

Management of eosinophilic esophagitis in children

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Eosinophilic esophagitis has recently emerged as a distinct clinical entity in children. The clinical spectrum varies with age and ranges from failure to thrive and food aversion in the toddler to gastroesophageal reflux disease-like symptoms in school-age children to solid food dysphagia and food impaction in adolescents. The diagnosis is based on the presence of at least 15 eosinophils per high power field in the esophageal biopsy in children pretreated with at least 8 weeks of adequate acid-suppression therapy. Although elemental diet is a more effective therapy than other less restrictive elimination diets, the latter has practical advantages over elemental therapy. Topical and systemic corticosteroids have also been used. Studies are underway to establish the safety and efficacy of anti-interleukin-5 monoclonal antibodies. The natural history of eosinophilic esophagitis is not known and prospective studies are required to understand the etiopathogenesis, optimal therapies and find noninvasive surrogate tests to monitor histological remission and the natural history of this enigmatic disorder.

Eosinophilic esophagitis (EE), an enigmatic disorder, is characterized pathologically by dense eosinophilia isolated to the esophageal epithelium. The typical clinical presentation mimics gastroesophageal reflux disease (GERD)-symptoms resistant to aggressive acid suppression. Although EE was first described in an adult by Landres and colleagues in 1978 [1], it was not until 1995 that the first case series of EE in children was published [2]. The past 10 years has witnessed the emergence of EE as a distinct clinical entity that differs from severe peptic disease due to GERD [3–9]. The increased recognition of the clinical, endoscopic and histological features has led to increased diagnosis of patients and a dramatic increase in the number of publications.

The treatment of children with EE remains controversial and challenging. There is currently no standard approach to management. Most current therapies are recommended based on observational and uncontrolled data. Prospective, controlled, double-blind studies are lacking and treatment options, such as elemental diets, elimination diets or pharmacological treatment options, are all based on descriptive studies [9–11], with the exception of two recent prospective studies demonstrating the efficacy of topical steroids in adults and children [12,13]. Furthermore, because clinical symptoms of this disorder vary widely (by age), children are often incidentally diagnosed with EE while

undergoing endoscopy for other complaints. Such situations present a quandary for the clinician since the recommended options, including an exclusive diet of elemental formula (often administered by nasogastric tube feeding), elimination diets or drug therapy, are often met with skepticism by the family. Thus, it is important to review the etiopathogenesis of this disorder in order to make rational treatment choices and individualize the treatment to the needs of each patient and their family.

Etiology & pathogenesis

The etiology and pathogenesis of EE remains poorly understood. Recent research supports an interaction of genetic and environmental factors as the underlying basis for this condition [14]. EE has been reported in several members of the same family [15]. The presence of atopy in most affected children and a positive family history of atopy in more than 50% of children with EE supports an allergic basis for this disorder [16]. Improvement in clinical symptoms and resolution of esophageal inflammation with an allergen-free diet provides further evidence for the food allergy hypothesis [11]. Recent demonstration that specific aero-allergens, such as *aspergillus fumigatus* or the T-helper type 2 (Th2) cytokine interleukin (IL)-13, delivered to mice lung induce esophageal eosinophilia suggests a possible role of aero-allergens as additional etiological agents [17].

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This mechanism has since been confirmed in humans in a case report of a young adult with pollen-induced EE [18].

At present, the esophageal eosinophilia in children is considered to be predominantly food allergen-mediated and EE can now be classified as a food hypersensitivity disorder [19]. The increased number of mast cells and T cells found in the esophageal epithelium of EE patients supports the notion that both immediate (immunoglobulin [Ig]E-mediated) and delayed (cell-mediated) mechanisms are operative [20]. Since exclusion diets guided by skin prick test and radioallergosorbent test (RAST) do not induce remission in esophageal inflammation, EE does not appear to be IgE-mediated [8,9]. By contrast, resolution of esophageal inflammation based upon combined skin prick and patch food test elimination diet supports a cell-mediated food hypersensitivity mechanism [16]. It would be interesting to see if these positive results can be reproduced using a diet based on the results of skin patch testing alone.

Evidence for the role of T-cell immunity is provided by a placebo-controlled study demonstrating that overexpression of cytokine IL-5 leads to Th2-mediated eosinophilic inflammation [20]. Our current understanding is that allergen(s) induce the Th2 inflammatory cascade, in which the cytokine IL-5 leads trafficking of eosinophils to target the esophagus, and their subsequent activation induces esophageal inflammation [20]. Further support for the critical role of IL-5 in the induction of aeroallergen-induced EE was provided by the complete attenuation of experimental EE in animal models of IL-5-deficient mice [21]. Moreover, since IL-4 and IL-13 are potent inducers of eotaxin, it is speculated that IL-13 may induce EE by upregulating the production of eotaxin-3 [22]. Eotaxin-3 expression by the esophageal epithelial cells was above normal levels in patients with EE with a 50- to 100-fold induction compared with control individuals, thereby suggesting that the eotaxin pathway may also play a role in causing EE [23]. Research has recently identified a single nucleotide polymorphism in the *eotaxin-3* gene that confers increased susceptibility to developing EE. This finding, if confirmed, may have far-reaching applications, both in contributing to the better understanding of this disease, and possibly by leading to research in developing eotaxin-3-blocking agents to treat EE [23]. Preliminary data from a prospective cross sectional

analysis demonstrated significant correlation of blood levels of peripheral absolute eosinophil counts, eosinophil-derived neurotoxin and eotaxin-3 with tissue eosinophil density in patients with EE, and offers promise of one or more of these tests having value as noninvasive biomarkers for monitoring EE instead of the current invasive endoscopic biopsies [24].

Diagnosis

EE is more common in males, with a male to female ratio of 3:1 [5]. Clinical presentation varies by age. Food aversion and failure to thrive are common symptoms in toddlers, whereas regurgitation, vomiting and epigastric abdominal pain are the more frequent clinical symptoms in school-aged children [25,26]. Adolescents commonly present with intermittent episodes of food impaction and solid food dysphagia. History of reactive airway disease, allergic rhinitis or eczema is encountered in the majority of children [5]. Endoscopically, the visual appearance of the esophagus varies from normal to those with edema, vertical furrowing along the long axis or with tiny multiple adherent white plaques. In adolescents, as in adults, esophageal rings or 'trachealization' are commonly observed. Demonstration of dense esophageal mucosal eosinophilia with greater than 15 eosinophils per high power field (hpf), in children pretreated with aggressive acid-suppression therapy for at least 8 weeks, is diagnostic of EE. Large numbers of eosinophils can also be seen in peptic esophagitis, thus, this histological finding must be interpreted in the context of the clinical situation [26]. The presence of eosinophilic microabscesses (aggregation of four or more eosinophils/hpf) cannot be considered pathognomonic for EE, as this was recently demonstrated in patients with GERD [26].

A recent prospective study in adults showed that EE can coexist with GERD [12]. Similar observations of GERD symptoms in children with EE responsive to proton pump inhibitors has confirmed that acid reflux can be a comorbid condition [27] and, in a few, can be the sole cause of the dense eosinophilic inflammation [26].

Treatment

Treatment of EE should be individualized for each patient based on discussion of the different treatment options with the advantages and disadvantages of each treatment with the family [28]. The goals of treatment include resolution of symptoms, prevention of relapse and maintenance of histological remission to prevent complications,

such as esophageal strictures. Minimizing side effects of therapy, while attempting to maintain quality of life are additional treatment goals. Treatments are broadly classified into dietary approaches and pharmacological therapy, as listed in Box 1.

Dietary treatment

Dietary treatment is based on the hypothesis that food allergen(s) cause mucosal injury in children with EE. The dietary approach involves identifying and eliminating the offending food allergen(s), which leads to resolution of mucosal inflammation with the potential for a cure, unlike pharmacological approaches, which are palliative. Dietary treatments include:

- Amino acid-based liquid elemental diets
 - Elimination diets based on allergy skin testing
- Standard elimination diets based on exclusion of foods most commonly known to cause food allergies.

Elemental diet

A crystalline amino acid-based exclusive elemental diet was first used successfully in treating a cohort of ten children with medically resistant GERD whose diet was replaced with the amino acid-based formula [2]. Subsequent controlled reintroduction of solid foods resulted in recurrence of gastrointestinal symptoms specific to individual foods. A clear link between food allergy and esophageal injury was thus established in this cohort of patients [2]. Since this seminal publication by Kelly and associates, a large series of 172 children treated with elemental diet (Neocate, Neocate EO28, Neocate 1+, SHS International, UK; or Elecare,

Ross Pediatrics, Abbott Laboratories, Abbott Park, IL, USA) achieving a remission rate of greater than 90% without any reported complications has been published [7]. The likelihood of achieving mucosal healing is higher with this modality than other dietary or pharmacological interventions. Additionally, the residual eosinophil counts are much higher with the latter two therapies, establishing the superiority of this treatment over all other current treatments. The disadvantage of this otherwise highly effective approach is taste-related: poor patient compliance and impaired quality of life secondary to inability to consume regular foods. Nasogastric or gastrostomy tubes are often used to overcome compliance resistance and these may lead to patient discomfort and parental distress [29]. The exclusion of solid foods, coupled with the same monotonous liquid nutrient diet, can also be frustrating and increases the likelihood of possible noncompliance with this diet. Furthermore, limiting the child to an exclusive elemental diet restricts their participation in social activities. Most childhood activities revolve around food and this leads to impaired quality of life [30,31]. This formula is expensive and the cost is not always covered by most traditional insurance plans. This places a significant financial and social burden on families. There are also additional costs related to maintenance and replacement of the tubes [32].

Elimination diet-based results of allergy testing

Children treated with partial elimination diets based on RAST or skin prick test results have failed to demonstrate clinical and histological remission [8,9]. However, exclusion diets based on a combination of skin prick and patch skin test results, in one center, have demonstrated remission in 49% of the patients [16]. In this series, 146 patients underwent both skin prick and atopy patch testing with common foods including meats (chicken, turkey, beef and pork), vegetables (peas, string beans, squash, sweet potatoes, potatoes and carrots), fruits (apples, pears and peaches) and grains (wheat, rice rye, oats, barley and corn). Patients were also tested with milk protein, soy, eggs and peanuts. Most common allergenic foods identified on skin prick test included egg, milk, soy, peanut, chicken, wheat and beef, whereas the atopy patch testing identified corn, soy, wheat, milk, rice, chicken, beef and potatoes. Of the 146 subjects treated with a combined test-based

Box 1. Treatment options.

Dietary management

- Elemental diet
- Allergy test-directed diet
- Standard elimination diet (e.g., six-food elimination)

Pharmacological treatments

- Corticosteroids
 - Systemic
 - Swallowed
- Mast cell stabilizers
 - Cromolyn sodium
- Leukotriene inhibitors
 - Montelukast
- Anti-interleukin-5 monoclonal antibody
 - Mepolizumab

elimination diet, 72 responded with nearly complete histological improvement (eosinophil count $<5/\text{hpf}$) for a response rate of 49%. Interestingly, 39 of these 72 patients were allergic to specific foods, including milk, egg, soy and beef. A total of 14 did not follow the elimination diet and responded to elemental diet; an additional 26 were treated with elemental diet for nutritional reasons since they were allergic to multiple foods. It should be noted that the patch skin test lacks standardization and further studies on the validation of this test are needed [33].

Standard elimination diets

In a retrospective observational study, an elemental diet and a standard six-food elimination diet were used to treat two cohorts of children over two different time periods [34]. A total of 22 out of 25 (88%) treated with elemental diet demonstrated significant histological improvement with decrease in esophageal eosinophilia of 10 eosinophils/hpf or fewer. A total of 35 children were treated with elimination diet, which excluded foods with cow's milk protein, soy, egg, wheat, peanut/tree nuts and all seafoods, while allowing all other solid foods. Significant clinical and histological improvement (esophageal eosinophil count $\leq 10/\text{hpf}$) was demonstrated in 74% (26 out of 35) of children. There was complete mucosal healing with 0–1 eosinophils/hpf in esophageal biopsies in seven of these 26 children. The advantage of this approach over an exclusive elemental diet is that it allows most table foods in the diet, is not as monotonous, does not have an unacceptable taste and, thus, does not require tube feedings. Additionally, this diet does not place significant constraints on the families' budgets.

Pharmacological treatment

Currently, the data on EE treatment with pharmacological agents in children is limited. Corticosteroids are the most commonly used medication to treat children with EE [6–9].

Corticosteroids

Systemic and topical corticosteroids have been efficacious in resolving symptoms and in inducing histological remission in children. However, both recur once medication is discontinued following short-term use. The only possible role for short-term parenteral steroids is in children presenting acutely with

severe inability to swallow. Oral corticosteroid use is limited owing to concerns of potential side effects, including adrenal and/or growth suppression and cataracts [35,36]. Posttreatment residual esophageal eosinophil counts after steroid treatment are much higher compared with elemental diet [7]. Recommended oral prednisone dose in children is 1–1.5 mg/kg/day typically for 4–6 weeks. Topical or swallowed steroid therapy using aerosolized fluticasone propionate has been shown to produce clinical improvement and significant decrease in esophageal eosinophilia in children [7–10,12]. In a cohort of children with EE, the clinical and histological remission to swallowed steroids in those with nonallergic history was demonstrated, whereas those with atopic histories were relatively refractory to therapy, with 20% demonstrating partial and an additional 20% not demonstrating any improvement. These data suggest that patients with identifiable allergies who fail dietary elimination may respond poorly to steroids [9]. In a prospective, placebo-controlled study, 50% of children treated with 880 $\mu\text{g}/\text{day}$ of swallowed steroids and 9% of controls demonstrated histological remission (esophageal eosinophil count 0–1/hpf) [13]. The empirical recommended doses range from two puffs twice a day of 110 $\mu\text{g}/\text{puff}$ -strength fluticasone in children aged 5–10 years, to two puffs twice a day of 220 $\mu\text{g}/\text{puff}$ -strength in older children and adolescents. To enhance the esophageal delivery of the steroid preparation, the spacer should be removed before the medication is sprayed and food or drink should be avoided for at least 30 min before and after use. A reasonable duration of treatment to achieve remission is 6 weeks. Treatment can be repeated if symptoms recur, as is recommended in adults, or patients can be maintained on a lower dose. However, specific recommendations cannot be made since there are currently no long-term data on the safety and efficacy of such maintenance therapy. Oral and esophageal candidiasis is a known side effect of this form of therapy and is easily treated with fluconazole [7].

Montelukast

The use of montelukast, a selective inhibitor of the leukotriene D₄ receptor, has resulted in symptom relief in adults but without a concurrent decrease in the esophageal eosinophilic infiltration [37]. There are currently no data on the effectiveness of this drug in children.

Cromoyln sodium

Cromoyln sodium has been used to treat eosinophilic gastroenteritis but is not efficacious in resolving either the symptoms or esophageal inflammation [7].

Mepolizumab

Mepolizumab, an anti-IL-5 humanized monoclonal blocking antibody against Th2 cytokine IL-5 has been beneficial for treating adults with hypereosinophilic syndromes [38]. There is also a report of success in relieving symptoms in a 19-year old with intractable EE unresponsive to an elemental diet and both topical and systemic steroids [38]. A soon to be published open label Phase I/II study in four adults with long-standing EE demonstrated better clinical outcome, improved quality of life and a marked decrease in esophageal eosinophilia, thus offering the promise of anti-IL-5 as a therapeutic intervention in EE [39]. At present, data on the long-term safety and efficacy of this drug in children

are not available and there are no reports of successful use of the product in children. Phase II trials using three different doses are underway for children with intractable EE unresponsive to elemental diet and steroids.

Finally, concomitant acid suppression should be considered at the discretion of the physician where considered judicious to treat coexisting GERD in selected patients.

Expert commentary & outlook

The past 10 years has witnessed dramatic strides in the awareness and diagnosis of this clinical entity. The future challenges lie in improving outcomes, decreasing morbidity associated with currently available treatments and establishing more effective evidence-based therapies. At present, there is only a single study on the natural history of EE in adults [40]. The long-term outcome of this disease in children remains unknown. In a recent report of 381 children aged over 10 years, only three children outgrew their food allergies [7]. How many children outgrow specific food allergen-induced EE and over what timeframe remains to be seen. Research is needed to evaluate the role of both dietary and pharmacological treatment in preventing complications such as strictures. Well-designed prospective epidemiological studies would help in the understanding of the natural history and explain the reason for the male predominance and higher prevalence in urban areas. Finally, studies that compare the effectiveness of the different treatments and their effect on disease outcome will enhance our ability to provide better therapies.

Highlights

- Eosinophilic esophagitis is a newly recognized and evolving clinopathological disorder.
- Clinical manifestations vary with age.
- Food allergens appear responsible for esophageal inflammation in most children.
- Dietary therapy with either elemental or elimination diet is the most widely used therapeutic approach.
- Corticosteroids have also proven beneficial in temporarily suppressing esophageal inflammation and alleviating symptoms.
- Future therapeutic targets include blockade of cytokine interleukin (IL)-5, IL-13 or eotaxin-3.

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