Management Guidelines of Eosinophilic Esophagitis in Childhood

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ABSTRACT

Objectives: Eosinophilic esophagitis (EoE) represents a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. With few exceptions, 15 eosinophils per high-power field (peak value) in ≥ 1 biopsy specimens are considered a minimum threshold for a diagnosis of EoE. The disease is restricted to the esophagus, and other causes of esophageal eosinophilia should be excluded, specifically proton pump inhibitor–responsive esophageal eosinophilia. This position paper aims at providing practical guidelines for the management of children and adolescents with EoE.

Methods: Relevant literature from searches of PubMed, CINAHL, and recent guidelines was reviewed. In the absence of an evidence base, recommendations reflect the expert opinion of the authors. Final consensus was obtained during 3 face-to-face meetings of the Gastroenterology Committee and 1 teleconference.

Results: The cornerstone of treatment is an elimination diet (targeted or empiric elimination diet, amino acid–based formula) and/or swallowed, topical corticosteroids. Systemic corticosteroids are reserved for severe symptoms requiring rapid relief or where other treatments have failed. Esophageal dilatation is an option in children with EoE who have esophageal stenosis unresponsive to drug therapy. Maintenance treatment may be required in case of frequent relapse, although an optimal regimen still needs to be determined.

Conclusions: EoE is a chronic, relapsing inflammatory disease with largely unquantified long-term consequences. Investigations and treatment are tailored to the individual and must not create more morbidity for the patient and family than the disease itself. Better maintenance treatment as well as biomarkers for assessing treatment response and predicting long-term complications is urgently needed.

Key Words: amino acid–based formula, empiric elimination diet, eosinophilic esophagitis, local steroids, systemic steroids, targeted elimination diet

E osinophilic esophagitis (EoE) is a chronic immune/antigen-mediated esophageal inflammatory disease associated with esophageal dysfunction resulting from severe eosinophil-predominant inflammation (1,2). In 2007, a multidisciplinary group of

experts published the first consensus recommendations for the diagnosis and treatment of EoE (1), which were recently updated (2). The updated definition of the disease includes the histological presence of ≥15 eosinophils per high power field (eos/hpf) in at least 1 endoscopic esophageal mucosal biopsy (peak value) taken at upper gastrointestinal endoscopy; and/or the presence of other microscopic features of eosinophilic inflammation such as eosinophilic microabscesses, superficial layering, or extracellular eosinophil granules (2). These publications provide extensive information on pathogenesis, epidemiology, clinical presentation, diagnosis, and management of EoE in both adults and children; however, a practical algorithm on the optimal treatment of children with EoE, to guide clinical practice, is lacking. This position paper of the Eosinophilic Esophagitis Working Group (see Appendix) and the Gastroenterology Committee of ESPGHAN aims at providing practical guidelines for the management of children and adolescents with EoE, based on available evidence where possible. If sufficient evidence is lacking, our recommendations are based on expert opinion and personal practice.

PREVALENCE AND INCIDENCE OF EoE

Data mainly come from pediatric regional referral centers for upper endoscopy. Noel et al (3) reported between the years 2000 and 2003 an annual incidence of EoE in children in Ohio of ∼1/10,000, leading to an estimated prevalence of 4/10,000 children by the end of 2003. Cherian et al (4) reported a prevalence of 0.89/10,000 in 2004 in Western Australia, whereas Dalby et al (5) reported an incidence of 0.16/10,000 in the region of southern Denmark. It is not clear whether childhood EoE is increasing in incidence and, if so, to what extent. Re-evaluations for eosinophilic counts of esophageal biopsies from a histopathology database taken from pediatric patients during the years 1982–1999 applying the same criteria (<5, 5–14, and ≥15 eos/hpf) identified 198 patients fulfilling the criteria for EoE (≥15 eos/hpf) (6). After correcting for the 40-fold increase in the total number of endoscopies during this time period, the proportion of biopsies with the diagnosis of EoE did not change. In contrast, van Rhijn et al (7) checked through a nationwide registry the pathology reports in the Netherlands from 1996 through 2010 and classified according to the diagnosis made by the pathologist. Of 674 cases with newly diagnosed EoE, 20% were younger than 18 years and 74% were male patients. The incidence of the diagnosis increased from 0.01/100,000 people in 1996 to 1.31 in 2010. Fifty-six percent of all cases were diagnosed within the last 2 years of the registry. These results are heavily biased because of the higher awareness and knowledge of EoE from 2000 onwards. Neither the same objective criteria (eos/hpf) nor the proportion of biopsies taken in the different age groups was taken into account. Therefore, the reported changes in the incidence of the disease depend on the methods that were applied and must be interpreted with caution. Population-based prevalence data of EoE are only available from the study by Ronkainen et al (8), in which 1000 unselected Swedish adults underwent esophagogastroduodenoscopy (EGD), of which 1.1% fulfilled the histological criteria of EoE.

CLINICAL, ENDOSCOPIC, AND HISTOLOGICAL CHARACTERISTICS

There are no pathognomonic clinical or endoscopic features. Epidemiologic studies and case series show that EoE is more commonly seen in male patients and in patients with atopic diseases such as food allergy, asthma, and allergic rhinitis (5,9,10). Clinical symptoms vary according to age. Infants and toddlers develop mainly nonspecific symptoms with feeding difficulties (including vomiting, regurgitation and feeding refusal), which can result in

failure to thrive. During childhood, vomiting and/or abdominal or retrosternal pain are reported, whereas during adolescence, gastroesophageal reflux disease (GERD) symptoms, dysphagia, and food impaction are the most frequent symptoms (9,11).

Peripheral eosinophilia (>700 cells/mm^3) has been reported in children with EoE (12). Furthermore, specific immunoglobulin E (IgE) antibodies to foods (13) may be found in children with EoE identifying sensitization to foods which may (or may not) be the causative foods of the disease. Typical endoscopic findings include esophageal rings, a thickened, sometimes pale mucosa with linear furrows and white exudates and less often, narrowing of the caliber of the esophagus. A normal esophagus at endoscopy does not exclude the diagnosis of EoE. Mucosal breaks (erosions or ulceration) are not findings of EoE and are indicative for GERD, Crohn disease, or other diagnoses. According to Shah et al, at least 3 esophageal biopsy specimens taken from different parts of the esophagus are necessary to achieve a diagnosis of EoE in 97% of patients (14). According to Gonsalves et al (15), 1 biopsy specimen has a sensitivity of only 55%, whereas 5 biopsies increase this to 100%. To maximize diagnostic sensitivity, it is therefore recommended that at least 2 to 4 biopsies should be taken from both the proximal and distal esophagus, regardless of the endoscopic appearance of the esophagus (2). The main histological findings are dense eosinophilia of the esophageal mucosa, which tends to be panesophageal, basal zone hyperplasia, lamina propria fibrosis, and sometimes eosinophilic microabcesses (16). It should be noted, however, that the size of a high-power field has not been standardized. This may alter the sensitivity/specificity of the lower threshold of diagnosis at 15 eos/hpf. Furthermore, it should be considered that diagnostic biopsies are predominantly or entirely epithelial and as such may underestimate deeper disease activity, particularly as eosinophil recruitment begins within the subepithelial compartment (17,18). Moreover, esophageal wall thickening, subepithelial fibrosis, and neural dysfunction occur beneath the epithelium (19,20). This recruitment pattern has implications for both diagnosis and treatment.

DIFFERENTIAL DIAGNOSIS AMONG EoE, PROTON PUMP INHIBITOR–RESPONSIVE ESOPHAGEAL EOSINOPHILIA, AND GERD

The main differential diagnosis for symptoms and histopathological findings is GERD, although other diseases that are also associated with esophageal eosinophilia, such as infectious esophagitis, esophageal achalasia, celiac disease, Crohn disease, connective tissue disorders, graft-versus-host disease, drug hypersensitivity, and hypereosinophilic syndromes, should also be excluded (1,2,21). The relation between GERD and EoE is complex. GERD with mucosal breaks because of erosions and ulcerations may impair the barrier function and increase the risk for food sensitization. This mechanism may explain that patients with an increased risk for GERD, such as children after esophageal atresia repair, have an increased risk for developing EoE (22–24); however, food allergy may induce upper gastrointestinal dysmotility, including gastric dysrhythmia, and increased numbers of transient lower esophageal sphincter relaxations, promoting GERD. EoE may also induce dysmotility, impairing the clearance of the esophagus after GER episodes. Furthermore, the inflammatory process of EoE may lead to a hypersensitivity to acid exposure, even in the absence of erosions, comparable with nonerosive reflux disease. In summary, EoE and GERD (both erosive and nonerosive reflux disease) are not mutually exclusive or may even exacerbate each other. The differentiation based on clinical symptoms remains almost impossible in pediatrics.

Recently, Mulder et al (25) proposed a scoring system of clinical and endoscopic features (male gender, dysphagia, history of

food impaction, absence of pain/heartburn, linear furrowing, and white papules) to differentiate EoE from GERD, which may be useful in older children and adolescents. Histopathological differentiation between EoE (atopic and nonatopic) and reflux esophagitis may also be attempted by immunohistochemical staining for intraepithelial mast cells and IgE-bearing cells (26). Furthermore, a recent study reported that the measurement of eosinophil-derived proteins in luminal secretions could be used to distinguish children with EoE from those with GERD (27).

THE ROLE OF ANTISECRETORY DRUGS IN ESTABLISHING THE DIAGNOSIS OF EoE

In patients with esophageal dysfunction and esophageal eosinophilia, taking proton pump inhibitors (PPIs) for 8 weeks are useful to help eliminate PPI-REE (responsive esophageal eosinophilia) (28). The mechanisms responsible for the clinical effect of PPIs on esophageal eosinophilia are unclear. It is postulated that GERD mechanisms are also activated in esophageal eosinophilia (29,30). Yoshida et al (31) suggested that lansoprazole and omeprazole (but not famotidine and ranitidine), in addition to their acid-suppressing effects, modulate inflammatory status. In vitro studies have shown that PPIs inhibit the increased expression of vascular adhesion molecules, the activation of neutrophils, and the production of proinflammatory cytokines (32). A more recent study showed that PPIs inhibit interleukin (IL)-4–stimulated eotaxin-3 expression in EoE esophageal cells and block STAT6 binding to the promoter (33). Although the mechanism of PPIs is thought to primarily involve acid blockade, PPIs may also affect esophageal eosinophilia by means of other mechanisms and thus be helpful in a subset of patients described as having PPI-REE (1); however, the proportion of children with esophageal eosinophil counts $\geq$15 eos/hpf that are PPI responsive is unclear because only retrospective data on selected patients are presently available. Sayej et al (34) reported that treatment with PPI was associated with histological improvement in 14 of 36 (39%) patients, with at least 15 eos/hpf in esophageal biopsies taken from $\geq$1 esophageal levels. Three of these 14 responders showed macroscopic signs of EoE (furrows) during EGD, whereas 6 had erosions or a normal mucosa. In some PPI-responsive children, symptomatic and histopathological relapses have been reported in spite of continuing PPI treatment (35). Another retrospective study showed that 40% of children with significant esophageal eosinophilia demonstrated histological response to PPI therapy at endoscopies carried out at 4 to 5 months following the start of treatment (28). According to the authors, the response could not be predicted by either the symptoms or the results of a preceding pH study (28). A study in 35 adults with symptoms suggesting either GERD or EoE evaluated the histological response to a 2-month treatment with rabeprazole. Significant regression of eosinophilic infiltration was reported in both groups, with 50% of patients with EoE symptoms responding to rabeprazole therapy (36). The only data from a prospective randomized controlled double-blind trial in children with confirmed EoE showed that lansoprazole alone failed to induce histological response or symptom improvement compared with lansoprazole combined with oral viscous budenoside (37).

To identify children with PPI-REE and avoid unnecessary elimination diets or drug treatment, a trial of 8 weeks of PPIs is recommended. The optimal dose of PPI depends on the chosen PPI preparation. In general, the PPI dose ranges between 1 and 2 mg · kg^{-1} · day^{-1}, with maximum dose reaching adult dose 20 to 40 mg once or twice daily depending on the patient and PPI. This should then be followed by endoscopic and histological reassessment, irrespective of whether or not there is symptom relief. If eosinophilic inflammation persists after PPI treatment, and other causes of

esophageal eosinophilia are unlikely, then the diagnosis of EoE can be confirmed (Fig. 1). In this case, specific treatment for EoE is initiated (Fig. 2), whereas the decision to continue or not continue PPIs is individualized. If there is evidence for coexisting GERD, PPIs may need to be continued for a longer period.

Further studies are required to show whether the diagnosis of EoE can be assumed without PPI treatment in individual, often older children with specific symptoms of dysphagia or food impaction and typical microscopic and endoscopic findings of EoE. Well-designed prospective randomized studies of PPIs versus placebo are required in treatment-naïve children with esophageal eosinophilia (without additional dietary intervention) to help clarify any spontaneous fluctuation of eosinophil numbers and characterize PPI-responsive and PPI-nonresponsive children with esophageal eosinophilia.

Furthermore, there are some prospective data from healthy adults indicating that PPI therapy increases the risk of sensitization to dietary antigens and even manifestation of food allergy (38). PPIs should ideally not be given for prolonged periods of time, unless there is a clear and sustained benefit for the child. Without any clinical improvement after a trial of PPI, particularly in young children and infants with significant symptoms (eg, vomiting, food refusal, failure to thrive), a repeat endoscopy may be performed earlier than 8 weeks to allow prompt treatment escalation. In children with <15 eos/hpf in the esophageal biopsies following PPI treatment, factors such as compliance and/or premature discontinuation of treatment should be considered and a close follow-up for future changes is suggested.

RECOMMENDATION

In symptomatic children with histological findings of esophageal eosinophilia, a trial of PPIs is recommended for 8 weeks. A second EGD should be performed under PPI therapy in all children, even if symptoms resolve (Fig. 1). If histology is still suggestive of EoE and other causes of esophageal eosinophilia are unlikely, then the diagnosis of EoE can be made. If the first endoscopy is performed after the patient has already had an adequate trial of PPI, the diagnosis of EoE can also be made and specific treatment for EoE be initiated.

TREATMENT OF PROVEN EoE

The management of the disease includes dietary and pharmaceutical interventions, each with its own advantages and drawbacks. The goal of the treatment should ideally be both the resolution of symptoms and the normalization of the macroscopic and microscopic abnormalities. Although there are no follow-up studies assessing the long-term consequences of persisting esophageal eosinophilia in asymptomatic patients, the possibility of esophageal fibrosis and narrowing cannot be excluded. Moreover, patient-reported outcome measures may be difficult to assess in children, particularly in infants, and young or learning-disabled children who are unable to provide accurate information on their symptoms (39). Hence, at present, histology with absolute eosinophil counts remains the best marker objective measure of the inflammatory disease activity.

Although EoE is considered a chronic, relapsing disease, its natural history is difficult to define as long-term data are available only in selected individuals. A long-term follow-up of >500 children treated with different regimens identified 11 patients who maintained complete remission on a normal diet without any medication (9). Another subgroup of 24 patients, in which parents had decided against any intervention, showed no

Evaluation of child/adolescent with symptoms suggestive of EoE
(otherwise unexplained feeding difficulty, vomiting, dysphagia, hx. of food impaction)

On PPI treatment?

No

Yes

EGD with biopsies of proximal and distal parts of esophagus

≥ 15 eos/hpf

Trial of PPI's for 8 weeks (*).
Monitor for symptoms

EGD with biopsies on PPIs (independent of symptoms)

EOE

≥ 15 eos/hpf

< 15 eos/hpf

Consider
GERD/NERD/
PPI-REE or
other diagnosis

(*) PPI trial may be stopped earlier if no improvement occurs in young children and infants with clinically significant symptoms
(eg, frequent vomiting and/or feeding refusal with failure to thrive) to avoid delay in making diagnosis and commencing treatment.

FIGURE 1. Algorithm for the evaluation of children and adolescents with symptoms suggestive of eosinophilic esophagitis (EoE). EGD = esophagogastroduodenoscopy; eos/hpf = eosinophils per high-power field; GERD = gastroesophageal reflux disease; NERD = nonerosive reflux disease; PPI = proton pump inhibitors; PPI-REE = proton pump inhibitor–responsive esophageal eosinophilia.

Confirmed diagnosis of EoE

Consider allergy history +/– food allergy testing

Discuss therapeutic options (diet and/or steroids)

Diet
Empiric elimination diet
Targeted elimination diet
Amino acid formula

Steroids
Off-label topical swallowed steroids
Rarely - systemic oral steroids
(see main text)

Monitor for symptoms!
Repeat EGD and biopsies in 4–12 weeks

Follow-up endoscopy
• If symptoms reoccur
• If asymptomatic —
   consider on individual basis

Poor adherence?
Adapt treatment

No resolution
of inflammation
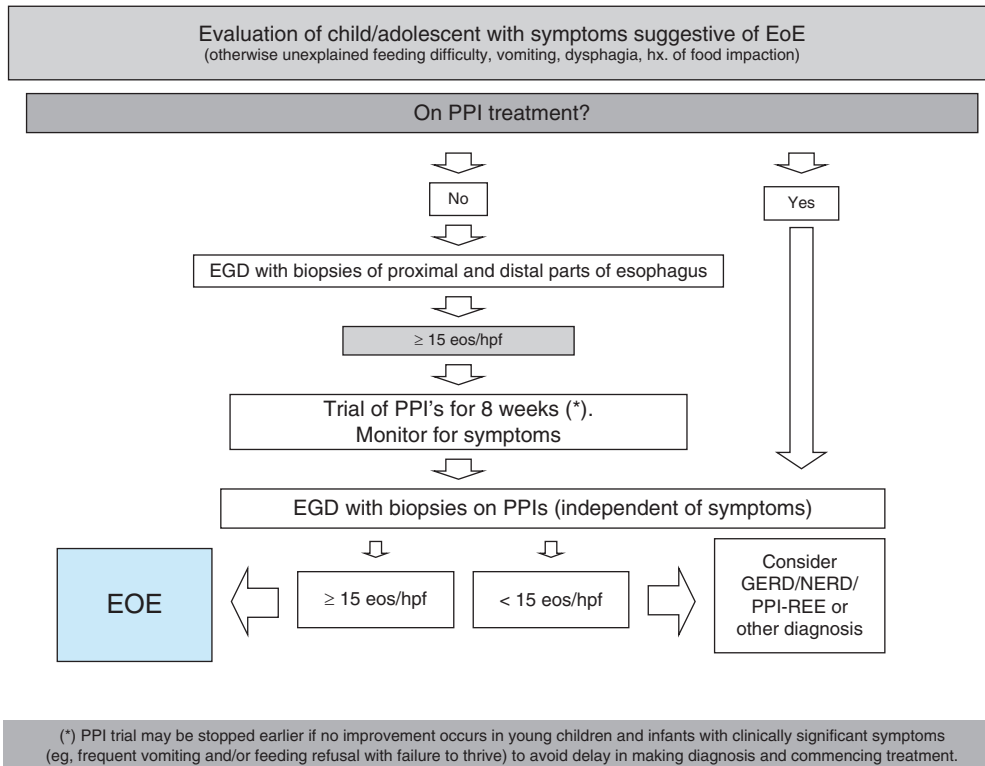
Resolution
of inflammation

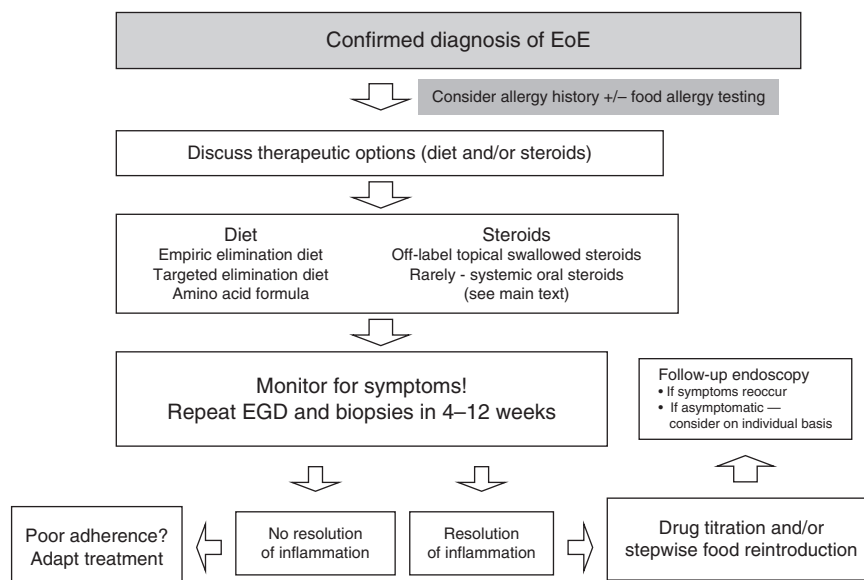Drug titration and/or
stepwise food reintroduction

FIGURE 2. Algorithm for the management of children and adolescents with eosinophilic esophagitis (EoE). EGD = esophagogastroduodeno-scopy.

histological improvement during a 6.2 ± 3.6–year follow-up with symptoms worsening over time, including dysphagia and food impaction (9).

Dietary Aspects of EoE Management

Amino acid feeds were the first dietary intervention assessed for efficacy in reducing esophageal eosinophilia and treating the symptoms of EoE (40). Only later were the efficacies of other elimination diets more formally assessed.

Elimination Diets for Inducing Remission

Elimination diets are successful at achieving resolution of symptoms and normalization of eosinophil counts in eosophageal biopsies in children with EoE (10,13,41,42). Spergel et al (10) reported that within a definitive EoE population, approximately one-third of children were clinically responding after excluding 1 food, whereas approximately 25% of children had multiple food allergies requiring the exclusion of ≥ 4 foods. There was an inverse relation between number of foods to be excluded and age (10). Milk was the most common food identified, followed by wheat, soy, and eggs; however, the combination of skin prick testing (SPT) and atopy patch testing identified only half of the patients who positively responded to milk elimination (7). The positive and negative likelihood ratios for these tests for the different foods were mostly unhelpful for clinical decision making. Erwin et al reported sensitization to cow's milk, identified either by specific serum IgE antibodies or by positive SPTs, in 43% of children with EoE, whereas sensitization to other food allergens (most commonly to rye, wheat, and soy), identified by positive atopy patch tests (APT), in 39% of patients. It should be noted, however, that food antigens triggering the disease vary from patient to patient and the detection of sensitization to foods may be indicative of concomitant food allergies and does not mean necessarily that these foods are causative of EoE (13). The elimination of the responsible food allergens from the child's diet was associated with disease remission. It should be noted, however, that food antigens triggering the disease vary from patient to patient. Therefore, the optimal dietary intervention needs to be individualized and requires dietetic support to ensure nutritional adequacy, whereas ongoing difficulties in adhering to a complex exclusion diet may require additional psychosocial support (43).

Three different dietary approaches to induce a remission in EoE have been developed: amino acid–based formula (AAF) for complete removal of food allergens from the diet (41); targeted elimination diet (TED), which removes foods based on a suggestive history of food triggers and results of specific IgEs, SPT, and APT (where available) (1); and empiric elimination diet, which removes from the diet the most common food allergens that have been associated with EoE, that is, dairy, soy, eggs, wheat, peanuts, fish/shellfish (44).

It should be noted that to date, there are no randomized controlled trials investigating the efficacy of any of these diets in unselected patients with EoE, although large case series suggest they can be highly effective (10). At least in part, this is because of the lack of agreement on clear and objective measures of efficacy. A single retrospective study in 98 children comparing the efficacy of AAF formula, 6-food elimination diet (SFED), and TED at decreasing esophageal eosinophilia (45) suggested that AAF is more effective than SFED and TED.

AAF. AAF was first used >15 years ago in 10 children with chronic symptoms attributed to GERD that persisted despite antireflux treatment, including a Nissen fundoplication in 6 of them (41). The authors introduced AAF for a minimum of 6 weeks and reported resolution of symptoms in 8 and improvement in 2 patients. Esophageal eosinophilia reversed with the median maximal intraepithelial eosinophil count decreasing from an average of 41 eos/hpf pre-AAF to 0.5 eos/hpf post-AAF (41).

Markowitz et al introduced AAF for 4 weeks in 51 children with vomiting, abdominal pain, or dysphagia with biopsy-proven EoE (46). A significant improvement was seen at a median of 8.5 days following the introduction of the diet, whereas esophageal eosinophilia was reversed at the end of 4 weeks, with the median number of esophageal eos/hpf decreasing from 33.7 before the diet to 1.0 after the diet ($P < 0.01$) (46).

Peterson et al (47) introduced AAF for 4 weeks to 20 adults with esophageal obstructive symptoms such as dysphagia, chest pain, food impaction, or heartburn resulting from EoE (>20 eos/hpf in esophageal biopsies, taken on 2 separate occasions 2–3 weeks apart while receiving high-dose acid suppression). A decrease in esophageal eosinophilia was reported at 2 weeks from the initiation of AAF (median distal and proximal esophageal eosinophil counts decreased from 44 and 33 eos/hpf to 13 and 14 eos/hpf, respectively, at 2 weeks, and to 11 and 8 eos/hpf, respectively, at 4 weeks). This improvement was associated with a clinical response at 4 weeks (47). Of the patients, 52% were reported to have <8 eos/hpf after 4 weeks of receiving AAF (47).

In infants, dietary treatment with AAF is better accepted and tolerated than in older children. In older patients, despite the encouraging reports on remission induction with the use of AAF, its use is limited by several disadvantages. The principal disadvantage is the significant burden of such a severe food restriction in children, whereas the frequent need for nasogastric tube or gastrostomy placement and the high cost are also problematic. For these reasons, AAF is mostly an option for treating EoE in children with multiple food allergies, failure to thrive, and severe disease in which a strict diet with multiple eliminations is ineffective or impossible.

TED. TED has evolved because of the perception of its better long-term tolerability. In a study by Spergel et al (42), 77% of children responded well to TED and only 10% did not respond. SPTs detected egg, dairy, and soy as triggering foods, whereas delayed hypersensitivity with APT revealed delayed reactions to corn, soy, and wheat (42). In a retrospective study in 63 children with EoE (mean age of 11.9 years), who all underwent SPT and APT for up to 20 foods, at least 1 positive test was reported in 61% of patients. Sixteen patients (26%) were managed effectively by TED alone, 27 patients (42%) failed TED, whereas 20 patients (32%) had negative food allergy testing and chose not to pursue dietary elimination but use drug therapy (48). Teitelbaum et al (49) prospectively assessed the response of 19 children with EoE clinically presenting with dysphagia, food impaction, vomiting, chest pain, and food refusal to TED and/or to topical fluticasone propionate. None of the 11 children who received TED for 8 weeks showed clinical improvement. In contrast, the administration of fluticasone propionate in 13 patients (9 with positive and 4 with negative allergy testing) was associated with resolution of symptoms. Furthermore, drug treatment in 11 children with EoE was associated with a significant reduction in the number of eosinophils, CD3, CD8, and CD1a cells in the esophageal mucosa (49).

The failure of TED to induce remission of EoE reported in some studies has been attributed to the inability of allergy tests to accurately detect causal food antigens. A recent study in children with EoE showed that positive and negative predictive values of SPTs ranged between 26% (for pork) and 86% (for milk) and 29% (for milk) and 99% (for peanut), respectively, whereas sensitivity

and specificity of the tests varied between 18% and 88% and 82% and 97%, respectively (10). Elimination diets based on serum radioallergosorbent test and/or SPT alone failed to achieve remission (49). With regard to APT, its negative predicted value in adults has been reported to be >90% (1), but in children, the test has yet to be validated and standardized. It should be noted, however, that an elimination diet based on a combination of SPT and APT was reported to achieve resolution of both symptoms and histological abnormalities in 77% of children with EoE (42). Recently presented follow-up data for this study showed a lower level of response (53%), which increased to 77% if the elimination of foods identified on SPTs/APTs was combined with the empiric elimination of cow's milk (10). This recent follow-up study showed that APTs had a high negative predictive value (>95%) for all foods except for milk, egg, wheat, and soy, whereas the positive predictive values were low for peanut, potato, and pork (0%–30%), with higher values (30% to 90%) for corn, beef, chicken, soy, wheat, egg, and milk (10). Furthermore, the authors reported a high average negative predictive value for the combination of SPTs and APTs (92%), with the exception of milk (44%), with an average positive predictive value at 44% (10).

The foods most commonly tested for with SPT and APT include milk protein, egg, peanuts, soy, a variety of grains (wheat, rice, corn, rye, oats, barley), and meat (beef, pork, chicken, turkey). Some centers also test for vegetables and fruits; however, even extensive testing may return false-negative results, potentially leading to incomplete elimination of offending food antigens if these results are taken in isolation. In particular, detecting cow's-milk sensitivity in patients with EoE, SPT, and APT were reported to have a negative predictive value, from 41% to 44% (10,50). The concordance rate between specific IgE antibodies and SPT results is not satisfactory, with 23% of discrepant results for milk and also a poor correlation for the quantitative results (51). In children with gastrointestinal manifestations of cow's-milk protein allergy, specific IgE tests results are commonly negative without excluding the diagnosis of cow's-milk protein allergy (52–54).

Because cow's-milk protein is a common food antigen and the leading cause of food allergy in infants and children younger than 3 years (55,56), the authors suggest that it is eliminated from the diet in this age group, regardless of the results of specific IgE or SPT/APT testing. More studies assessing the sensitivity and specificity of the above tests in children with EoE are required.

Whether TED has a role in maintaining clinical and histological remission of EoE is not clear. Although there are no long-term data available for children, Gonsalves et al presented in abstract form data in 9 adults with EoE who completed 1 year of TED, following 6 weeks of SFED to induce a remission. In this study, 8 of 9 patients remained asymptomatic and 1 of 9 had minimal symptoms (57). Food triggers identified on single-food reintroduction following elimination were the following: milk (55%), wheat (33%), nuts (33%), and seafood (11%), whereas 4 patients had >1 food trigger. The highest median eos/hpf pretreatment, following 6 weeks of SFED and after 1 year of TED were 19, 0, and 0, respectively, in the proximal esophagus and 60, 0, and 6, respectively, in the distal esophagus (57). According to the authors, all patients maintained >50% reduction in peak eos/hpf from baseline, 33% had ≤5 eos/hpf, and 67% had ≤10 eos/hpf at 1 year (57).

EED. The avoidance of only the 6 most commonly accepted allergenic food antigens (cow's milk, egg, wheat, soy, peanuts, and fish/shellfish) for at least 6 weeks was reported in an observational study to achieve clinical and histological (<10 eos/hpf) remission in 74% of 35 children with EoE (44), but in the most recent report from

Spergel et al (58), only 53% went into remission. This elimination was carried out independently of any known food sensitizations.

It is critical that both EED and TED are supervised by an experienced dietitian to maintain nutritional adequacy and minimize nonadherence to the diet. Key foods that are removed from a child's diet should be substituted appropriately.

The optimal duration of elimination diet to achieve remission in EoE is not clear. It seems that AAF needs less time to achieve clinical and histological remission than either SFED or TED (41,42,46,47). Furthermore, it is poorly defined which dietary intervention is associated with better mucosal healing of the esophagus. Rea et al (59) evaluated the efficacy of 3 therapeutic interventions (AAF, SFED, and topical fluticasone propionate) to induce remodeling of the esophagus in 18 children with EoE. The authors assessed resolution of epithelial mesenchymal transition (EMT), a measure that contributes to airway remodeling and fibrosis following environmental challenge in asthma (60). The investigators used a numerical EMT score based on 6 key factors. These included the number and location of vimentin-positive mesenchymal cells within the hyperplastic epithelium, and the loss of cytokeratin staining of the epithelium. The authors reported that both the pre- and posttreatment EMT scores highly correlated with peak eos/hpf in all treatment groups and that all 3 treatment approaches led to equal resolution in EMT score: AAF $r = 0.820$ ($P < 0.001$); SFED $r = 0.857$ ($P < 0.001$); topical fluticasone propionate, $r = 0.868$ ($P < 0.001$) (59).

Food Reintroduction Following Remission and Ongoing Monitoring

Following remission, foods can be gradually reintroduced, with careful observation for recurrence of symptoms of EoE (1). Food reintroduction is a key aspect of the long-term management of EoE. A recent study in adults suggested that a step-wise reintroduction of eliminated foods may be a better method to identify the precipitating food product than SPT (61).

No clear guidelines exist on how to reintroduce eliminated foods; however, Spergel and Shuker (40) suggest reintroducing the least allergic foods first, whereas the most allergenic foods (such as wheat, soy, beef, peanuts, egg, milk) are left to last. Some units advise that regular upper endoscopy should be performed to ensure maintenance of a histological remission, although the clinical value of repeat endoscopy with each food group has yet to be validated in larger prospective studies. Foods that repeatedly trigger recurrence of EoE symptoms may need to be eliminated indefinitely.

The long-term follow-up requirements for asymptomatic patients are poorly defined and differ widely among centers. Until better evidence is available on the long-term outcome of asymptomatic children with EoE, routine follow-up endoscopy in these children is a matter of local practice.

Recognition and Management of Seasonal Exacerbation

There is evidence in both humans and experimental models that inhaled aeroallergens (including pollens and molds) can induce esophageal epithelial eosinophilia and thus trigger symptom relapse (62). The clinical consequence may be a seasonal exacerbation in atopic patients, often characterized by food bolus impaction. It is important to enquire about seasonal exacerbations and, if present, to attempt to characterize potential triggering aeroallergens. There is not sufficient published data to make definitive recommendations; however, if there is an annually established pattern of significant exacerbation, planned increase in treatment (more stringent dietary

restrictions and/or augmented topical corticosteroids) should be considered. Evidence that nasal corticosteroids may attenuate asthma symptoms in patients with allergic rhinitis (63) suggests that this treatment approach may also benefit children with troublesome seasonal exacerbation of their EoE.

RECOMMENDATIONS

Dietary treatment for 4 to 12 weeks is a therapeutic option in all children with confirmed diagnosis of EoE (Fig. 2). The decision as to which of the specific dietary approaches to use should be individualized according to the child's specific needs and family circumstances. TED for 8 to 12 weeks is recommended if allergy to specific foods is strongly suspected by history and sensitization is supported by formal testing. In the absence of specific food sensitization, EED can be used for 8 to 12 weeks. AAF for 4 weeks is an option in patients with multiple food allergy, failure to thrive, or those with severe disease who do not respond, or are unable, to follow a highly restricted diet. Counseling by a dietitian experienced in pediatric nutrition is highly recommended to avoid hidden or cross-reactive antigens, to maintain nutritional adequacy and minimize nonadherence to the diet. Key foods that are removed from a child's diet should be substituted appropriately. The efficacy of the dietary intervention should be monitored by assessment of symptoms and evaluation of endoscopic and histological response. If there is no improvement at endoscopy, without resolution of eosinophilic inflammation, adherence to the diet should be evaluated and the elimination of other food antigens or initiation of drug therapy be considered, particularly if symptoms persist. In cases of clinical and histological remission, reintroduction of foods begins with the least allergenic food. If there is symptom recurrence following the reintroduction of a specific food, the triggering food should be avoided. Long-term follow-up of asymptomatic patients remains individualized and depends on local practice.

NONDIETARY ASPECTS OF EoE MANAGEMENT

Corticosteroids (systemic and topical) have been successful in treating pediatric patients with EoE, whereas other medications (sodium cromoglycate, leucotriene receptor antagonists, immunosuppressive drugs, and biologics) have generally not been found to be useful. It should be noted, however, that extremely few high-quality randomized controlled trials assessing the efficacy of different drugs exist. This highlights the urgent need for prospective intervention studies to achieve a more uniform, evidence-based approach to nondietary interventions in EoE treatment (64).

Corticosteroids

Corticosteroid preparations can be extremely effective at inducing remission in patients with EoE, but discontinuing treatment often results in symptom recurrence. The potential toxicity of long-term systemic steroids has led to the off-label use of topical corticosteroid preparations such as swallowed fluticasone propionate (FP) (65) and oral viscous budesonide (OVB) (66). When swallowed, both are effective at achieving resolution of symptoms in patients with EoE. The most important adverse effect of topical steroid preparations is esophageal candidiasis, which responds well to antifungal treatment (49,65–68).

Swallowed Corticosteroids

Swallowed FP. The efficacy of topical steroids in achieving remission has been reported in both adults (69,70) and in children

with EoE (49,68,71). A small, open-label cohort study of 11 children with EoE showed that swallowed FP achieved a significant reduction in the number of eosinophils, as well as CD3(+) and CD8(+) lymphocytes in the proximal and distal esophageal mucosa (49).

In the largest controlled trial, only 36 children with EoE were randomly assigned to swallowed FP (880 μg/day in 2 divided doses) or placebo during a 3-month period. In these children, a resolution of vomiting occurred in 67% receiving FP and in 27% of those receiving placebo, whereas histological remission was reported in 50% and 9%, respectively (65). A recent 6-week double-blind randomized trial comparing 21 FP-treated adults with 21 who received placebo reported comparable improvement of clinical symptoms in the 2 groups (57% and 33%, respectively), whereas histological resolution was reported in 62% of patients receiving FP compared with 0% of those receiving placebo (67).

Another randomized controlled trial comparing swallowed FP with oral prednisolone (68) showed that both were equally effective in achieving initial histological and clinical improvement at week 4, but discontinuation of therapy was associated in both groups with symptom relapse by week 24.

On the basis of expert opinion and present literature, the suggested starting dosages range from 88 to 440 μg 2 to 4 times daily for children, and 440 to 880 μg twice daily for adolescents/adults (1,2). Recommendations suggest patients should swallow the metered dose that is delivered into the oral cavity (and not inhaled), then not eat, drink, or rinse their mouth for 30 minutes (1).

OVB. The use of OVB was first described in 2005 in 2 children in whom FP had failed to achieve remission. OVB was prepared by the local pharmacy, by mixing a liquid solution of budesonide (the preparation used in nebulizers at a dose of 5 μg twice daily) and sucralose (a synthetic sugar substitute). In both children, resolution of symptoms and of histological abnormalities was reported (66). Another retrospective study in 20 children (mean age 5.5 years) with EoE reported OVB to be effective in achieving both clinical and histological remission (<7 eos/hpf) in 80% of patients (72).

The first double-blind randomized controlled trial was carried out in 24 children (mean age 7.8 years) with EoE in whom a 3-month treatment with OVB was compared with placebo (37). Both groups received concomitant treatment with lansoprazole. Eleven of these patients were food-sensitized/allergic children. The dose of OVB was 1 mg for patients <5 feet (1.52 m) in height and 2 mg for those >5 feet in height. OVB was associated with improvement of symptoms in 86.7% of children, whereas no patient improved while receiving placebo. Esophageal eosinophil counts decreased significantly in patients receiving OVB (mean pre-/posttreatment peak esophageal eosinophil counts were 66.7 and 4.8 eos/hpf, respectively; $P < 0.0001$) but not in those receiving placebo (mean pre-/posttreatment peak esophageal eosinophil counts were 83.9 and 65.6 eos/hpf, respectively; $P = 0.3$) (37).

Similar benefits have been described in adult studies (73). A recent double-blind randomized trial in 36 adolescents and adults with EoE compared the effect of swallowed OVB (1 mg twice daily) and placebo for 15 days (74). The authors reported a significantly greater improvement in dysphagia (72%) in patients receiving OVB compared with placebo (22%) ($P < 0.0001$), whereas endoscopic findings—white exudates and red furrows—were reversed only in patients given OVB. Furthermore, a reduction in the number of esophageal eosinophils posttreatment was observed in patients receiving OVB (68.2–5.5 eos/hpf, respectively; $P < 0.0001$), and not in those receiving placebo (62.3–56.5 eos/hpf, respectively; $P = 0.48$). Moreover, only OVB reduced apoptosis of epithelial cells and molecular remodeling in the esophagus. The authors reported that treatment with OVB was not associated with serious adverse events (74).

The optimal dose of OVB in children with EoE has not been formally assessed; however, Gupta et al (75) evaluated the efficacy and safety of different doses of OVB in treating childhood EoE in the Pediatric Eosinophilic Esophagitis Research (PEER) study, although these have only been presented in abstract form. Eighty-one children and adolescents ages 2 to 18 years with EoE symptoms were randomized to 12 weeks of treatment with placebo, low-dose, medium-dose, or high-dose OVB. Children 2 to 9 years old received placebo or 0.35 mg once-daily (QD), 1.4 mg QD, or 1.4 mg twice daily OVB; children and adolescents 10 to 18 years old received placebo or 0.5 mg QD, 2 mg QD, or 2 mg twice daily OVB. Endoscopies with biopsies were performed at baseline and the end of treatment. Seventy-one subjects (mean age 9.2 years; 80.3% boys) completed all efficacy assessments. Baseline median peak intraepithelial eosinophil count was 105 eos/hpf. At the end of treatment, there were significantly greater percentages of responders in both the median-dose and high-dose groups compared with placebo, with no age group differences. Furthermore, there was a significant dose-related histological improvement in the median-dose and high-dose groups compared with placebo. Symptoms alone could not distinguish active treatment from placebo, highlighting the dissociation between symptomatic and histological response. Low-dose OVB proved to have no/minimal effect on clinical and histological parameters. The authors reported no trends or significant dose-related increase in any adverse events (75).

Based on available evidence, the recommended starting dose of budesonide as a viscous suspension is 1 mg daily for children younger than 10 years and 2 mg daily for older children and adults split into 2 divided doses (2). In case of no response, the starting dose may be gradually increased to 2.8 and 4 mg, respectively (75).

Factors Influencing the Effectiveness of Treatment With Topical Steroids.   It is unclear whether the inadequate response to topical steroids in some patients is a result of patient nonadherence, difficulty in accurately delivering an adequate dose of topical corticosteroids, or true drug resistance; however, the esophageal wall thickening shown on endoscopic ultrasound (19), along with subepithelial fibrosis and neural dysfunction occurring beneath the epithelium, raises the question whether topical therapies can penetrate sufficiently deep to affect the disease process.

To date, only 2 steroid preparations, FP and OVB, have been shown to have a therapeutic benefit in EoE. Ciclesonide is topical steroid that has a 100-fold greater glucocorticoid receptor–binding capacity. It is nonhalogenated and converted by epithelial esterases to desisobutyryl-ciclesonide. In a study by Schroeder et al, 4 children with EoE (4–16 years of age) received 8 weeks of swallowed topical ciclesonide, and all experienced a clinical and histological response without adverse effects (76). These preliminary data need to be replicated in future studies in steroid-resistant patients with EoE.

As yet, there are no clear clinical predictors of steroid responsiveness. Konikoff et al (65) reported in a randomized placebo-controlled trial in children with EoE that the resolution of mucosal eosinophilia after a 3-month treatment with swallowed FP was more pronounced in nonallergic patients and in those of younger age, shorter height, and lower weight, suggesting a dose-response effect. Furthermore, a retrospective study in 20 pediatric patients with EoE showed that the coexistence of allergy, based on the results of SPT, influenced the therapeutic effect of swallowed FP. All of the nonallergic patients responded to treatment, whereas only 20% of the allergic patients showed partial and 20% no improvement (71). Other researchers suggested that steroid-refractory patients have higher tyrosine kinase activation in their esophageal epithelium (77).

Maintenance Treatment With Topical Steroids.   Although treatment of acute symptoms with topical steroids proves effective in achieving an apparent disease remission in adult and pediatric EoE, symptoms relapse following discontinuation of treatment. A study of 21 adults receiving 220 μg swallowed FP twice daily for 6 weeks reported relief of dysphagia lasting at least 4 months (69), whereas another retrospective study in 51 adults showed that 91% of the patients receiving FP for 6 weeks reported recurrent symptoms after a mean of 8.8 months (78), which may be because of inadequate duration of drug therapy, loss of treatment effect, or to other factors such as seasonal variation.

Straumann et al (79) carried out a randomized double-blind placebo-controlled 50-week trial in 28 adult patients with EoE and evaluated the efficacy of a low-dose (twice-daily 0.25 mg) OVB in maintaining remission of quiescent EoE. Pre- and post-treatment disease activity was assessed clinically, endoscopically, and histologically by high-resolution endosonography and by immunofluorescence. The authors reported that at the end of the study period, 35.7% of the patients with OVB were in complete and 14.3% in partial histological remission, whereas among patients who received placebo, none was in complete and 28.6% were in partial remission. The median time to relapse of symptoms was >125 days in patients receiving OVB and 95 days in those receiving placebo (79). Maintenance with OVB reduced the thickness of the superficial wall layers measured by high-resolution endosonography but had no significant effect on thickness of the deeper layers. No effect was seen in patients receiving placebo. The authors concluded that low-dose OVB was more effective than placebo in maintaining histological and clinical remission (79).

Systemic Corticosteroids

Despite oral corticosteroids being extremely effective at symptom control, they are infrequently used in patients with EoE because of their systemic adverse effects; however, systemic corticosteroids can be used for extremely severe symptoms, for example, when immediate relief of the patient's symptoms is required (eg, severe dysphagia, food impaction, dehydration, weight loss, esophageal strictures).

Liacouras et al (80) reported improvement of clinical symptoms within 1 week in 19 of 20 children receiving systemic oral corticosteroids for EoE. There was resolution of histological abnormalities at biopsy 4 weeks after treatment onset. The Indiana University group compared oral prednisone with swallowed FP in a randomized prospective trial. Both therapies proved effective in achieving clinical symptom resolution and histological remission at week 4; however, neither of the treatments prevented symptom relapse, which occurred in 45% of the patients by week 24 (68).

Although these trials demonstrate the clear efficacy of systemic steroids, they are still only recommended for extremely severe cases or where other formulations have been unsuccessful; however, the relative thickness of the esophageal epithelial barrier compared with that of the lung, together with the recruitment pattern of eosinophils from the deeper, subepithelial layers, may mean that topical treatment alone may be less successful than in asthma, and that courses of oral corticosteroids may be needed in selected cases with treatment-resistant exacerbations. Their dose is similar to that used in patients with inflammatory bowel disease (ie, $1–2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ of prednisolone orally, with a maximum 40 mg). This dose is then weaned down gradually. Intravenous methyl prednisolone may be considered initially if the patient cannot tolerate oral medication.

Swallowed FP or OVB for a minimum of 4 weeks and a maximum of 12 weeks can be a treatment option either alone or in combination with an elimination diet (Fig. 2). Systemic oral corticosteroids are only recommended when rapid relief is required for symptoms such as severe dysphagia, dehydration, weight loss, or esophageal strictures, or where the diagnosis is certain and other treatments have failed. The efficacy of the drug treatment should be monitored by assessment of symptoms and evaluation of endoscopic and histological response. Histologic remission is followed by drug titration and discontinuation of treatment. In case of symptoms persistence or recurrence, endoscopy and biopsies for the histological assessment of the esophagus are necessary. Long-term follow-up of asymptomatic patients remains individualized and depends on local practice.

Other Treatments

Sodium Cromoglycate and Leukotriene Receptor Antagonists

There is no evidence that cromolyn sodium is useful in EoE. A small trial in 14 patients reported that a 1-month administration of cromolyn sodium (100 mg 4 times per day) was not associated with clinical improvement (81). Although the drug does not have any significant adverse effects, present evidence does not support its use in children with EoE (2).

Furthermore, there is inadequate evidence to recommend leukotriene receptor antagonists (2). Gupta et al (82) reported comparable leukotriene levels in children with EoE and healthy controls. Attwood et al (83) reported clinical but not histological remission in 8 patients with EoE during 14 months of treatment with montelukast at doses up to 40 mg daily, with recurrence of symptoms in 6 patients 3 weeks following discontinuation. A recent study in adults showed that montelukast was not effective at maintaining either the clinical or the histological remission induced by a 6-month treatment course with FP (84).

RECOMMENDATION

Neither cromolyn sodium nor leukotriene receptor antagonists are recommended as treatment for children with EoE.

Immunomodulators and Biologics

Because corticosteroids fail to induce a long-lasting remission in patients with EoE, immunomodulation has been considered as a potential means of providing some maintenance efficacy.

A trial of thiopurines in 3 patients with EoE, who were resistant to corticosteroids, proved effective in achieving symptom resolution. Their use however has not been further studied and hence they cannot yet be recommended as maintenance therapy in patients with EoE (73).

Studies in animal models have shown that antibodies against IL-5 induce eosinophil trafficking to the esophagus (85). A double-blind randomized trial compared mepolizumab with placebo in 11 adults. There was a decrease in number of eosinophils in the esophagus compared with the control group, but this was not associated with symptom control (86). Reslizumab, a humanized monoclonal antibody with potent IL-5-neutralizing effects, was also evaluated in a double-blind randomized placebo-controlled trial involving 226 pediatric patients receiving 4 doses of treatment.

Reslizumab was again able to reduce the esophageal eosinophilia, but the latter did not correlate with the clinical improvement that was reported in both groups (58).

Omalizumab is a humanized anti-IgE monoclonal antibody that binds IgE, thus preventing activation of mast cells and basophils. A study of 9 patients with eosinophil-associated gastrointestinal disorders treated with omalizumab for 16 weeks showed decreased peripheral blood eosinophilia and eosinophilic tissue infiltration of stomach and duodenum, but not of the esophagus (87). A recent case report of 2 children with EoE and multiple food allergies showed that omalizumab was effective in improving food tolerance and symptoms, but did not improve endoscopic or histological abnormalities (88). A prospective randomized double-blind placebo-controlled trial in 30 adult patients (mean age 30 years), who received omalizumab for 16 weeks, reported no improvement in the esophageal eosinophil infiltration in either group, whereas dysphagia scores improved in both treatment and placebo groups (89).

Tumor necrosis factor (TNF) is more highly expressed in esophageal epithelial cells of active EoE compared with control tissue (90). This suggested a potential role for anti-TNF agents in patients with more severe EoE; however, a recent report of 3 adults with severe, corticosteroid-dependent EoE, who were treated with 2 doses of infliximab, showed only mild improvement in symptoms in 2 patients, whereas symptoms worsened in the third (91). The authors reported decreased eosinophil (but not mast cell) numbers in the responders, whereas TNF-α expression decreased markedly in the esophageal epithelial cells of only 1 of them.

Future potential therapeutic options for EoE that still warrant investigation include anti-IL-5 receptor monoclonal antibodies. These have been reported to decrease peripheral eosinophil counts in patients with mild asthma (92). Furthermore, local treatment, targeted at inhibition of IL-4 and -13 in the lung, substantially diminished the symptoms of asthma (93). The latter was tested in 2 randomized double-blind placebo-controlled, parallel-group, phase IIa clinical trials in patients with atopic asthma (93). The drug was introduced to the patients via 2 routes (by subcutaneous injection in the first study; by nebulizer in the second). The second study reported a significantly smaller decrease in forced expiratory volume in 1 second following allergen challenge in the study group compared with placebo (93).

RECOMMENDATION

Neither currently available immunomodulators nor biological agents can be recommended for treatment in children with EoE.

ESOPHAGEAL DILATATION

Esophageal dilatation can be helpful in acutely symptomatic patients who present with severe esophageal narrowing in whom medical treatment has failed to improve symptoms. Most of the studies report data from adult patients (94–97).

A recent database review of the effectiveness, safety, and tolerability of esophageal dilatation in EoE has been published in adults (98). Two hundred seven patients were examined, of whom 63 were treated with dilatation and 144 with dilatation and drug therapy. Dilatation proved to be effective and safe, although it caused postprocedural pain in 74% of patients and did not alter the underlying inflammatory process (98). In a recent review of 13 pediatric patients, dilatations were performed in 4 cases with good results (99). Esophageal dilatation can provide relief of dysphagia in highly selected children with a significant esophageal stricture

because of EoE, where there has been no response to drug therapy. It should be noted, however, that in the absence of severe esophageal stenosis, it is mandatory to try medical or dietary therapy before performing esophageal dilatation.

RECOMMENDATION

Esophageal dilatation is only recommended in highly selected cases with severe esophageal narrowing that persists despite other forms of treatment. In all of the cases, esophageal dilatation must be accompanied by medical treatment of EoE.

Future Directions

The lack of appropriate biomarkers to evaluate response to treatment and detect early relapse may require repeat endoscopy and biopsy during the course of the disease. Such biomarkers are presently under investigation (100). A better understanding of the disease phenotype and mechanisms governing treatment response should lead to more effective short- and long-term interventions. As this population grows in number and is followed up for longer periods, robust long-term outcomes should become available. Only this will truly inform us as to how persistently we must reassess the mucosa to achieve histologic normality, while minimizing the effect on the child and family, hence leading to a favorable long-term outcome.

CONCLUSIONS

EoE is a chronic, relapsing inflammatory disease of the esophagus, which often requires prolonged therapy. In recent years, there has been a significant increase in the number of publications on its treatment; however, many unresolved questions on treatment choice and duration remain (Table 1). Interpreting the results of these publications is difficult because of the variability of dosing regimens, durations of treatment, and study endpoints. The disease course is unpredictable and long-term complications are unknown. Furthermore, there is poor correlation between clinical symptoms and histological measures, making absolute recommendations for monitoring impossible. These factors mean that clinicians need to be particularly aware that investigations and treatment should be individualized and must not create more morbidity for the patient and family than the disease itself. This guidance provides a practical framework for the choices available in managing EoE in children.

TABLE 1. Unresolved questions and areas for further research in childhood EoE

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1. Definition of disease phenotypes (eg, stricturing/GERD-like/dysmotility) and correlation with treatment response and clinical outcome
2. Natural history of the disease, specifically potential progression to fibrosis in nonstricturing or asymptomatic disease
3. Role of food antigens and GERD in clinical and histological disease phenotypes
4. Further development of methodology to identify potentially significant food or aeroantigens
5. Development of biomarkers for disease diagnosis, monitoring, and prognosis
6. Effect of treatment duration on outcome
7. Role of maintenance treatment on long-term prognosis
8. Role of novel treatments in long-standing, treatment-resistant EoE
9. Need and importance of treatment and follow-up in asymptomatic patients with EoE

EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease.

REFERENCES

1. 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.
2. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3–20.
3. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;351:940–1.
4. Cherian S, Smith NM, Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child* 2006;91:1000–4.
5. Dalby K, Nielsen RG, Kruse-Andersen S, et al. Eosinophilic oesophagitis in infants and children in the region of southern Denmark: a prospective study of prevalence and clinical presentation. *J Pediatr Gastroenterol Nutr* 2010;51:280–2.
6. DeBrosse CW, Buckmeier Butz BK, Allen CL, et al. Identification, epidemiology, and chronicity of pediatric esophageal eosinophilia. *J Allergy Clin Immunol* 2010;126:112–9.
7. van Rhijn BD, VJ, Smout AJ, Bredenoord AJ. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol Motil* 2013;25:47–52.
8. Ronkainen J, Talley NJ, Aro P, et al. Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based Kalixanda study. *Gut* 2007;56:615–20.
9. 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.
10. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012;130:461–7.
11. Dellon ES, Gibbs WB, Fritchie KJ, et al. Clinical, endoscopic, and histologic findings distinguish eosinophilic esophagitis from gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2009;7:1305–13.
12. Sant'Anna AM, Rolland S, Fournet JC, et al. Eosinophilic esophagitis in children: symptoms, histology and pH probe results. *J Pediatr Gastroenterol Nutr* 2004;39:373–7.
13. Erwin EA, James HR, Gutekunst HM, et al. Serum IgE measurement and detection of food allergy in pediatric patients with eosinophilic esophagitis. *Ann Allergy Asthma Immunol* 2010;104:496–502.
14. Shah A, Kagalwalla AF, Gonsalves N, et al. Histopathologic variability in children with eosinophilic esophagitis. *Am J Gastroenterol* 2009;104:716–21.
15. Gonsalves N, Policarpio-Nicolas M, Zhang Q, et al. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc* 2006;64:313–9.
16. DeBrosse CW, Collins MH, Buckmeier Butz BK, et al. Identification, epidemiology, and chronicity of pediatric esophageal eosinophilia. *J Allergy Clin Immunol* 2010;126:112–9.
17. Hogan SP, Mishra A, Brandt EB, et al. A pathological function for eotaxin and eosinophils in eosinophilic gastrointestinal inflammation. *Nat Immunol* 2001;2:353–60.
18. Butt AM, MS, Ng CL, et al. Upregulated eotaxin expression and T cell infiltration in the basal and papillary epithelium in cows' milk associated reflux oesophagitis. *Arch Dis Child* 2002;87:124–30.
19. Fox VL, Nurko S, Teitelbaum JE, et al. High-resolution EUS in children with eosinophilic "allergic" esophagitis. *Gastrointest Endosc* 2003;57:30–6.
20. Korsapati H, Babaei A, Bhargava V, et al. Dysfunction of the longitudinal muscles of the oesophagus in eosinophilic oesophagitis. *Gut* 2009;58:1056–62.
21. Dahms BB. Reflux esophagitis: sequelae and differential diagnosis in infants and children including eosinophilic esophagitis. *Pediatr Dev Pathol* 2004;7:5–16.
22. Batres LA, Liacouras C, Schnaufer L, et al. Eosinophilic esophagitis associated with anastomotic strictures after esophageal atresia repair. *J Pediatr Gastroenterol Nutr* 2002;35:224–6.

23. Oliveira C, Zamakhshary M, Marcon P, et al. Eosinophilic esophagitis and intermediate esophagitis after tracheoesophageal fistula repair: a case series. *J Pediatr Surg* 2008;43:810–4.

24. Gorter RR, Heij HA, van der Voorn JP, et al. Eosinophilic esophagitis after esophageal atresia: is there an association? Case presentation and literature review. *J Pediatr Surg* 2012;47:e9–13.

25. Mulder DJ, Hurlbut DJ, Noble AJ, et al. Clinical features distinguish eosinophilic and reflux-induced esophagitis: an age-matched, case-controlled study and a novel scoring system. *J Pediatr Gastroenterol Nutr* 2013;56:263–70.

26. Kirsch R, Bokhary R, Marcon MA, et al. Activated mucosal mast cells differentiate eosinophilic (allergic) esophagitis from gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 2007;44:20–6.

27. Furuta GT, Kagalwalla AF, Lee JJ, et al. The oesophageal string test: a novel, minimally invasive method measures mucosal inflammation in eosinophilic oesophagitis. *Gut* 2013;62:1395–405.

28. Dranove JE, Horn DS, Davis MA, et al. Predictors of response to proton pump inhibitor therapy among children with significant esophageal eosinophilia. *J Pediatr* 2009;154:96–100.

29. Krarup AL, Villadsen GE, Mejlgaard E, et al. Acid hypersensitivity in patients with eosinophilic oesophagitis. *Scand J Gastroenterol* 2010;45:273–81.

30. Yoshida N, Uchiyama K, Kuroda M, et al. Interleukin-8 expression in the esophageal mucosa of patients with gastroesophageal reflux disease. *Scand J Gastroenterol* 2004;39:816–22.

31. Yoshida N, Yoshikawa T, Tanaka Y, et al. A new mechanism for anti-inflammatory actions of proton pump inhibitors–inhibitory effects on neutrophil-endothelial cell interactions. *Aliment Pharmacol Ther* 2000;14:74–81.

32. Handa O, Yoshida N, Fujita N, et al. Molecular mechanisms involved in anti-inflammatory effects of proton pump inhibitors. *Inflamm Res* 2006;55:476–80.

33. Zhang X, Cheng E, Huo X, et al. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. *PLoS One* 2012;7:e50037.

34. Sayej WN, Patel R, Baker RD, et al. Treatment with high-dose proton pump inhibitors helps distinguish eosinophilic esophagitis from noneosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2009;49:393–9.

35. Dohil R, Newbury RO, Aceves S. Transient PPI responsive esophageal eosinophilia may be a clinical sub-phenotype of pediatric eosinophilic esophagitis. *Dig Dis Sci* 2012;57:1413–9.

36. Molina-Infante J, Ferrando-Lamana L, Ripoll C, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011;9:110–7.

37. Dohil R, Newbury RO, Fox L, et al. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology* 2010;139:418–29.

38. Untersmayr E, Bakos N, Schöll I, et al. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. *FASEB J* 2005;19:656–8.

39. Rothenberg ME, Aceves S, Bonis PA, et al. Working with the US Food and Drug Administration: progress and timelines in understanding and treating patients with eosinophilic esophagitis. *J Allergy Clin Immunol* 2012;130:617–9.

40. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;109:1503–12.

41. Spergel JM, Shuker M. Nutritional management of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* 2008;18:179–94.

42. Spergel JM, Andrews T, Brown-Whitehorn TF, et al. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005;95:336–43.

43. Mosel MA, Schultz LS, Silverman AH, et al. Family psychosocial dysfunction is a prominent feature in eosinophilic esophagitis presenting as pediatric feeding disorder. *Gastroenterology* 2011;140:S243–4.

44. 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.

45. Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. *J Allergy ClinImmunol* 2012;129:1570–8.

46. Markowitz JE, Spergel JM, Ruchelli E, et al. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. *Am J Gastroenterol* 2003;98:777–82.

47. Peterson K, Clayton F, Vinson LA, et al. Utility of an elemental diet in adult eosinophilic esophagitis. *Gastroenterology* 2011;140:2011;suppl 1:AB180.

48. Lamba R, Feuling MB, Levy MB, et al. Allergy testing in pediatric eosinophilic esophagitis - identification of IgE and delayed hypersensitivity food reactions and its impact on management. *Gastroenterology* 2011;140:S243.

49. Teitelbaum JE, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology* 2002;122:1216–25.

50. Spergel JM, Brown-Whitehorn T, Beausoleil JL, et al. Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. *J Allergy Clin Immunol* 2007;119:509–11.

51. Mehl A, Niggemann B, Keil T, et al. Skin prick test and specific serum IgE in the diagnostic evaluation of suspected cow's milk and hen's egg allergy in children: does one replace the other? *Clin Exp Allergy* 2012;42:1266–72.

52. Eggesbo M, Botten G, Halvorsen R, et al. The prevalence of CMA/CMPI in young children: the validity of parentally perceived reactions in a population-based study. *Allergy* 2001;56:393–402.

53. Klemola T, Vanto T, Juntunen-Backman K, et al. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: a prospective, randomized study with a follow-up to the age of 2 years. *J Pediatr* 2002;140:219–24.

54. Koletzko S, NB, Arato A, Dias JA, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr* 2012;55:221–9.

55. Sicherer S. Epidemiology of food allergy. *J Allergy Clin Immunol* 2011;127:594–602.

56. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol* 2007;120:638–46.

57. Gonsalves N, Doerfler B, Hirano I. Long term maintenance therapy with dietary restriction in adults with eosinophilic esophagitis. *Gastroenterology* 2011;140:S180–1.

58. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis:results of a double-blind, randomised placebo controlled trial. *J Allergy Clin Immunol* 2012;129:456–63.

59. Rea B, Akhtar N, Jacques K, et al. Epithelial mesenchymal transition induced esophageal remodeling in eosinophilic esophagitis reverses with treatment. *Gastroenterology* 2011;140:S180.

60. Hackett T. Epithelial-mesenchymal transition in the pathophysiology of airway remodelling in asthma. *Curr Opin Allergy Clin Immunol* 2012;12:53–9.

61. Gonsalves N, Yang G, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 2012;42:1451–9.

62. Moawad FJ, Veerappan GR, Lake JM, et al. Correlation between eosinophilic oesophagitis and aeroallergens. *Aliment Pharmacol Ther* 2010;31:509–15.

63. Scichilone N, Arrigo R, Paternò A, et al. The effect of intranasal corticosteroids on asthma control and quality of life in allergic rhinitis with mild asthma. *J Asthma* 2011;48:41–7.

64. Elliott EJ, Thomas D, Markowitz JE. Non-surgical interventions for eosinophilic esophagitis. *Cochrane Database Syst Rev* 2010;3:CD004065.

65. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006;131:1381–91.

66. Aceves SS, Dohil R, Newbury RO, et al. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2005;116:705–6.

67. Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012;10:742–9.

68. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clin Gastroenterol Hepatol* 2008;6:165–73.

69. Arora AS, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. *Mayo Clin Proc* 2003;78:830–5.

70. Remedios M, Campbell C, Jones DM, et al. Eosinophilic esophagitis in adults: clinical, endoscopic, histologic findings, and response to treatment with fluticasone propionate. *Gastrointest Endosc* 2006;63:3–12.

71. Noel RJ, Putnam PE, Collins MH, et al. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2004;2:568–75.

72. Aceves SS, Bastian JF, Newbury RO, et al. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. *Am J Gastroenterol* 2007;102:2271–9.

73. Netzer P, Gschossmann JM, Straumann A, et al. Corticosteroid-dependent eosinophilic oesophagitis: azathioprine and 6-mercaptopurine can induce and maintain long-term remission. *Eur J Gastroenterol Hepatol* 2007;19:865–9.

74. 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.

75. Gupta SK, Collins MH, Lewis JD, et al. Efficacy and safety of oral budesonide suspension (OBS) in pediatric subjects with eosinophilic esophagitis (EoE): results from the double-blind, placebo-controlled PEER study. *Gastroenterology* 2011;140:S179.

76. Schroeder SS, Fleischer DM, Masterson JC, et al. Successful treatment of eosinophilic esophagitis with ciclesonide. *J Allergy Clin Immunol* 2012;129:1419–21.

77. Dellon ES, Bower JJ, TKeku TO, et al. Markers of tyrosine kinase activity for diagnosis and treatment response in eosinophilic esophagitis: a pilot study of pERK 1/2 and pSTAT5. *Gastroenterology* 2011;140:S187.

78. Helou EF, Simonson J, Arora AS. 3-yr-follow-up of topical corticosteroid treatment for eosinophilic esophagitis in adults. *Am J Gastroenterol* 2008;103:2194–9.

79. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2011;9:400–9.

80. Liacouras CA, Wenner WJ, Brown K, et al. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;26:380–5.

81. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;3:1198–206.

82. Gupta SK, Peters-Golden M, Fitzgerald JF, et al. Cysteinyl leukotriene levels in esophageal mucosal biopsies of children with eosinophilic inflammation: are they all the same? *Am J Gastroenterol* 2006;101:1125–8.

83. Attwood SE, Lewis CJ, Bronder CS, et al. Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut* 2003;52:181–5.

84. Lucendo AJ, De Rezende LC, Jimenez-Contreras S, et al. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. *Dig Dis Sci* 2011;56:3551–8.

85. Mishra A, Hogan SP, Brandt EB, et al. IL-5 promotes eosinophil trafficking to the esophagus. *J Immunol* 2002;168:2464–9.

86. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010;59:21–30.

87. Foroughi S, Foster B, Kim N, et al. Anti-IgE treatment of eosinophil-associated gastrointestinal disorders. *J Allergy Clin Immunol* 2007;120:594–601.

88. Rocha R, Vitor AB, Trindade E, et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. *Eur J Pediatr* 2011;170:1471–4.

89. Fang JC, Hilden K, Gleich GJ, et al. A pilot study of the treatment of eosinophilic esophagitis with omalizumab. *Gastroenterology* 2011;140:S235.

90. Straumann A, Bauer M, Fischer B, et al. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954–61.

91. Straumann A, Bussmann C, Conus S, et al. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. *J Allergy Clin Immunol* 2008;122:425–7.

92. Busse WW, Katial R, Gossage D, et al. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma. *J Allergy Clin Immunol* 2010;125:1237–44.

93. Wenzel S, Wilbraham D, Fuller R, et al. Effect of an interleukin-4 variant on late phase asthmatic response to allergen challenge in asthmatic patients: results of two phase 2a studies. *Lancet* 2007;370:1422–31.

94. Schoepfer AM, Gschossmann J, Scheurer U, et al. Esophageal strictures in adult eosinophilic esophagitis: dilation is an effective and safe alternative after failure of topical corticosteroids. *Endoscopy* 2008;40:161–4.

95. Pasha SF, Sharma VK, Crowell MD. Current concepts and treatment options in eosinophilic esophagitis. *Curr Opin Investig Drugs* 2006;7:992–6.

96. Cantu P, Velio P, Prada A, et al. Ringed oesophagus and idiopathic eosinophilic oesophagitis in adults: an association in two cases. *Dig Liver Dis* 2005;37:129–34.

97. Zimmerman SL, Levine MS, Rubesin SE, et al. Idiopathic eosinophilic esophagitis in adults: the ringed esophagus. *Radiology* 2005;236:159–65.

98. Schoepfer AM, Gonsalves N, Bussmann C, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety, and impact on the underlying inflammation. *Am J Gastroenterol* 2010;105:1062–70.

99. Robles-Medranda C, Villard F, le Gall C, et al. Severe dysphagia in children with eosinophilic esophagitis and esophageal stricture: an indication for balloon dilation? *J Pediatr Gastroenterol Nutr* 2010;50:516–20.

100. Konikoff MR, Blanchard C, Kirby C, et al. Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1328–36.

APPENDIX

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