Diagnosis and treatment of eosinophilic esophagitis

Jonathan Spergel

Address: Division of Allergy and Immunology, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Market Street, Philadelphia, PA 19104-4399, USA

Email: spergel@email.chop.edu

F1000 Medicine Reports 2009, 1:46 (doi:10.3410/M1-46)

The electronic version of this article is the complete one and can be found at: <http://F1000.com/Reports/Medicine/content/1/46>

Abstract

Eosinophilic esophagitis is a newer disease entity that has been diagnosed with increasing frequency over the past 10 years. Patients present with a variety of symptoms including vomiting, failure to thrive, abdominal pain, dysphagia, and/or food impaction depending on the age of the patient. The diagnosis is confirmed by endoscopy with eosinophilic inflammation localized to the oesophagus, an area typically void of eosinophils.

Introduction and context

Eosinophilic esophagitis (EE) is a disease entity that has been diagnosed with increasing frequency. The first reported case of EE was in 1977 in an adult patient with food allergies, gastroesophageal reflux disease (GERD) symptoms, and esophageal eosinophilia [1]. The definitive link between food allergies and EE was shown by Dr Kelly and colleagues in 1995 [2], when they described 10 patients with isolated esophageal eosinophilia unresponsive to acid blockade who improved with an elemental formula. In fact, eight had complete normalization of esophageal eosinophilia after 6 weeks. Their findings introduced the role of food allergy in EE [2].

Since the mid-nineties, there has been a dramatic rise in the number of patients diagnosed with EE. EE has now been reported in every continent except for Africa, including every state in the United States and most of Western Europe. Several reports have suggested that the prevalence of EE has increased in both pediatric and adult patients by 18- to 35-fold in the past 20 years [3-6].

What is the general approach to management of eosinophilic esophagitis?

Management of EE involves elimination/control of eosinophils with either medications or diet. Medical treatment involves treating the symptoms but not the cause of the disease. It is important to note that there are no current

approved medications for the treatment of EE, however, the use of 'topical' corticosteroids has been shown to be successful. The patients typically swallow inhaled corticosteroids used for asthma in moderate to high doses (given without use of spacer and avoiding foods/liquids for 30 minutes). The goal of this therapy is to deposit steroids in the esophagus leading to apoptosis of the eosinophils and reduction of symptoms. These methods have been shown to have a varying rate of success. Konikoff *et al.* [7] completed a randomized double-blind placebo-controlled trial of 36 pediatric patients with EE who either refused or failed dietary modification. They reported improved control of symptoms and less eosinophils per high power field (eosinophils/HPF) in biopsy in 50% of the patients. The success rate was 50% compared to an 80-90% success rate in the open-label trials with fluticasone or budesonide [8,9].

Cromolyn, montelukast (a leukotriene receptor antagonist), and omalizumab (an anti-IgE antibody), did not show any histological improvement in open-label clinical trials [5,10,11]. At this point, these drugs cannot be recommended for EE. A recent open label trial of mepolizumab (an anti-interleukin (IL)-5 antibody) showed a significant improvement in four patients, with biopsy improving from 150 to 40 eosinophils/HPF; however, this was still well above the normal level of 0 eosinophils/HPF [12].

Dietary approach

A second approach is to treat the cause of EE by eliminating the appropriate food. An elemental diet has been successful in both pediatric and adult patients, with success rates surpassing 95% [5,13]. However, due to the poor palatability of these formulas, it is difficult for patients to remain on them. A more directed approach to eliminating the particular food antigen is possible; two possible ways to remove the food antigen include removing the most common food allergens or removing the allergens based on allergy testing. The first method has been primarily studied by Kagalwalla *et al.* [14] in pediatric patients and by Gonsalves in adults (N Gonsalves, personal communication). They found that a 'six-food' elimination diet [no milk, soy, egg, wheat, seafood (fish and shellfish), and peanuts (peanuts and tree nuts)] led to a significant reduction of esophageal eosinophilia. In their pediatric trial, Kagalwalla *et al.* [14] started 35 children on the 'six-food' elimination diet; 74% of the children had resolution (<10 eosinophils/HPF) on this diet. In adult trials, the success rate is reported to be 50% with the elimination diet and 90-95% for the elemental diet (N Gonsalves, personal communication).

The alternative dietary approach is to remove foods based on allergy testing. Three standard methods are used for food testing: prick skin testing, *in vitro* specific IgE assays and atopy patch tests. In a study on children, diets based on positive specific IgE assays had a response rate near 0% when foods were eliminated based purely on the *in vitro* specific IgE assay results [15]. In the same study, the prick skin test had only a slightly better success rate of about 50%. This strongly suggests that the food allergy in EE is not strictly IgE mediated, consistent with the results with omalizumab. Based on this finding, we started to use atopy patch testing for EE [16]. Atopy patch testing is designed to look for non-IgE-mediated food reactions, presumably T cell-mediated. We have found that the combination of both the prick skin and atopy patch tests, looking for both IgE- and non-IgE-mediated disease, has been highly successful in the treatment of EE. A food that was negative on both the prick skin and atopy patch tests was unlikely to cause EE, with a predictive value of 90% or more for all foods except milk [17]. Additionally, the combination of the skin prick and atopy patch tests resulted in resolution of EE symptoms and normalization of biopsies in 80% of patients [17-19].

What is the prognosis?

EE is a chronic disorder. If any treatment, medical or dietary, is stopped, the symptoms return and esophageal eosinophilia reoccurs with very rare exceptions.

Longitudinal studies in adults over a 12 year period have not shown resolution [20].

Recent advances

One of the major advances in the past 2 years was the First International Gastrointestinal Eosinophil Research Symposium (FIGERS), a consensus meeting of allergists, gastroenterologists, and pathologists that developed clinical recommendations for the diagnosis and treatment of EE [21]. This group defined EE as a 'primary clinicopathological disorder of the esophagus' with diagnosis made by esophageal biopsy with a finding of ≥ 15 eosinophils/HPF in one or more specimens. The report emphasized that gastroesophageal reflux must be aggressively managed prior to endoscopy with a high dose proton pump inhibitor or the patient must have evidence of normal distal esophageal pH as detected by pH probe; this was based on a case report by Ngo and colleagues [22] describing three patients whose esophageal eosinophil count of up to 52 eosinophils/HPF resolved with reflux medications. Besides gastroesophageal reflux, clinicians must keep in mind that esophageal eosinophils can be seen in other disease entities, including eosinophilic gastroenteritis (increased eosinophils throughout the gastrointestinal tract), Crohn's disease, collagen vascular disease, hypereosinophilic syndrome, and drug-associated diseases, and are occasionally associated with infections.

Additional recent studies have indicated that EE is a chronic disease, with less than 10% of patients outgrowing it [10,23,24]. The relationship was confirmed in studies in both adults and children, approximately 75% of whom had other atopic diseases (allergic rhinitis, asthma or atopic dermatitis) [25,26] and associations with celiac disease [27-30] and tracheoesophageal fistula [31].

Recent studies have confirmed that symptoms of EE vary by age. Young infants and toddlers typically present with GERD or failure to thrive due to the assumed pain associated with eating. School-age children typically present with abdominal pain or persistent GERD symptoms. The most common symptoms in adolescents and adults include dysphagia and food impaction [3,21,24]. These symptoms are more unusual and should immediately suggest the possibility of EE. These patients were all diagnosed at an early age and were treated aggressively through avoidance of allergens. Because the symptoms of EE do not correlate with endoscopy and histological findings, it is important to use endoscopy for diagnosing and following patients with EE [32].

Several articles by the Rothenberg and Justinich laboratories have made advances in determining the potential mechanism of EE, showing that IL-13 and fibroblast growth factor-9 have important roles in the proliferative responses in the esophagus [33-36]. Straumann *et al.* [37] examined the use of infliximab (an anti-tumor necrosis factor- α antibody) in treating EE, but it had no effect on histological findings.

Implications for clinical practice

The most recent studies suggest there is a certain phenotype that should be examined carefully for EE. The stereotypical patient is a male Caucasian with classic symptoms (dysphagia or food impaction in adolescents and adults; abdominal pain in school-age children; GERD symptoms in young children). Also, the lack of correlation of symptoms with endoscopy findings indicates the importance of using endoscopy for diagnosing and following patients with EE. Management of this disease is primarily through diet as foods are causative in more than 90% of adults and children. Medical therapies are being developed for patients with restrictive and socially difficult diets.

Abbreviations

EE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; HPF, high power field; IL, interleukin.

Competing interests

The author was a local principal investigator for multicenter studies by Ception Therapeutics (Rockville, MD, USA) and Nutricia North America (Gaithersburg, MD, USA).

References

- Dobbins JW, Sheahan DG, Behar J: **Eosinophilic gastroenteritis with esophageal involvement.** *Gastroenterology* 1977, **72**:1312-6.
 - Kelly K, Lazenby A, Rowe P, Yardley JH, Perman J, Sampson H: **Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula.** *Gastroenterology* 1995, **109**:1503-12.
 - Noel RJ, Putnam PE, Rothenberg ME: **Eosinophilic esophagitis.** *N Engl J Med* 2004, **351**:940-1.
 - Straumann A, Simon HU: **Eosinophilic esophagitis: escalating epidemiology?** *J Allergy Clin Immunol* 2005, **115**:418-9.
 - Liacouras CA, Spergel JM, Ruchelli E, Verma R, Mascarenhas M, Semeao E, Flick J, Kelly J, Brown-Whitehorn T, Mamula P, Markowitz JE: **Eosinophilic esophagitis: a 10-year experience in 381 children.** *Clin Gastroenterol Hepatol* 2005, **3**:1198-206.
 - Cherian S, Smith NM, Forbes DA: **Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia.** *Arch Dis Child* 2006, **91**:1000-4.
 - Konikoff MR, Noel RJ, Blanchard C, Kirby C, Jameson SC, Buckmeier BK, Akers R, Cohen MB, Collins MH, Assa'ad AH, Aceves SS, Putnam PE, Rothenberg ME: **A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis.** *Gastroenterology* 2006, **131**:1381-91.
- F1000 Factor 3.0 Recommended
Evaluated by Prateek Sharma 27 Dec 2006
- Aceves SS, Dohil R, Newbury RO, Bastian JF: **Topical viscous budesonide suspension for treatment of eosinophilic esophagitis.** *J Allergy Clin Immunol* 2005, **116**:705-6.
 - Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME: First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees: **Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment.** *Gastroenterology* 2007, **133**:1342-63.
- F1000 Factor 3.0 Recommended
Evaluated by Jonathan Spergel 17 Oct 2007
- Attwood SE, Lewis CJ, Bronder CS, Morris CD, Armstrong GR, Whittam J: **Eosinophilic oesophagitis: a novel treatment using Montelukast.** *Gut* 2003, **52**:181-5.
 - Foroughi S, Foster B, Kim N, Bernardino LB, Scott LM, Hamilton RG, Metcalfe DD, Mannon PJ, Prussin C: **Anti-IgE treatment of eosinophil-associated gastrointestinal disorders.** *J Allergy Clin Immunol* 2007, **120**:594-601.
 - Stein ML, Collins MH, Villanueva JM, Kushner JP, Putnam PE, Buckmeier BK, Filipovich AH, Assa'ad AH, Rothenberg ME: **Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis.** *J Allergy Clin Immunol* 2006, **118**:1312-9.
 - Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA: **Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents.** *Am J Gastroenterol* 2003, **98**:777-82.
 - Kagalwalla AF, Sentongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, Melin-Aldana H, Li BU: **Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis.** *Clin Gastroenterol Hepatol* 2006, **4**:1097-102.
 - Teitelbaum JE, Fox VL, Twarog FJ, Nurko S, Antonioli D, Gleich G, Badizadegan K, Furuta GT: **Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate.** *Gastroenterology* 2002, **122**:1216-25.
 - Spergel JM, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA: **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.
 - Spergel JM, Brown-Whitehorn T, Beausoleil JL, Shuker M, Liacouras CA: **Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis.** *J Allergy Clin Immunol* 2007, **119**:509-11.
 - Spergel J, Andrews T, Brown-Whitehorn T, Beausoleil J, Liacouras C: **Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of prick skin test and patch tests.** *Ann All Asthma Immunol* 2005, **95**:336-43.
 - Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA: **The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis.** *J Allergy Clin Immunol* 2002, **109**:363-8.
 - Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU: **Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years.** *Gastroenterology* 2003, **125**:1660-9.
 - Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME: First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees: **Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment.** *Gastroenterology* 2007, **133**:1342-63.
 - Ngo P, Furuta GT, Antonioli DA, Fox VL: **Eosinophils in the esophagus - peptic or allergic eosinophilic esophagitis? Case**

series of three patients with esophageal eosinophilia. *Am J Gastroenterol* 2006, **101**:1666-70.

F1000 Factor 3.0 Recommended

Evaluated by Jon Markowitz 31 Aug 2006

23. Assa'ad AH, Putnam PE, Collins MH, Akers RM, Jameson SC, Kirby CL, Buckmeier BK, Bullock JZ, Collier AR, Konikoff MR, Noel RJ, Guajardo JR, Rothenberg ME: **Pediatric patients with eosinophilic esophagitis: an 8-year follow-up.** *J Allergy Clin Immunol* 2007, **119**:731-8.
24. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, Franciosi J, Shuker M, Verma R, Liacouras CA: **14 years of eosinophilic esophagitis: clinical features and prognosis.** *J Pediatr Gastroenterol Nutr* 2009, **48**:30-6.
25. Veerappan GR, Perry JL, Duncan TJ, Baker TP, Maydonovitch C, Lake JM, Wong RK, Osgard EM: **Prevalence of eosinophilic esophagitis in an adult population undergoing upper endoscopy: a prospective study.** *Clin Gastroenterol Hepatol* 2008, **7**:420-6.
26. Jyonouchi S, Brown-Whitehorn TA, Spergel JM: **Association of eosinophilic gastrointestinal disorders with other atopic disorders.** *Immunol Allergy Clin North Am* 2009, **29**:85-97.
27. Ooi CY, Day AS, Jackson R, Bohane TD, Tobias V, Lemberg DA: **Eosinophilic esophagitis in children with celiac disease.** *J Gastroenterol Hepatol* 2008, **23**:1144-8.
28. Heine RG: **Eosinophilic esophagitis in children with celiac disease: new diagnostic and therapeutic dilemmas.** *J Gastroenterol Hepatol* 2008, **23**:993-4.
29. Verzeegnassi F, Bua J, De Angelis P, Dall'oglio L, Di Leo G, Ventura A: **Eosinophilic oesophagitis and coeliac disease: is it just a casual association?** *Gut* 2007, **56**:1029-30.
30. Quaglietta L, Coccorullo P, Miele E, Pascarella F, Troncone R, Staiano A: **Eosinophilic oesophagitis and coeliac disease: is there an association?** *Aliment Pharmacol Ther* 2007, **26**:487-93.
31. Oliveira C, Zamakhshary M, Marcon P, Kim PC: **Eosinophilic esophagitis and intermediate esophagitis after tracheoesophageal fistula repair: a case series.** *J Pediatr Surg* 2008, **43**:810-4.
32. Pentiuk S, Putnam PE, Collins MH, Rothenberg ME: **Dissociation between symptoms and histological severity in pediatric eosinophilic esophagitis.** *J Pediatr Gastroenterol Nutr* 2009, **48**:152-60.

F1000 Factor 6.0 Must Read

Evaluated by Jonathan Spergel 09 Mar 2009

33. Mulder DJ, Pacheco I, Hurlbut DJ, Mak N, Furuta GT, MacLeod RJ, Justinich CJ: **FGF9-induced proliferative response to eosinophilic inflammation in oesophagitis.** *Gut* 2009, **58**:166-73.
34. Mishra A, Wang M, Pemmaraju VR, Collins MH, Fulkerson PC, Abonia JP, Blanchard C, Putnam PE, Rothenberg ME: **Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia.** *Gastroenterology* 2008, **134**:204-14.
35. Bullock JZ, Villanueva JM, Blanchard C, Filipovich AH, Putnam PE, Collins MH, Risma KA, Akers RM, Kirby CL, Buckmeier BK, Assa'ad AH, Hogan SP, Rothenberg ME: **Interplay of adaptive th2 immunity with eotaxin-3/c-C chemokine receptor 3 in eosinophilic esophagitis.** *J Pediatr Gastroenterol Nutr* 2007, **45**:22-31.
36. Blanchard C, Mingler MK, Vicario M, Abonia JP, Wu YY, Lu TX, Collins MH, Putnam PE, Wells SI, Rothenberg ME: **IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids.** *J Allergy Clin Immunol* 2007, **120**:1292-300.

F1000 Factor 3.0 Recommended

Evaluated by Jonathan Spergel 18 Feb 2008

37. Straumann A, Bussmann C, Conus S, Beglinger C, Simon HU: **Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis.** *J Allergy Clin Immunol* 2008, **122**:425-7.