded as the cause of EoE until treatment with an elemental diet is followed.

No consensus has yet been reached on the optimal duration of the avoidance diet. In the short term, the reintroduction of offending foods reactivates lesions, as was demonstrated in the patients with positive challenge tests in our study. Some long-term studies have reported that under 10% of patients come to tolerate the food, and that this proportion decreases when the number of implicated foods increases [14].

An easier alternative to this form of treatment is the use of corticosteroids. Although EoE responds well to topical corticosteroids, studies conducted to date have reported a high rate of recurrences after withdrawal [15,16]. Recurrences may be severe and require treatment with systemic corticosteroids, suggesting that steroids should be restricted to patients who reject or do not respond to an avoidance diet.

The identification of food allergens should be a treatment priority because it is currently the only way to find a definitive cure and prevent disease progression. Although EoE does not

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seem to shorten life expectancy, morbidity seems to be high because chronic eosinophilic infiltration of the esophagus can produce structural changes with fibrosis, strictures, and functional alterations that may be permanent [17].

We are aware of the difficulties in achieving remission. Repeat endoscopic procedures and oral food challenges in particular are both time-consuming and disabling for patients. However, we believe that the inconveniences associated with our protocol are outweighed by the fact that 9 of the 17 patients in our series achieved remission.

In summary, adherence to the established protocol allowed us to identify the cause of EoE and to prescribe successful treatment in 47% of patients. As a diagnostic tool, the allergy study was useful but insufficient. The evaluation of response to treatment after food avoidance and challenge periods allowed us to identify the offending foods in 8 patients. Finally, before excluding foods as the cause of disease, an elemental diet should be attempted.

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