IAPO-Interamerican Association of
Pediatric Otorhinolaryngology

Otorhinolaryngologic Manifestations of Eosinophilic Esophagitis in Children

Dana M Thompson

Introduction

Eosinophilic Esophagitis (EoE) is a chronic inflammatory disorder of the esophagus that is rapidly emerging as a distinct disease entity. EoE was first described in 1977[1] but was not recognized as a distinct entity until 1995 when Kelly and colleagues reported ten pediatric patients diagnosed with symptomatic gastroesophageal reflux but did not respond to acid suppression therapy or fundoplication. All these patients had increased esophageal eosinophils. The esophageal eosinophilia and symptoms all respond to an amino acid based formula. [2]

The presenting symptoms are usually gastrointestinal in nature and often assumed to be due to acid reflux. Common symptoms in adults and children include epigastric pain, chest pain, dysphagia, and food impaction. Recent reports highlight the spectrum of associated symptoms outside of the esophagus such as croup and hoarseness that may primarily present to the otolaryngologist. [3-6] With the crossover of upper airway symptoms and findings along with the expanding role of otolaryngologist in the treatment and management of esophageal disorders and dysphagia it is important for otolaryngologist to recognize and appropriately treat or refer patients with EoE for further management. This chapter will provide an overview of the clinical features, diagnosis and treatment of this intriguing disease, with emphasis pertaining to the otolaryngologist.

Epidemiology

EoE appears to be a worldwide problem selectively in developed Westernized countries. To date there are 367 publications since its first description in 1977, and publications come from every continent except for Africa; 269 publications have occurred in the last 5 years. In a population based study in Hamilton County, Ohio Noel and colleagues showed that in the year 2000 that EoE affected 1/10,000 children. Within three years, (2000-2003) there was a 4 fold increase in prevalence to 4.3/10,000.[7] An Olmsted County, Minnesota population based study shows the incidence increasing from 1 per 100,000 population in 1976 to 1985 to 9 per 100,000 population between 1996 and 2005.[8] Population based studies in other westernized countries show similar trends over the past 15 years [9,10]. The factors contributing toward this increase in prevalence are not clearly understood. Either EoE was previously under-recognized or the prevalence is increasing due to dietary changes and the increasing incidence of environmental and aeroallergens. Fifty to 70% of patients with will have other allergic conditions such as atopic dermatitis, allergic rhinitis, and/or asthma.[7,11] Seasonal variation of the onset of symptoms of EoE similarly reflects peaks in seasonal allergic symptoms.[12]

Additionally, up to 45% of patients affected with EoE will have a first degree relative with either asthma or allergies.[11]

EoE is a disease with a 3:1 male predominance in both children and adults.[3,13,14] A familial pattern has been reported through case reports of affected siblings[15] and other reports of families with multiple generations affected.[11,16,17] These familial cases highlight the need for careful family histories in these patients, not only for diagnosed EoE, but also for common presentations such as dysphagia or food impaction. Gender predisposition, familial allergic history and familial clustering suggest a genetic predisposition to EoE. A nucleotide polymorphism defect in gene encoding of eotaxin-3, a promoter of eosinophil recruitment into the esophagus, has been described in affected individuals[18]however genetic encoding studies of affected family members is not available.

Pathophysiology

The exact pathogenesis of EoE is unknown. The strong association between allergic diseases and EoE provides indirect information that the pathophysiology is related to a T helper cell 2 (Th2) dependent mechanism. Th2 active cytokines IL-5, IL-13 and IL-4 are found in increased levels in the esophagus of patients with EoE. Antigenic stimulation from aeroallergens and food allergens elicit a Th2 response. Removal of both aeroallergens and specific food allergens in affected individuals results in both symptomatic and histologic improvement of EoE. [18]

Under normal conditions, eosinophils are not found in the pediatric esophagus, although they can be found in the stomach, small bowel and colon. In EoE, suspected antigens (aeroallergen or food allergen) are believed to activate Th2 helper cells- to release IL-5. Il-5 then triggers eosinophilic migration from the bone marrow into the circulation and eventually into the esophagus. In addition to eosinophilic recruitment Il-5 up-regulates proliferation, differentiation, activation and survival of the eosinophil. This mechanism is further evidenced by the finding that in-vitro stimulation of peripheral blood mononuclear cells using allergen specific antigens of soy, peanut, dust and ragweed increases IL-5 production in EoE patients when compare to healthy controls. [18,19] However, IL-5 does not work alone to promote the migration of the eosinophil to the esophagus.

The Th2 cytokine IL-13 is also involved in facilitating migration of the eosinophil to the esophagus. Intratracheal placement of IL-13 in the mouse model will promote development of EoE. IL-13 increases the expression of Eotaxin-3. Eotaxin -3 has been shown to have increased expression in epithelial cells of the esophagus in patients with EoE and is believed to be a chemoattractant for eosinophils in the esophagus.[18] Most likely IL-5, IL-13 and eotaxin-3 work together to promote esophageal migration and activation of the eosinophil in patients with EoE. Mast cells are also seen in increased numbers and may be effector cells in the mechanism of developing EoE. Additionally, activated mast cells are another source of IL-5.

At present, it appears that EoE may occur in a genetically predisposed individual at higher rates, where the exposure to a certain antigen results in a TH2 cell dependent mechanism with IL5, IL-13 and eotaxin-3 involved in recruitment of the activated eosinophil to the esophagus.[18,19]

Once the eosinophil is in the esophagus and becomes activated it releases inflammatory and cytotoxic mediators that then have potential to cause damage. The activated eosinophil granular proteins are cationic toxins which further activate eosinophils, basophils, mast cells neutrophils and potentially bronchial epithelial cells. These specific cytotoxic granular proteins such as Major basic protein, eosinophil derived neurotoxin and eosinophil peroxidase, are present in the esophageal mucosa of patients with EoE and not in controls. It is postulated that the release of these cytotoxic mediators cause the symptoms and esophageal damage in EoE. Additionally activated eosinophils also express TGF beta1 which is believed to play a role in the development of esophageal fibrosis. [18,19]

Gastrointestinal Symptoms and Manifestations of EoE

The typical clinical presentation of EoE is gastrointestinal symptoms that are assumed to be caused by gastroesophageal reflux (GERD) but are refractory to standard reflux therapies. In children the symptom presentation tends to be age dependent; infants to toddler age present with recurrent emesis or failure to thrive; Children ages 3-7 present primarily with a feeding disorder and food refusal behavior; Children aged 8-10 present with recurrent vomiting, feeding and swallowing problems; Children aged 11-16 present with chronic abdominal pain or dysphagia and older children present with food impaction or odynophagia.[3,4,12o,14,20] Any child that presents with food impaction that requires endoscopic extraction should be assumed to have EoE until proven otherwise. Other common associated diseases and findings that increase the index of suspicion for EoE in the symptomatic child include peripheral blood eosinophilia, increased IgE levels, and a patient or first degree family history of atopic conditions, including asthma, allergy, atopic dermatitis and food allergy. The most common food allergies are cow milk, egg, soy, wheat and peanuts.

Otorhinolaryngologic Symptoms and Manifestations of EoE

Extraesophageal symptoms include upper airway and respiratory symptoms of rhinitis, sinusitis, adenoiditis, pneumonia, wheezing, globus, hoarseness, dysphonia and cough.[3-6] Additionally, EoE has been attributed as an etiologic factor in upper airway diseases managed by the otolaryngologist. These laryngeal diseases include subglottic stenosis,[21-24] vocal fold cyst and nodules,[5,24,25] recurrent croup,[6,26]and chronic laryngeal edema refractory to traditional gastroesophageal reflux therapy.[21,23]

Nasal symptoms and rhinosinusitis are reported in 19-25% of children with EoE.[3,4] Whether these children have an allergen as the antigenic trigger is unknown, however up to 62% of the children have a personal or family history of allergy.[3,4] There are several common features that may link rhinosinusitis and EoE. Common symptoms are chronic cough, hoarseness and dysphagia. Common concurrent diseases are allergic rhinitis, allergic conjunctivitis, asthma and atopic diseases such as eczema and food allergy.[5]

Laryngeal symptoms of EoE include hoarseness, cough, croup, globus sensation, stridor and sleep disordered breathing. The larynx is a prime target as it is located at the interface of the oronasal cavity and the esophagus. The younger the child, the closer the relationship of the larynx to the nasal cavity and esophagus. Any

antigenic stimulation of eosinophils in the nose or esophagus has high potential to affect the larynx. Most patients with diffuse laryngeal edema are assumed to have extra-esophageal acid reflux disease as the etiology. [27] However recent reports describe patients with persistent laryngeal disease refractory to maximal acid reflux therapy or fundoplication who were eventually diagnosed with EoE. Aggressive treatment of EoE resulted in reversal or improvement in the laryngeal symptoms. [6,21,23,24,28] The patient characteristics and co-morbidities in patients with EoE associated laryngeal disease are similar to those with gastrointestinal symptoms. They commonly present with persistent airway symptoms refractory to GERD treatment. There is a male predominance. Many will have a history of allergic rhinitis, atopy, and asthma. Some will have peripheral eosinophilia counts or elevated total IgE levels. Similar to patients with typical gastrointestinal symptoms of EoE, those with laryngeal symptoms may go unrecognized for long periods of time, thus a high index of suspicion is required.

Subglottic stenosis is also an extraesophageal finding associated with EoE. The first report of EoE and SGS was in a child who had failed multiple laryngotracheal reconstructive procedures despite meticulous surgical care and control for GERD.[21] Subsequent reports also verify this association. [5,6,22,23,26] Because of the potential association of untreated EoE as a contributing factor to persistent airway stenosis, some consider evaluation for and treatment of eosinophilic esophagitis in this population warranted before committing to elective airway surgery. [6]

Esophagoscopy and Diagnosis EoE

Establishing diagnosis of EoE requires an index of suspicion based on clinical symptoms to prompt the clinician to proceed with esophagoscopy and biopsy. Key esophageal endoscopic findings that suggest the presence of eosinophils include linear streaking, white specks, rings, furrows, strictures, mucosal fragility and small caliber esophagus. Up to 40% of affected individuals may have a visually normal appearing esophagus,[3,11]therefore in the suspected patient, is it prudent for the clinician to obtain biopsies regardless of visual findings. Additionally, eosinophilia within the esophagus is heterogeneous; therefore it is prudent to obtain biopsies from multiple sites to increase the likelihood of establishing a diagnosis.

The Consensus opinion from the First International Gastrointestinal Eosinophil Research Symposium is that EoE is a histologic diagnosis that is made when there is a minimum of 15 eosinophils/hfp from a biopsied affected area of the esophagus. Additionally, the Consensus diagnostic criteria states that patients cannot have eosinophilic inflammation of the rest of the gastrointestinal tract, and GERD must be ruled out by non-response to proton-pump inhibitor (PPI) therapy or normal esophageal pH monitoring.[29] In addition to eosinophils, other histologic findings include an increased basal cell layer thickness, lymphocytes and mast cell presence, but these are not part of the diagnostic criteria at present.[6]

The challenge with Consensus recommendation of the strict histopathologic criteria of 15 eosinophils/hpf is that there are patients who demonstrate less than 15 eosinophils/hpf who are unresponsive to GERD medical or surgical therapy or who have normal pH probe findings who do respond to treatment for EoE.[28]

Many of these patients will have condominant symptoms and findings that suggest EoE, such as an elevated peripheral eosinophil count, elevated IgE levels, or a strong atopic history or airway symptoms. Additionally resolution of histologic EoE has been seen as a result of dietary antigenic elimination, thus establishing the diagnosis of EoE. The histologic diagnosis must be taken in light of clinical circumstances and the clinical diagnosis should be made by the clinician by examining all of the relevant data.[30]

Extraesophageal Endoscopic Features at Diagnosis

Similar to the findings seen during esophageal endoscopy, examination findings in the nose, larynx, subglottis and trachea in patient with eosinophilic esophagitis can be non-specific and seen in other diseases including GERD. Findings typically include diffuse mucosal inflammation. Patients with EoE who have sinonasal symptoms the nasal endoscopic findings are similar to patients with allergic rhinosinusitis.[5]

Endoscopic examination of patients with EoE and laryngeal symptoms similarly shows diffuse mucosal inflammation that can involve all or specific portions of the larynx. Findings of diffuse laryngeal edema involving all areas including lingual tonsil tissue hypertrophy, swelling with thickening of the epiglottis and, supra-arytenoid tissue edema with poor visualization of the vocal folds. Vocal fold cystic changes are amongst the laryngeal findings in patients with EE. Edematous and nodular changes are seen in the mucosa of the subglottis and trachea.

Natural History

There are few long-term studies describing the natural history of EoE. Assa'ad and colleagues reported an 8 year experience, in which 14% of their 57 patients had resolution following treatment, 33% persisted even with treatment, and 53% relapsed after treatment ended.[31] In contrast, Konikoff and colleagues found rates of spontaneous remission of 9-18% in pediatric patients in the placebo arm of a treatment trial, indicating that some patients may have at least short term spontaneous resolution of their disease.[32] The natural course history in patients with primarily airway symptoms of EoE is unknown

Because of this lack of natural history data, long term consequences of poorly treated EoE remain unclear. It appears clear that some patients will develop strictures or narrow caliber esophagus, and that in some pediatric patients EoE can be associated with development of a Schatzki ring. These can, in turn, predispose to food impaction. Other patients have been shown to develop marked dysmotility on esophageal manometry, which might occur following deeper eosinophilic inflammation of muscles or nerves.[33] There have not been any reports of patients developing either Barrett's esophagus or esophageal malignancies.

Management/Treatment

Optimal treatment for eosinophilic esophagitis is still being determined. Because proper therapeutic endpoints have not been determined, treatment and management strategies continue to evolve and may require individualization for specific patients. While resolution of symptoms is an easily measurable goal, the lack of natural history data makes it unclear whether histologic resolution is needed as well. There are a number of patients who become asymptomatic while still having

a lower level esophageal eosinophilia and our current state of knowledge does not allow us to know whether these reduced numbers of eosinophils might still predispose susceptible patients to long-term complications such as stricture formation, food impaction, or malignant transformation.

To date, systemic or topical corticosteroids have been the primary pharmacologic therapy modality. Use of systemic steroids can improve both symptoms and histology, but both can worsen again once treatment is stopped.[11,34] The risk of other side effects and complications of chronic systemic steroids also preclude their use as first line therapy. Topical steroid therapy is often an effective first line therapy modality for management of EoE. Success has been demonstrated using swallowed fluticasone or a viscous formulation of budesonide.[14,35-37] A recent double-blind, placebo controlled trial of swallowed fluticasone showed a 50% response rate for symptoms and histologic findings in pediatric EoE patients, compared to a 9% response rate with placebo. Interestingly, response followed an "all or none" pattern, with either complete remission or no response at all, and patients with an atopic history were less likely to respond. [32]The major side effect reported with the use of topical steroids is oral candidal infections.[35]

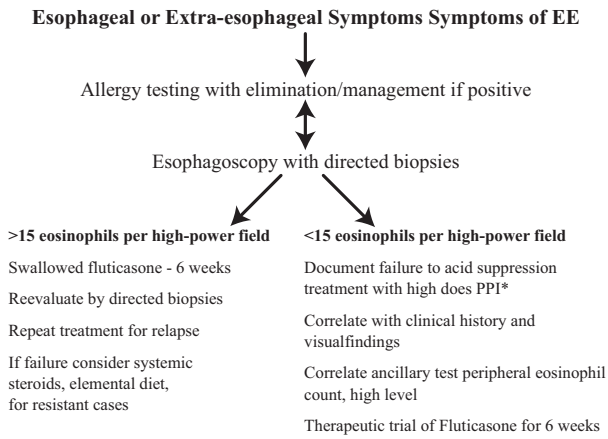
Because of the association with atopic disease and the increased numbers of mast cells seen in some EoE patients, various other treatments for allergy have been tried which include cromolyn sulfate [11] and large doses of the leukotriene receptor antagonist montelukast [38] with varied results and no change in histology. The use of anti IL-5 antibodies has been mostly experimental for refractory cases.

Nutritional management has a role in some patients and has demonstrated good outcomes. Histologic improvement can be seen in patients by first identifying offending foods by a combination of skin prick and atopic patch testing, and then eliminating these foods[39]. Additionally implementation of an empiric elimination of the 6 most allergenic foods has also proven to result in a 74% clinical and histologic response rate.[40] Exclusive use of an elemental formula is a very effective treatment option showing response rate of 92-98%[2,41] however unpalatable taste and high cost preclude its practical use and compliance.

Patients who progress to develop strictures may benefit from esophageal dilation. While there have been reports of successful relief of strictures in series from both the adult and pediatric literature following balloon or bougie dilations, significant risks such as pain, mucosal tears, and perforation can occur. Narrowed areas can also recur following therapy, requiring repeated dilations.[42]

The treatment algorithm of the author is presented in **Figure 1**, with emphasis to consider obtaining ancillary test and other clinical data when the eosinophil count <15 eosinophils/hpf particularly if the presenting symptoms include extraesophageal or airway disease.[3]

Figure 1. Treatment algorithm



* PPI: proton-pump inhibitor

Conclusions

The symptoms of EoE are primarily gastrointestinal in nature. Because of the expanding practice of otolaryngologist in the management of swallowing disorders and the increasing knowledge of EoE as a causative factor in common conditions seen by the otolaryngologist, heightened awareness of this disease is important for establishing the diagnosis and directing symptomatic relief of symptoms typically attributed to GERD. A team collaboration between otolaryngologist, gastroenterologist and allergist will assure the best treatment in predisposed children.

Acknowledgement: Copyritght: © Mayo Foundation, 2009

References

1. Dobbins J, Sheahan D, Behar J. Eosinophilic gastroenteritis with esophageal involvement. Gastroenterology. 1977;72:1312-1316.
2. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. Gastroenterology. 1995;109:1503-1512.
3. Dauer EH, Freese DK, El-Youssef M, Thompson DM. Clinical characteristics of eosinophilic esophagitis in children. Annals of Otology, Rhinology & Laryngology. 2005;114:827-833.

4. Orenstein SR, Shalaby TM, Di Lorenzo C, et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children.[erratum appears in Am J Gastroenterol 2001 Jul;96(7):2290]. American Journal of Gastroenterology. 2000;95:1422-1430.
5. Thompson DM, Orvidas LJ. Otorhinolaryngologic manifestations of eosinophilic esophagitis. Gastrointestinal Endoscopy Clinics of North America. 2008;18:91-98; ix.
6. Putnam PE. Eosinophilic esophagitis in children: clinical manifestations. Gastroenterology Clinics of North America. 2008;37:369-381.
7. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. New England Journal of Medicine. 2004;351:940-941.
8. Prasad GA, Talley NJ, Romero Y, et al. Prevalence and predictive factors of eosinophilic esophagitis in patients presenting with dysphagia: a prospective study. American Journal of Gastroenterology. 2007;102:2627-2632.
9. Straumann A, Simon H-U. Eosinophilic esophagitis: escalating epidemiology? Journal of Allergy & Clinical Immunology. 2005;115:418-419.
10. Esposito S, Marinello D, Paracchini R, Guidali P, Oderda G. Long-term follow-up of symptoms and peripheral eosinophil counts in seven children with eosinophilic esophagitis. Journal of Pediatric Gastroenterology & Nutrition. 2004;38:452-456.
11. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic Esophagitis: A 10-Year Experience in 381 Children. Clinical Gastroenterology and Hepatology. 2005;3:1198-1206.
12. Spergel JM, Brown-Whitehorn TF, Beausoleil JL, et al. 14 Years of Eosinophilic Esophagitis: Clinical Features and Prognosis. Journal of Pediatric Gastroenterology & Nutrition. 2009;48:30-36.
13. Liacouras CA. Eosinophilic esophagitis in children and adults. Journal of Pediatric Gastroenterology & Nutrition. 2003;37 Suppl 1:S23-28.
14. Teitelbaum JE, Fox VL, Twarog FJ, et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate.[see comment]. Gastroenterology. 2002;122:1216-1225.
15. Patel SM, Falchuk KR. Three brothers with dysphagia caused by eosinophilic esophagitis. Gastrointestinal Endoscopy. 2005;61:165-167.
16. Zink DA, Amin M, Gebara S, Desai TK. Familial dysphagia and eosinophilia. [see comment]. Gastrointestinal Endoscopy. 2007;65:330-334.
17. Meyer GW. Eosinophilic esophagitis in a father and a daughter.[comment]. Gastrointestinal Endoscopy. 2005;61:932.
18. Blanchard C, Rothenberg ME. Basic pathogenesis of eosinophilic esophagitis. Gastrointestinal Endoscopy Clinics of North America. 2008;18:133-143; x.
19. Rothenberg ME, Mishra A, Collins MH, Putnam PE. Pathogenesis and clinical features of eosinophilic esophagitis. Journal of Allergy & Clinical Immunology. 2001;108:891-894.
20. Markowitz JE, Liacouras CA. Eosinophilic esophagitis. Gastroenterology Clinics of North America. 2003;32:949-966.

21. Hartnick C, Liu J, Cotton R, Rudolph C. Subglottic stenosis complicated by allergic esophagitis: case report. Ann Otol Rhinol Laryngol. 2002;111:57-60.
22. Johnson LB, Rutter MJ, Putnam PE, Cotton RT. Airway Stenosis and Eosinophilic Esophagitis. In: Har-El G, ed. The 83rd Annual Meeting of the American Broncho-Esophagological Association Nashville, Tennessee: The American Broncho-Esophagological Association 2003:137.
23. Dauer EH, Ponikau JU, Smyrk TC, Murray JA, Thompson DM. Airway manifestations of pediatric eosinophilic esophagitis: a clinical and histopathologic report of an emerging association. Annals of Otology, Rhinology & Laryngology. 2006;115:507-517.
24. Thompson DM, Arora AS, Romero Y, Dauer EH. Eosinophilic esophagitis: its role in aerodigestive tract disorders. Otolaryngologic Clinics of North America. 2006;39:205-221.
25. Mandell DL, Yellon RF. Synchronous airway lesions and esophagitis in young patients undergoing adenoidectomy. Archives of Otolaryngology -- Head & Neck Surgery. 2007;133:375-378.
26. Thompson DM, Orvidas LJ. Eosinophilic Esophagitis: A Cause of Recurrent Spasomidic Croup Symptoms. Arch Otolaryngol Head Neck Surg. 2009.
27. Koufman JA. Laryngopharyngeal reflux is different from classic gastroesophageal reflux disease. Ear, Nose, & Throat Journal. 2002;81:7-9.
28. Brigger MT, Misdraji J, Hardy SC, Hartnick CJ. Eosinophilic esophagitis in children: a pathologic or clinicopathologic diagnosis? Archives of Otolaryngology – Head & Neck Surgery. 2009;135:95-100.
29. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic Esophagitis in Children and Adults: A Systematic Review and Consensus Recommendations for Diagnosis and Treatment: Sponsored by the American Gastroenterological Association (AGA) Institute and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition. Gastroenterology. 2007;133:1342-1363.
30. Putnam P, Rothenberg M. Eosinophilic esophagitis: Concepts, controversies, and evidence. Current Gastroenterology Reports. 2009;11:220-225.
31. Assa'ad AH, Putnam PE, Collins MH, et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. Journal of Allergy & Clinical Immunology. 2007;119:731-738.
32. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis.[see comment]. Gastroenterology. 2006;131:1381-1391.
33. Lucendo AJ, Pascual-Turrion JM, Navarro M, et al. Endoscopic, bioptic, and manometric findings in eosinophilic esophagitis before and after steroid therapy: a case series. Endoscopy. 2007;39:765-771.
34. Liacouras CA, Wenner WJ, Brown K, Ruchelli E. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids.[see comment]. Journal of Pediatric Gastroenterology & Nutrition. 1998;26:380-385.

35. Faubion WA, Jr., Perrault J, Burgart LJ, Zein NN, Clawson M, Freese DK. Treatment of eosinophilic esophagitis with inhaled corticosteroids.[see comment]. Journal of Pediatric Gastroenterology & Nutrition. 1998;27:90-93.
36. Noel RJ, Putnam PE, Collins MH, et al. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. Clinical Gastroenterology & Hepatology. 2004;2:568-575.
37. Aceves SS, Bastian JF, Newbury RO, Dohil R. Oral viscous budesonide: a potential new therapy for eosinophilic esophagitis in children. American Journal of Gastroenterology. 2007;102:2271-2279; quiz 2280.
38. Attwood SE, Lewis CJ, Bronder CS, Morris CD, Armstrong GR, Whittam J. Eosinophilic oesophagitis: a novel treatment using Montelukast.[see comment]. Gut. 2003;52:181-185.
39. 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.[see comment]. Annals of Allergy, Asthma, & Immunology. 2005;95:336-343.
40. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clinical Gastroenterology & Hepatology. 2006;4:1097-1102.
41. Markowitz JE, Spergel JM, Ruchelli E, Liacouras CA. Elemental diet is an effective treatment for eosinophilic esophagitis in children and adolescents. [see comment]. American Journal of Gastroenterology. 2003;98:777-782.
42. Kaplan M, Mutlu EA, Jakate S, Bruninga K, Losurdo J, Keshavarzian A. Endoscopy in eosinophilic esophagitis: “feline” esophagus and perforation risk. Clinical Gastroenterology & Hepatology. 2003;1:433-437.