

Eosinophilic Esophagitis

James P. Franciosi, MD, MS, MSCE^{a,*}, Chris A. Liacouras, MD^b

KEYWORDS

• Eosinophilic esophagitis • Diagnosis • Treatment

Eosinophilic esophagitis (EoE) is a clinicopathologic diagnosis that involves a localized eosinophilic inflammation of the esophagus. Our understanding and recognition of EoE has evolved over the past 30 years from isolated case reports of patients with esophageal eosinophilia to a well-defined clinical disorder with the first consensus recommendations published in 2007.¹ This disease has been given several names, including eosinophilic esophagitis, allergic esophagitis, primary eosinophilic esophagitis, and idiopathic eosinophilic esophagitis. Other recognized causes of esophageal eosinophilia should be excluded before making the diagnosis (**Box 1**). Currently, there are no pathognomonic symptoms, physical examination findings, serologic markers, or visual endoscopic findings. Esophageal endoscopic biopsies are required to establish the diagnosis. On endoscopic mucosal biopsies, EoE is defined as 15 or more eosinophils per high-powered field isolated to the esophagus and associated with characteristic clinical symptoms, which either do not respond to acid-blockade medication or are associated with normal pH monitoring of the distal esophagus.

CLINICAL MANIFESTATIONS

Although current reports suggest that patients with EoE are predominantly young Caucasian males, EoE can occur at any age and in either sex.² Manifestations of EoE may be protean or even clinically silent, but typical symptoms tend to correlate with age at presentation. In most children, predominant symptoms include, but are not limited to, abdominal pain, chest pain, symptoms like those of gastroesophageal reflux disease, vomiting, and, rarely, isolated nausea. Adolescents and adults frequently present with

This work was not supported by any institutional, National Institutes of Health, or industry grant.

^a Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, 3333 Burnet Avenue, ML 2010, Cincinnati, OH 45229, USA

^b Division of Gastroenterology, Hepatology and Nutrition, The Children's Hospital of Philadelphia, and University of Pennsylvania School of Medicine, 324 South 34th Street, Philadelphia, PA 19104-4399, USA

* Corresponding author.

E-mail address: james.franciosi@cchmc.org (J.P. Franciosi).

Immunol Allergy Clin N Am 29 (2009) 19–27

doi:10.1016/j.iac.2008.09.001

immunology.theclinics.com

0889-8561/08/\$ – see front matter © 2009 Elsevier Inc. All rights reserved.

Box 1
Differential diagnosis of esophageal eosinophilia
Food allergy
Gastroesophageal reflux
Candida esophagitis
Eosinophilic gastroenteritis
Inflammatory bowel disease
Celiac disease
Parasitic infection
Connective tissue disease
Drug allergy
Hypereosinophilic syndrome
Autoimmune enteropathy
Viral esophagitis (herpes or cytomegalovirus)
Churg-Strauss syndrome

dysphagia and esophageal food impaction. Infants and young children may present with feeding refusal, feeding intolerance, and, less commonly, failure to thrive. Therefore, in evaluations of feeding disorders, it is important that the treatment teams have an understanding of EoE and make the appropriate referral to a gastroenterologist.

Symptom severity can be highly variable, ranging from minimal or no clinical symptoms in a minority of patients, to intermittent symptoms of dysphagia in teenagers, to frequent and severe symptoms of abdominal pain or vomiting in others. Because many EoE patients may compensate for their dysphagia, a careful history should be obtained with regard to particular food avoidance, eating slowly, excessive chewing, and having to drink after each bite of food.³ EoE should be strongly considered in those patients who have severe or medically refractory symptoms of gastroesophageal reflux or with any history of esophageal food impaction. Personal or family history of atopic disease (asthma, eczema, rhinitis) and either environmental or food allergies is particularly important and demonstrated in up to 75% of patients.¹

EPIDEMIOLOGY

Incidence and prevalence estimates of EoE in children up to 19 years of age are 1.25 and 4.3 per 10,000 children respectively.⁴ Current literature makes clear that the prevalence of the diagnosis of EoE is increasing. Given that EoE is a chronic, nonfatal condition, a rise in the prevalence (total number cases in a given time period) is to be expected. However, there is debate as to whether the incident (new) cases being diagnosed represent a true increase in the number of cases or rather increased recognition of latent disease. As EoE is often regarded as an allergic, inflammatory disorder of the esophagus, a true rise in the incidence of EoE in parallel with the rising incidence of asthma and inflammatory bowel disease would not be surprising.⁵ However, esophageal endoscopic biopsies are currently required to establish the diagnosis of EoE. Therefore, changes in referral patterns to gastroenterologists, acid-suppression medication prescribing practices, indications for upper endoscopy, and endoscopy practices may all bias epidemiologic studies. Possibly many EoE cases are missed

because esophageal biopsies are not routinely performed today for adult esophagogastroduodenoscopy. Meanwhile, esophageal biopsies are only now beginning to be implemented for the evaluation of dysphagia. A study by Ronkainen and colleagues⁶⁻⁸ has cast doubt on the use of endoscopic procedures as a basis for disease prevalence rates. In this study, investigators looked at results from a random sample of people who electively underwent esophageal endoscopy with biopsy without any clinical indication from endoscopic procedures. Investigators compared those results with those from other epidemiologic studies with prevalence rates based on patients referred to a gastroenterologist and where the number of esophageal biopsies was at the discretion of the endoscopist. The study found that the rate of disease prevalence in the general population may be 10 times that extrapolated from studies based on referred patients. Further population-based studies are needed to investigate the prevalence of EoE using current definitions and noninvasive markers of disease.

PATHOPHYSIOLOGY

Clinical experience and experimental animal models support the strong association between EoE and allergic disease. EoE is believed to be a Th2-mediated disease in the context of genetically predisposed individuals and an inciting environmental trigger.⁹ An important discovery has been the identification of a conserved EoE gene transcript signature with overexpression of the chemokine eotaxin-3.¹⁰ IL-5 and IL-13 are key Th2 cytokines that represent only part of a complex cellular and molecular cascade of interactions between Th2 cells, mast cells, and eosinophils.¹¹

With regard to environmental etiologies, EoE is believed to be a mixed IgE- and non-IgE-mediated allergic response to food antigens, with non-IgE cell-mediated responses predominating. In 1995, Kelly and colleagues¹² published a sentinel paper on EoE with a case series of 10 pediatric patients who demonstrated symptomatic and histologic improvement on an elemental diet (resolution in 8 patients; improvement in 2). Upon reintroduction of foods, all patients reverted to previous symptoms. Successful symptomatic and histologic improvement with elemental diets and food-elimination diets with return of symptoms and esophageal eosinophilia upon food reintroduction support food antigens as an important component in the pathophysiology of this disorder. Experimental and case report data have also suggested that aeroallergens may play a role in the development of EoE, albeit to a much lesser extent.¹³ A current working hypothesis is that EoE subjects have an underlying genetic predisposition in combination with an environmental trigger, resulting in an esophageal eosinophilic inflammatory response. Whether the food antigenic reaction identified in a majority of patients is the manifestation of (1) a cross-reaction to various exposed esophageal epitopes secondary to mucosal injury, (2) increasingly hygienic populations with lack of environmental sensitization, or (3) principally non-IgE-mediated food allergies presenting with previously unrecognized and misclassified gastrointestinal symptoms remains to be determined.

ENDOSCOPY

Currently, upper endoscopy with esophageal biopsies is the only way to diagnose EoE. Although linear furrowing, concentric esophageal rings, white surface exudate, Schatzki ring, small-caliber esophagus, and linear tears ("rents") have all been described as visual endoscopic findings in EoE patients, a visually normal esophageal appearance does not preclude the finding of significant esophageal eosinophilia on histology (**Figs. 1–3**). EoE has also been described as a patchy disease, and at least four esophageal biopsies are required to obtain a sensitivity of at least 94% to detect EoE.¹⁴

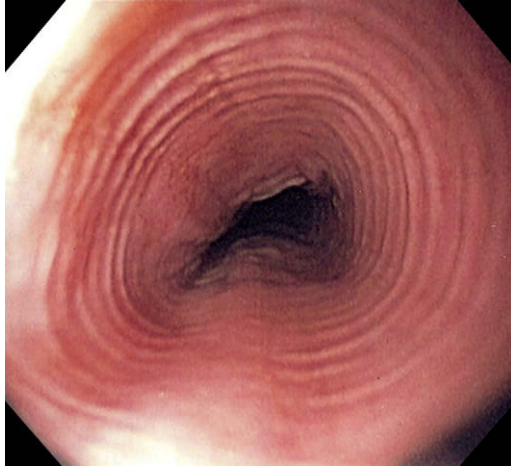


Fig. 1. Esophageal endoscopic picture of concentric esophageal rings.

ALLERGY TESTING

Food and environmental allergen testing is an important component to the evaluation of EoE patients. To identify both respective IgE-based and non-IgE-based causative food allergens, a combination of skin prick testing (SPT) and atopy patch testing (APT) is recommended. SPT is commercially available for a variety of foods (panels ranging from 13 to 42 foods) and environmental allergens. Results have been described in a cohort of 786 EoE patients from aggregated case series data.¹ In EoE patients, SPT most frequently identifies positive reactions to egg, milk, and soy (as well as to wheat, peanuts, beans, rye, and beef) among other various foods. The mean number of foods identified is reported to be $2.7 (\pm 3.6)$ to $6 (\pm 4.2)$ foods and at least one food identified in two thirds of patients. Theoretically, APT should be a better tool for identifying food allergens in EoE patients that are predominately non-IgE mediated. However, unlike SPT, which has been standardized and is commercially available, APT preparations,

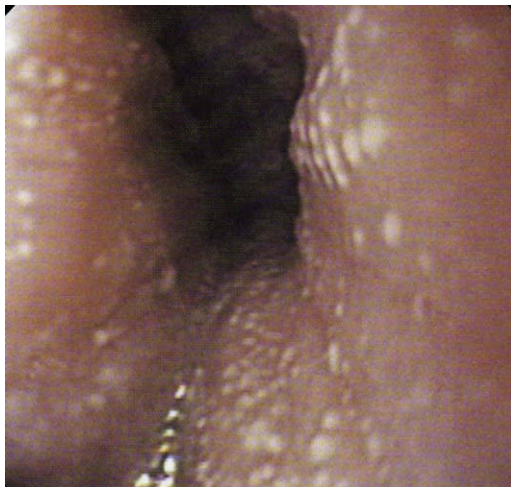


Fig. 2. Esophageal white plaques representing mucosal eosinophilic abscesses.

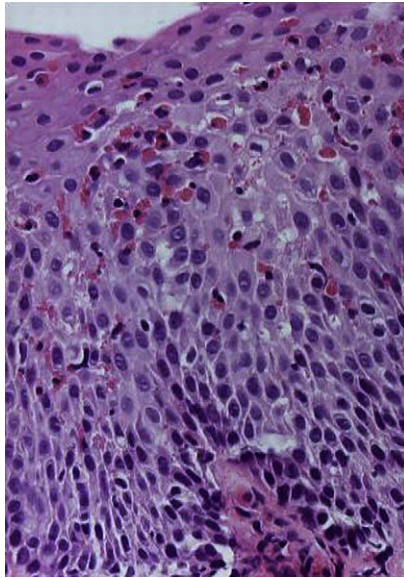


Fig. 3. Magnification of esophageal mucosa demonstrating numerous tissue eosinophils and an expanded basal cell layer.

methodologies, and results are highly variable among different practices. Therefore, there has not been widespread use of APT. The most common foods identified by APT are corn, soy, and wheat.¹⁵ Resolution of esophageal eosinophilia has been reported in 67% of patients, and histologic improvement in 82% of patients using a combination of SPT- and APT-directed dietary elimination.¹⁶

Serum IgE levels, peripheral eosinophilia, and radio-allergo-sorbent testing are not sensitive indicators of the presence of isolated esophageal eosinophilic disease or disease activity. Biomarkers, such as eosinophil-derived neurotoxin and eotaxin-3, are under investigation.¹⁷

PERSPECTIVES FOR MANAGEMENT

Dietary Therapy

Although there have been no randomized clinical trials on dietary therapy for EoE, case series data from several centers in both adults and children support a 92% to 98% patient response to amino acid–based elemental formula with both symptomatic and histologic improvement.^{16,18} Exclusive elemental formula is administered either orally or via nasogastric tube. A repeat esophagastroduodenoscopy is then performed after a period of 4 to 6 weeks to determine histologic improvement. Foods are then reintroduced in a sequential fashion beginning with least allergenic (fruits and vegetables) to highly antigenic (dairy, soy, egg, wheat, beef, peanut, and corn) in a sequential reintroduction of one new food per week and endoscopic surveillance after five to seven new foods (**Table 1**). Although highly effective, the psychosocial impact and quality-of-life issues on the patient and family as well as the number of endoscopies performed must be strongly considered when using this approach.

Directed elimination diets are often employed before considering an elemental diet, and have been shown to be effective in approximately 70% of patients.^{16,19} From these directed elimination diets, the most common foods associated with EoE food allergy response include dairy, soy, egg, wheat, beef, peanut, and corn. However,

Table 1 Food introduction following an elemental diet			
Diet A	Diet B	Diet C	Diet D
Vegetables (non-legume)	Other fruits	Peas	Milk
Carrots	Apples	White potatoes	
Squash	Bananas		Corn
Sweet potatoes	Kiwis	Grains	
Spinach	Pineapples	Rice	Peanuts
Broccoli	Mangos	Oats	
Lettuce	Watermelons	Barley	Wheat
	Honeydew melons	Rye	
Fruit	Cantaloupes		Beef
Grapes	Papayas	Meat ^a	
Pear	Guavas	Lamb	Soy
Peaches	Avocados	Chicken	
Plums		Turkey	Eggs
Apricots	Legumes	Pork	
Cherries	Lima beans		
Oranges	Chickpeas	Fish/Shellfish	
Grapefruit	White/black/red beans		
Lemons	String beans	Tree nuts	
Limes		Almonds	
Cherries		Walnuts	
Strawberries		Hazelnuts	
Blueberries		Brazil nuts	
		Pecans	

^a Progress from well-cooked to increasingly rare

currently, results based on SPT and APT are center-specific and standardization of APT is sorely needed. Given the limitations of APT with regard to generalizability of results across centers, another dietary approach has been the empiric elimination of the most common cited allergenic foods. In a cohort of 35 EoE patients, Kawgawalla and colleagues²⁰ showed that approximately 74% responded symptomatically and histologically to the removal of the six most likely foods that cause EoE: dairy, soy, egg, wheat, peanut, and fish/shellfish. Although empiric diets are effective, strict amino acid-based diets demonstrate a significantly greater histologic and clinical improvement.

Pharmacologic Therapy

According to current diagnostic criteria put forth by the First International Gastrointestinal Eosinophilic Research Symposium Consensus Statement in 2007 for EoE, an empiric 6- to 8-week trial of acid-suppression therapy is needed before performing a diagnostic upper endoscopy with biopsy.¹ Therefore, without the use of high-dose acid-suppression therapy (proton pump inhibitor therapy of 2 mg/kg/d divided twice a day to a maximum of 40 mg twice a day) before endoscopy, patients cannot be confirmed to have EoE because gastroesophageal reflux disease is still a possibility. Acid-suppression therapy also has a role in established EoE patients as these patients often have reflux symptoms secondary to chronic esophageal inflammation and altered esophageal motility.

Among the first medical treatments for EoE shown to be effective were systemic corticosteroids, which improved both symptoms and esophageal histology in approximately 95% of patients.²¹ However, upon discontinuation of corticosteroids, 90% have had recurrence of symptoms. When symptoms of EoE are severe enough to

consider hospitalization or have led to the development of esophageal stricture formation, short-term systemic corticosteroids may be indicated (average dose 1.5 mg/kg/d; maximum dose 60 mg/d). However, the long-term use of systemic corticosteroids is associated with various adverse effects, including bone abnormalities, poor growth, mood abnormalities, and adrenal suppression.

In contrast to systemic corticosteroids, swallowed corticosteroid therapy is a mainstay of EoE therapy in adults and children. A randomized clinical trial comparing systemic corticosteroids (2 mg/kg/d, maximum 60 mg/d) with swallowed fluticasone propionate (880 µg/d for ages 1–10 years and 1760 µg/day for ages 11 years or older) demonstrated both histologic and symptomatic improvement in excess of 90% of patients in each group.²² Therefore, high-dose swallowed corticosteroids may be as effective as systemic corticosteroids with less toxicity. In the only randomized, double-blind, placebo-control trial of swallowed fluticasone (880-µg/d dosage in all ages 3–30 years old) in patients with active EoE, 50% of the fluticasone-treated patients achieved complete histologic remission compared with 9% of patients who received placebo.²³ The discrepancy between the two clinical studies may be related to fluticasone dosing and different study methodologies.

Oral viscous budesonide is another steroid preparation that has been used with some success in pediatric EoE patients. Aceves and colleagues²⁴ reported an 80% histologic response and an improvement in symptoms in a case series of 20 pediatric EoE patients (1 mg/d in children ages 1–10 and 2 mg/d in children over 10 years of age; 0.5 mg Pulmicort Respule with 5 g [packets] of sucralose [Splenda]). The advantage of using topical steroids is that their side effects are less severe than those seen with systemic steroids. The disadvantages include incomplete treatment of the disease (the disease generally recurs when the treatment is discontinued) and the development of possible side effects, including esophageal candidiasis. When using topical, swallowed corticosteroids, patients do not eat, drink, or rinse their mouth for 20 to 30 minutes after using the medication. Allergic rhinitis and environmental allergies should also be controlled with medication as these environmental allergies may have some role in EoE.

Additional atopic therapies, such as cromolyn sodium and leukotriene receptor antagonists, have also been used to treat EoE without success.² A case series of three adult EoE patients did not show efficacy of infliximab with regard to histologic symptomatic response.²⁵ Finally, other biologic agents that target the eosinophilic inflammatory cascade are currently in clinical trials or in various stages of development. Anti-IL-5 therapy is a particularly promising agent that has shown some efficacy in an open-label phase II study by Stein and colleagues.²⁶ Investigators performed an open-label phase safety and efficacy study of anti-IL-5 in four adult patients with EoE who had chronic dysphagia and esophageal strictures. Patients each received three infusions of anti-IL-5. The levels of plasma IL-5, peripheral blood eosinophils, and CCR3+ cells in blood, quality-of-life measurements, and histologic analysis of esophageal biopsies were determined before treatment and 1 month after treatment. The study showed a decrease in peripheral blood eosinophilia and CCR3+ cells as well as a significant decrease in esophageal eosinophils and a reduction in clinical symptoms. Currently, two pediatric studies using anti-IL-5 therapy are underway in patients with EoE.

Endoscopic Therapy

Although esophageal endoscopic dilation is a mainstay for peptic strictures, such dilation should be avoided for most EoE patients because of higher rates of esophageal perforation reported among such patients.²⁷ Dilation of the esophagus is useful to

achieve immediate improvement in symptomatology for food impaction in those patients who have significant anatomic esophageal abnormalities. In patients with EoE, dilatation is not recommended as first-line therapy secondary to concerns of significant side effects (pain, bleeding, perforation) and not addressing the underlying pathogenesis. For example, a 17-year-old who presented with food impaction and long-segment esophageal stenosis developed minor bleeding and perforation of her esophagus postoperatively. Esophageal biopsy at the time revealed more than 100 eosinophils per high-power field and her perforation developed as a complication of dilation.²⁷ While dilatation has been associated with esophageal perforation, Schoepfer²⁸ recently reported the successful use of esophageal dilatation in a subset of EoE patients. As a rule, whenever possible, other modes of therapy should be used before performing dilatation.

SUMMARY

EoE is specific disease that involves an isolated esophageal eosinophilic inflammation and clinical symptoms that do not respond to proton pump inhibitor therapy. Upper endoscopy with esophageal biopsies is required to establish the diagnosis. Referral to an allergist and food allergen testing is recommended. Dietary and topical corticosteroid therapies are commonly used and are effective in the majority of patients.

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(4):1342–63.
2. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005;3(12):1198–206.
3. Putnam PE. Eosinophilic esophagitis in children: clinical manifestations. *Gastroenterol Clin North Am* 2008;37(2):369–81, vi.
4. Noel RJ, Putnam PE, Rothenberg ME. Eosinophilic esophagitis. *N Engl J Med* 2004;351(9):940–1.
5. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002;347(12):911–20.
6. Attwood SE. Eosinophilic oesophagitis is common: a difficult message to swallow? *Int J Clin Pract* 2008;62(7):978–9.
7. Basavaraju KP, Wong T. Eosinophilic oesophagitis: a common cause of dysphagia in young adults? *Int J Clin Pract* 2008;62(7):1096–107.
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(5):615–20.
9. Rothenberg ME, Mishra A, Collins MH, et al. Pathogenesis and clinical features of eosinophilic esophagitis. *J Allergy Clin Immunol* 2001;108(6):891–4.
10. Blanchard C, Wang N, Stringer KF, et al. Eotaxin-3 and a uniquely conserved gene-expression profile in eosinophilic esophagitis. *J Clin Invest* 2006;116(2):536–47.
11. Blanchard C, Mingler MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol* 2007;120(6):1292–300.
12. Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: improvement with an amino acid-based formula. *Gastroenterology* 1995;109(5):1503–12.

13. Spergel JM. Eosinophilic oesophagitis and pollen. *Clin Exp Allergy* 2005;35(11):1421–2.
14. Gonsalves N, Policarpio-Nicolas M, Zhang Q, et al. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc* 2006;64(3):313–9.
15. 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(2):509–11.
16. 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(4):336–43.
17. 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(11):1328–36.
18. 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(4):777–82.
19. Spergel JM, Shuker M. Nutritional management of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am* 2008;18(1):179–94, xi.
20. 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(9):1097–102.
21. Liacouras CA, Wenner WJ, Brown K, et al. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;26(4):380–5.
22. 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(2):165–73.
23. 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(5):1381–91.
24. Aceves SS, Dohil R, Newbury RO, et al. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2005;116(3):705–6.
25. Straumann A, Bussmann C, Conus S, et al. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. *J Allergy Clin Immunol* 2008;122(2):425–7.
26. Stein ML, Collins MH, Villanueva JM, et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006;118(6):1312–9.
27. Eisenbach C, Merle U, Schirmacher P, et al. Perforation of the esophagus after dilation treatment for dysphagia in a patient with eosinophilic esophagitis. *Endoscopy* 2006;38:E43–4.
28. 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(2):161–4.