



One-year outcomes in children with eosinophilic esophagitis

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Abstract

Background and aims Despite rising incidence of eosinophilic esophagitis (EoE), data on the follow-up and treatment outcomes in pediatric patients are scarce. Therefore, the aim of this study was to present data on the treatment outcomes in children diagnosed with EoE who were treated in a tertiary medical center.

Patients and methods A retrospective study involving patients younger than 18 years who were diagnosed with EoE in our center between January 2011 and June 2017.

Results Thirty-two patients met inclusion criteria and were followed up for a mean of 3 years (range 0.5–6.8). Six months after the diagnosis, 28 (87.5%) children were still followed up; 21 (75%) were in clinical remission, including 10 (36%) who were in histological remission. After 12 months, 27 patients were still followed up; 21 (78%) achieved clinical remission, including 10 (37%) with histological remission. During follow-up, three patients developed gastroesophageal reflux disease (GERD). There was no difference in body mass index (BMI) Z score between baseline and 12 months follow-up (median -0.3 vs -0.3 SD, $p=0.862$).

Conclusions Absence of symptoms does not indicate mucosal healing; therefore, patients should be followed up endoscopically. Additionally, despite restricted diet, nutritional status remains unaffected. Finally, patients with EoE can develop significant GERD even years after the EoE diagnosis.

Keywords Children · Dysphagia · Eosinophils · Esophagitis · Reflux

Introduction

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory esophageal disease characterized by symptoms of esophageal dysfunction and finding of 15 or more eosinophils in the most severely involved high-power field of esophageal mucosa [1, 2]. The incidence of EoE is increasing and in children it is estimated to be between

0.7 and 10/100 000 per person-year [3]. EoE is considered a distinct form of food allergy [2] in which food antigens trigger an immune response leading to esophageal eosinophilia. Interrelation between genetic, environmental and host immune system factors is responsible for disease development [4, 5].

Recently published guidelines for adults and children propose diagnostic and treatment modalities based on available evidence [2]. Dietary exclusions and topical corticosteroids are two treatment modalities with comparable effectiveness [6], but dietary protocols are better in maintaining long-term remission [2]. Another obstacle in the diagnosis and classification is a differential diagnosis to other conditions that cause eosinophilic infiltration of mucosa—especially gastroesophageal reflux disease (GERD) and proton-pump inhibitor-responsive EoE. EoE and GERD are the most common causes of chronic esophagitis with overlapping symptoms and histological findings, but different treatment [7]. Since they can coexist or even exacerbate each other [2, 8], the priority is to define their relationship and improve diagnostic guidelines (Fig. 1).

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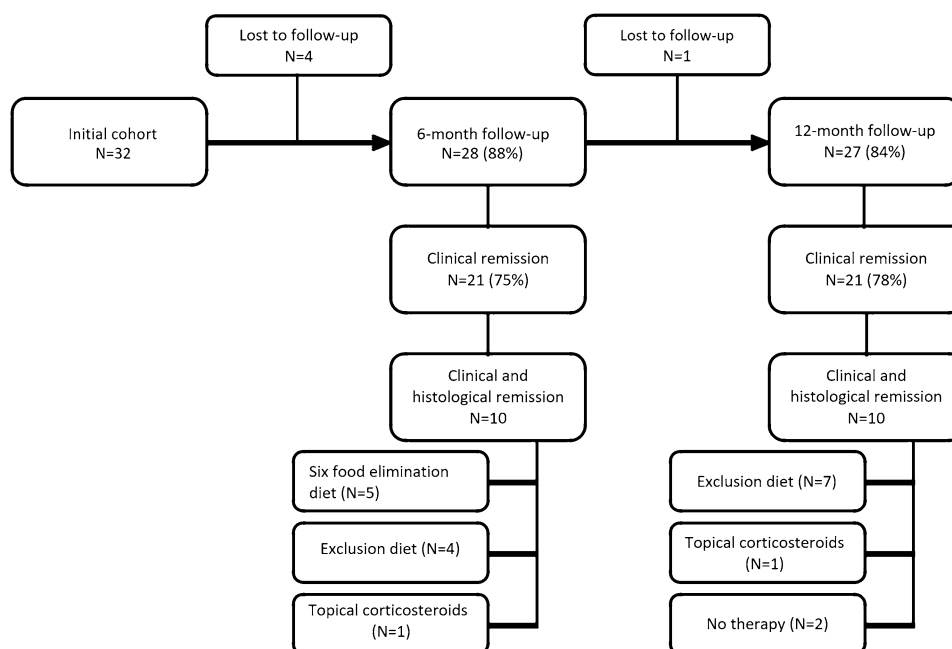
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Fig. 1 Clinical and histological remission in our patients at the 6- and 12-month follow-up



Although the incidence of EoE has been rising in the last decade and therefore the number of studies increasing [2], the number of pediatric studies is still low; therefore, the aim of this study was to present the data and the outcomes in children with EoE who are treated in a tertiary center.

Methods

Study design

This was a retrospective follow-up study conducted in compliance with the local ethical board guidelines on human experimentation and with the Helsinki Declaration of 1964 and revised in 2000. All children younger than 18 years of age who were diagnosed with eosinophilic esophagitis from January 2011 until June 2017 by a pediatric gastroenterologist, in a tertiary medical center, using standard diagnostic criteria [1], were included in the study. Six esophageal biopsies were taken from different parts of the esophagus and diagnosis was based on at least 15 eosinophils per standard size high-power field in the esophageal mucosa.

All patients had 8 weeks trials with PPIs to rule out patients with disease responsive to PPI treatment. In this study, we included only patients with EoE which was not responsive to PPI. Patients were treated either with six food elimination diet (SFED), elimination diet based on allergic testing or local corticosteroids. Local corticosteroids comprised swallowed fluticasone or budesonide. The treatment modality was chosen based on symptom severity and the preferences of patient and parents.

Anthropometric data including body mass index (BMI) were expressed as standard deviation (SD) Z scores for age and sex (World Health Organization growth-charts, available at: <http://www.who.int/childgrowth/standards/en/>).

Outcomes

Primary outcome was to compare treatment success of exclusion diet and local corticosteroids in the treatment of children with EoE. Treatment success was evaluated through clinical remission (complete resolution of symptoms) and histological remission (number of eosinophils lower than 15 per HPF on two esophageal levels). Secondary outcome measures were to: a) to describe the characteristics of children with EoE including anthropometric follow-up; b) describe the characteristics of children in clinical and histological remission 6 months and 1 year after the diagnosis and to see whether initial therapy, presence of other allergic diseases or positive allergic test(s) had impact on remission at 6 and 12 months after diagnosis. Time points of 6 and 12 months after the diagnosis were chosen because the great majority of patients had regular clinical and endoscopic evaluation at these time points.

Statistics

Descriptive statistics were used to describe the basic features. Normality of the data distribution was analyzed with the Shapiro–Wilk test. Differences in quantitative variables, according to their distribution, were analyzed with the parametric *t* test or the non-parametric Mann–Whitney *U* test, and for paired data nonparametric Wilcoxon rank test was

used. The Chi square test was used to estimate differences in the distribution of qualitative variables. *p* values of <0.05 have been considered as statistically significant. Statistical analysis was performed using SPSS 19.0 (Chicago, IL) statistical software.

Results

Epidemiology data

During the study period, 32 children fulfilled the inclusion criteria. The mean age at diagnosis was 11 years (range 1.1–17 years) and the majority were male ($n=22$, 69%). The mean follow-up time was 3 years, range 0.5–6.8 years. The most frequent symptom (some children presented with more than one symptom) was epigastric and retrosternal pain presented in 18 (56%) patients, followed by dysphagia in 11 (34%) and improper weight gain in 9 (28%) patients. Concomitant atopic dermatitis was present in 7 (22%) patients and respiratory allergies in 13 (41%): asthma in 7 and allergic rhino-conjunctivitis in 6 patients. The results of the diagnostic procedures are presented in Table 1. Most patients had nutritive allergies proven with at least one allergic testing ($n=24$, 75%); the majority had multiple allergies ($n=19$, 59%). From allergenic foods, the most common allergen was cow's milk protein ($n=14$), followed by egg ($n=11$), gluten ($n=9$), nuts ($n=8$), fish ($n=7$) and soy ($n=7$).

Most of the patients were well nourished; normal BMI Z score (defined as -2 to 2 SD) was found in 75% ($n=24$) of the patients. Median Z score for weight for age was 0 SD (range -4 to 2.5); height for age 0.43 SD (range -1.45 to 2.8) and BMI for age -0.33 SD (range -2.85 to 2.76).

Table 1 Results of diagnostic procedures performed in our patients

Diagnostic procedure	Number of patients (%)
Endoscopic finding	
Linear furrowing	20 (63%)
Ringed appearance (trachealization)	5 (16%)
Stenosis	1 (3%)
Normal	6 (19%)
Skin prick test on nutritive allergens	
Positive	15 (47%)
Negative	14 (44%)
Not performed	3 (9%)
Specific IgE test on nutritive allergens	
Positive	19 (59%)
Negative	11 (34%)
Not performed	2 (6%)

Primary outcomes

The initial treatment modalities are presented in Table 2. In the majority of patients, SFED (47%) was initiated, followed by exclusion diet based on allergic testing (37%) and corticosteroids (16%). In the first 6 months, 67% of patients ($n=8$) initially treated with exclusion diet based on allergic testing required escalation of therapy to SFED ($n=5$) or corticosteroids ($n=2$) or combination of SFED and corticosteroids ($n=1$). From children initially treated with SFED, in 4 (27%) local corticosteroids were introduced, and 5 (33%) children remained on SFED even 6 months after the diagnosis (meaning that the attempt to introduce excluded foods failed).

Secondary outcome

From the initial cohort, 28 (88%) children were followed up for 6 months. From these children, 21 (75%) were in clinical (symptom free remission), and of these 10 (36%) were in histological remission as well. All children in remission still received some form of therapy: 5 were on SFED, 4 had exclusion of some allergens (majority cow's milk and/or egg) and one was on corticosteroids. There was no association between remission at 6 months and type of the first therapy, presence of positive allergic tests (at least one) or history of other atopic disease (not significant for any factor).

Furthermore, after 12 months 27 (84%) patients were still followed up; at that point 21 (78%) children had no symptoms, including 10 (37%) of them who were in both clinical and histological remission. From those 10 patients, 2 received no therapy, one received local corticosteroids and 7 received exclusion diet (in 2 patients only cow's milk exclusion diet, in other combination of different allergens).

There was no association between remission at 12 months and type of the first therapy, presence of positive allergic tests (at least one) or history of other atopic disease (not significant for any factor).

None of the patients developed EoE-related strictures during the follow-up. One patient presented with esophageal stenosis which required endoscopic balloon dilatation. However, 2 patients whose EoE was in histological and clinical

Table 2 Initial treatment modality

Initial treatment	<i>n</i> (%)
Six food elimination diets	15 (47%)
Elimination diet based on allergic testing	12 (37%)
Topical corticosteroids*	5 (16%)

n Number of patients started on that treatment modality

*Swallowed fluticasone or budesonide

remission (during diet therapy) developed GERD (4.4 and 5.3 years after EoE diagnosis). GERD was diagnosed based on symptoms (heartburn) and endoscopic finding of hiatal hernia and grade A esophagitis [LA classification (11)] on endoscopy, together with relief of symptoms after introduction of PPI. One patient, whose EoE was not in stable remission, developed erosive esophagitis (B grade, LA classification) with cardiac metaplasia of esophagus.

There was no difference in BMI Z score between baseline and 12 months follow-up (median -0.3 vs -0.3 SD, $p=0.862$), weight Z score (0.1 vs 0.4 SD, $p=0.241$) and height Z score (0.43 vs 0.82 SD, respectively; $p=0.149$) (data available for 26 patients).

Discussion

This study found that although the majority of patients would be symptom free during the follow-up, it is still difficult to maintain histological remission. Therefore, although without symptoms, patients need to be followed up endoscopically to assure mucosal healing and prevent remodeling and fibrosis caused by eosinophilic inflammation [9]. Furthermore, almost all patients required maintenance therapy during the follow-up, mainly exclusion of culprit food(s). This finding is in line with previous reports indicating that relapse will occur in the majority of patients after stopping the treatment [10].

As in previous reports, treatment modalities varied in our cohort, which is mainly related to the long recruitment period. Therefore, some of our early patients were treated with allergy test-guided elimination diet which eliminates foods with positive results on skin prick test or atopy patch test. Our study confirmed previous findings [11, 12] that this is the least effective therapy. SFED [13] elicited much better treatment result. A meta-analysis from 2014 [12] included 7 studies and reported the combined efficacy of SFED of 72.1%. According to the research, in up to 75% of patients who responded to SFED, only one or two food triggers were found [14]—mostly cow's milk and egg [15, 16], which was confirmed by our study as well.

In contrast to nutritional therapy, a smaller proportion of patients in our study received topical corticosteroids. Recent studies [17, 18] have shown that budesonide and swallowed fluticasone are safe and successful in inducing remission in children with EoE. In this study, 43 out of 44 patients treated with corticosteroids achieved remission [17]. Similarly, a study by Straumann et al. [18] showed that budesonide led to rapid clinical and histological improvement of esophageal inflammation after only 15 days of treatment. However, there are two main reasons why topical corticosteroids are not chosen more often as the first line therapy in children. First of all, when

treating EoE, the main goal is to reduce or discontinue any form of therapy after achieving remission, which is often impossible in patients who achieved remission on corticosteroids due to high relapse rate [19, 20]. A study by Greuter [19] found that among patients aged 5–62 years (mean age 46.9) during a median follow-up of 6 years, 85% responded to therapy with topical corticosteroids, but only 9.4% achieved complete remission and relapse occurred in 78.8% of patients after discontinuation of therapy. The second reason is a fear of possible side effects of long-term corticosteroid use, such as recurrent candida infections and alteration of the hypothalamic–pituitary–adrenal axis with suppressed growth. The above-mentioned study [17] with long follow-up, however, found very low incidence of candida infection and no impact on growth.

After 6 months, only 36% (10/28) of our patients were in clinical and histological remission and all of them required some form of therapy. Nine out of 10 of these patients were on diet (4 on exclusion diet and 5 on SFED) and only one used topical corticosteroids. After 12 months, 37% of patients achieved clinical and histological remission; of those patients, the majority were on an exclusion diet of culprit allergenic food (mainly cow's milk). We found that 7.4% of patients were in remission and received no therapy. Our findings confirm that EoE is a chronic disease, and to maintain remission, either long-term exclusion of identified food triggers, confirmed by food reintroduction, or topical corticosteroids are needed. This is supported by one of the few long-term studies of children with EoE [15] where only around 2% of patients were in a remission on a normal diet without any medications and an additional 6% developed tolerance to one or more culprit foods during an average 5.2 years of follow-up. A study by Liacouras et al. [21] reported that in only 1.2% of children, it was possible to reintroduce the identified and previously excluded food antigens (31, 38 and 46 months after exclusion) without relapse. We noticed dissociation between clinical and histological remission both at the 6- and 12-month follow-up—only about half of the patients in clinical remission were in histological remission as well. Unfortunately, symptoms often do not correlate with histologic disease activity [22] and for now endoscopy with histologic analysis remains necessary for monitoring the disease activity [2].

Similarly, 19% of our patients had normal macroscopic finding on endoscopy at presentation, and other studies reported an even higher percentage [21, 23, 24]. These findings further emphasize the need for esophageal biopsy regardless of the macroscopic (endoscopic) appearance in all children in whom EoE is suspected.

Even though a failure to thrive might be a part of disease manifestation prior to diagnosis [25], our patients were well nourished at the time of diagnosis and their nutritional status did not deteriorate during follow-up, although in many of

them food restrictions were implemented. This finding was confirmed by previous reports [21, 25].

As previously mentioned, differential diagnosis between GERD and EoE is challenging, since they have similar clinical presentation and can both cause esophageal eosinophilia. However, treatment is different and, therefore, establishing a correct diagnosis is of importance.

In the first guidelines [26], EoE and GERD were considered mutually exclusive disorders, but according to the latest guidelines [1, 2] they might coexist or even exacerbate each other. To our best knowledge, there are no data on long-term risk of developing GERD in pediatric EoE patients. In our cohort, 3 patients with primary diagnosed EoE subsequently developed GERD.

Our study has some limitations mainly related to its retrospective nature, relatively small number of included children and different duration of follow-up. However, the study had relatively long follow-up and provides interesting data to the limited literature of pediatric EoE.

In conclusion, this study confirms that absence of symptoms does not indicate mucosal remission of EoE, emphasizing the need for endoscopy follow-up. In pediatric patients, exclusion diet remains the most important treatment modality, especially in the long term. This is even more supported by the fact that nutritional status would not deteriorate, although some foods are excluded. Finally, patients with EoE can develop significant GERD even years after the EoE diagnosis.

Although knowledge and understanding of EoE increased in the last several years, more prospective, well-designed studies are needed to further elucidate the possible cause of the disease, help to improve the diagnostic algorithm and determine the long-term course of the disease.

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Compliance with ethical standards

Ethical Statement This work conforms to the guidelines set forth in the Helsinki Declaration of 1975 and revised in 2000 concerning Human and Animal Rights, and the policy concerning Informed Consent was followed.

Conflict of interests No conflict of interest.

References

- Papadopoulou A, Koletzko S, Heuschkel R, et al. Management guidelines of eosinophilic esophagitis in childhood. *J Pediatr Gastroenterol Nutr.* 2014;58:107–18.
- Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *U Euro Gastroenterol J.* 2017;5:335–58.
- Soon IS, Butzner JD, Kaplan GG, et al. Incidence and prevalence of eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr.* 2013;57:72–80.
- Gonzalez-Cervera J, Arias A, Redondo-Gonzalez O, et al. Association between atopic manifestations and eosinophilic esophagitis: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol.* 2017;118(582–590):e2.
- Jensen ET, Kappelman MD, Kim HP, et al. Early life exposures as risk factors for pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr.* 2013;57:67–71.
- Cotton CC, Eluri S, Wolf WA, et al. Six-food elimination diet and topical steroids are effective for eosinophilic esophagitis: a meta-regression. *Dig Dis Sci.* 2017;62:2408–20.
- Lipka S, Kumar A, Richter JE. PPI trial for eosinophilic esophagitis: chaos in the community. *J Clin Gastroenterol.* 2018;52:590–5.
- Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol.* 2007;102:1301–6.
- Aceves SS. Remodeling and fibrosis in chronic eosinophil inflammation. *Dig Dis.* 2014;32:15–21.
- Ruffner MA, Brown-Whitehorn TF, Verma R, et al. Clinical tolerance in eosinophilic esophagitis. *J Allergy Clin Immunol Pract.* 2018;6:661–3.
- Molina-Infante J, Gonzalez-Cordero PL, Arias A, et al. Update on dietary therapy for eosinophilic esophagitis in children and adults. *Expert Rev Gastroenterol Hepatol.* 2017;11:115–23.
- Arias A, Gonzalez-Cervera J, Tenias JM, et al. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology.* 2014;146:1639–48.
- Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol.* 2006;4:1097–102.
- Philpott H, Gibson PR. Letter: dietary therapy in eosinophilic oesophagitis—do not test, just eliminate and reintroduce the most common food triggers. Authors' reply. *Aliment Pharmacol Ther.* 2016;44:905–6.
- Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 years of eosinophilic esophagitis: clinical features and prognosis. *J Pediatr Gastroenterol Nutr.* 2009;48:30–6.
- Lucendo AJ, Arias A, Gonzalez-Cervera J, 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.
- Andreae DA, Hanna MG, Magid MS, et al. Swallowed fluticasone propionate is an effective long-term maintenance therapy for children with eosinophilic esophagitis. *Am J Gastroenterol.* 2016;111:1187–97.
- Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology.* 2010;139:1526–37 (1537 e1).
- Greuter T, Bussmann C, Safroneeva E, et al. Long-term treatment of eosinophilic esophagitis with swallowed topical corticosteroids: development and evaluation of a therapeutic concept. *Am J Gastroenterol.* 2017;112:1527–35.
- Eluri S, Runge TM, Hansen J, et al. Diminishing effectiveness of long-term maintenance topical steroid therapy in PPI non-responsive eosinophilic esophagitis. *Clin Transl Gastroenterol.* 2017;8:e97.
- Liaccouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol.* 2005;3:1198–206.
- Pentiuk S, Putnam PE, Collins MH, et al. Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr.* 2009;48:152–60.

23. Lucendo AJ, Arias A, Molina-Infante J, et al. Diagnostic and therapeutic management of eosinophilic oesophagitis in children and adults: results from a Spanish registry of clinical practice. *Dig Liver Dis.* 2013;45:562–8.
24. Okimoto E, Ishimura N, Morito Y, et al. Prevalence of gastroesophageal reflux disease in children, adults, and elderly in the same community. *J Gastroenterol Hepatol.* 2015;30:1140–6.
25. Paquet B, Begin P, Paradis L, et al. High rate of failure to thrive in a pediatric cohort with eosinophilic esophagitis. *Ann Allergy Asthma Immunol.* 2016;116(73–74):e1.
26. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology.* 2007;133:1342–63.