

Idiopathic eosinophilic disorders of the gastrointestinal tract in children

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Over the last decade, eosinophilic gastrointestinal diseases have emerged as increasingly recognised diseases affecting both adults and children. While the exact morbidity is uncertain, it has become evident that they carry a significant cost to affected patients. Recent investigations shed light on basic mechanisms of eosinophilic recruitment and inflammation, and suggest a critical role for Th2 cytokines, such as eotaxin, and allergen exposure in their pathogenesis. Eosinophilic oesophagitis (EO) is the best characterised of these diseases, and improved understanding of its basic biology stimulated development of new treatment regimens. Current evidence supports the use of elemental diets and systemic or topical corticosteroids to treat EO. A major clinical problem is the fact that most patients relapse when medical treatment is discontinued, thus making nutritional management an attractive long term option. Many areas remain unanswered in the management of patients with EGIDs, including identification of optimal treatment protocol, development of appropriate non-invasive monitoring, and choice of appropriate therapeutic endpoints.

Key words: eosinophils; esophagitis; esophageal stricture; eosinophilic gastrointestinal diseases; gastroesophageal reflux.

INTRODUCTION

Eosinophilic gastrointestinal diseases (EGIDs) are an emerging group of diseases linked by the existence of an eosinophil predominant inflammatory infiltrate of the gastrointestinal mucosa. This has been best described in the context of eosinophilic

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oesophagitis, and thus the bulk of this report describes the current state of knowledge focusing on EO. During the last decade, diagnosis of these diseases has steadily increased, which likely reflects their previously unappreciated role in pediatric and adult gastrointestinal disease, markedly increased awareness of their existence, and increasing incidence.

DEFINITION

Eosinophilic gastrointestinal diseases (EGIDs) are defined as eosinophil predominant inflammatory diseases affecting any section of the gastrointestinal tract, in which other causes for eosinophilic inflammation (malignancy, infection, gastrooesophageal reflux disease (GORD), IBD, and drug reactions) have been excluded. As stated above, the best characterised of these diseases is eosinophilic oesophagitis (EO), which can be defined as an eosinophilic inflammation of the oesophageal mucosa in a patient in whom GORD has been ruled out.¹

DIAGNOSTIC CRITERIA

A multi-disciplinary panel of clinicians and scientists convened at the First International Gastrointestinal Eosinophilic Research Symposium to determine diagnostic guidelines based on a thorough review of the literature and expert opinion. As a result of this meeting, the group determined that EO is a clinicopathological disease defined by oesophageal symptoms in the setting of a peak eosinophil count of greater than or equal to fifteen eosinophils per high-powered field (HPF). In order to meet this definition, gastrooesophageal reflux disease (GORD) must be ruled out on the basis of non-response to high dose proton pump inhibitors or normal pH monitoring of the distal oesophagus, and there cannot be any eosinophilic inflammation of the stomach or duodenum.¹

The importance of excluding other causes for oesophageal eosinophils is underscored by a case report from Ngo et al which documented 3 patients with dysphagia, vomiting, and impaction and oesophageal eosinophil counts greater than 20. Each of them had complete symptomatic and histological resolution following treatment with proton pump inhibitors.² The converse situation is seen in the fact that several series describe EO patients who had inappropriate fundoplications performed for presumed GORD without any relief in their symptoms or histological abnormalities.³

EPIDEMIOLOGY

The epidemiology of EO is currently undergoing definition. In one recent retrospective study at a large referral centre, diagnoses peaked at age 1, followed by smaller peaks at 7 and 11 years of age.^{4,5} There is a marked gender predominance, with ~70% of cases occurring in males. While the incidence of EO seems to be steadily increasing, its prevalence is still unclear. Several different reports defined the prevalence of this disease in different parts of the world. Liacouras et al report that in Philadelphia in the United States, eight to 10% of their patients presenting with GORD-like symptoms eventually received the diagnosis of EO.⁶ Noel et al presented an incidence of EO of 1/10,000 in the pediatric age group in one county in Ohio, USA and noted that prevalence increased 4 fold in this population from 2000 to 2003 to 4.3/10,000.⁷ These findings were echoed in another study by Cherian et al from

Western Australia, which showed an 18 fold increase in prevalence of EO from 0.05/10,000 children in 1994 to 0.89/10,000 in 2004. In this study, the authors addressed the concern that the increase in reported incidence and prevalence of EO was due to increased awareness and thus likelihood to diagnose the illness. A pathologist blinded to all clinical data reevaluated all biopsies with oesophagitis from 1995, 1999, and 2004. A significant proportion of patients (19%) initially thought to have normal biopsies or other forms of oesophagitis were reclassified as having EO. The authors also noted an increase in the average number of lymphocytes and eosinophils seen per high power field in biopsies obtained over the course of the study, indicating an increase in inflammation seen in these patients over time.⁸ These results are similar to a recent retrospective review by Gill et al which reports a prevalence of EO of 0.73/10,000 children- in West Virginia in the United States.⁹ Unpublished data from Fox et al estimated that six percent of children presenting with oesophagitis at the Children's Hospital of Boston suffered from EO.¹⁰ EO has now been reported in all continents except for Africa.

Clinical observations suggest a familial pattern for EO; patients with EO relate family histories involving unexplained food impaction, dysphagia, and need for oesophageal dilation. Support for a genetic link comes from a number of case reports which describe several family groups. These include a set of 3 brothers, as well as several families with eosinophilic disease spanning multiple generations.¹¹⁻¹³ Liacouras et al reported that seven percent of 381 children with EO had parents with oesophageal strictures or oesophageal eosinophilia and five percent had siblings with EO.⁶ Blanchard et al reported a genome wide microarray analysis of patients with EO that revealed a specific gene profile, with significant upregulation of eotaxin-3 compared to control patients with GORD or normal mucosa. This finding may shed light on the pathogenesis of familial EO cases.¹⁴

CLINICAL PRESENTATION

The presentation of EO tends to differ based on the age of the patient. In very young patients, non-specific symptoms dominate. For instance, vomiting, abdominal pain, feeding intolerance, chest pain, and/or failure to thrive are common symptoms. As children grow older (and are able to articulate their symptoms more clearly), dysphagia with associated food impactions becomes a more frequent complaint.⁶ Baxi et al stratified patients into 3 groups based on the number of eosinophils seen on biopsies and found that patients in the 2 groups with higher eosinophil numbers (from 6 to 14 eosinophils/HPF or 15 or more eosinophils/HPF) tended to present with dysphagia more commonly than patients with lower eosinophil counts (less than 5 per HPF), who were more likely to suffer from heartburn or chest pain. This study also reinforced the point that symptoms alone are not specific enough for a diagnosis of EO, and that all patients require mucosal biopsy, as the history alone is often misleading.¹⁵ Dysphagia occurs at a similar frequency in older children and adults; in one series, 50% of adults presenting with food impaction at a single institution had dysphagia attributable to EO.¹⁶ pH monitoring of the distal oesophagus may be useful to separate patients with GORD from those with EO, since patients with EO typically have normal distal pH/impedance monitoring.^{17,18}

An intriguing relationship with atopic conditions and allergy has also been observed. Between 50 and 80% of patients with EO also have atopic manifestations including atopic dermatitis, allergic rhinitis, and/or asthma in conjunction with positive skin prick or

plasma allergen specific IgE levels.⁶ While many patients may have IgE sensitisation, few report anaphylaxis. In contrast, Baxi et al reported a higher rate of type I allergic response in their younger EO patients as compared to older children.¹⁵ The possible connection to allergic disease also has support from several basic studies demonstrating a predominantly Th2 cytokine milieu in oesophageal biopsies from EO patients.^{14,19,20}

ENDOSCOPIC FEATURES

While several findings have been reported as characteristic for EO, none can be considered pathognomonic. Because of this, and the similarity of symptoms to gastro-oesophageal reflux, there is frequently a significant delay in diagnosis; in an 8 year follow-up study, there was an average of 3 year delay from the time of first symptoms to diagnostic endoscopy.⁵

Unlike GORD, which typically involves the distal oesophagus, endoscopic findings in EO may be identified along the oesophageal length. Some characteristic findings include oesophageal furrowing, 'trachealisation' of the oesophagus (which refers to the presence of linear ridges reminiscent of the tracheal rings), and whitish exudate, which corresponds histologically with eosinophilic microabscesses (Figure 1).^{6,15} To date the one finding reported exclusively in EO is the so-called 'crepe-paper mucosa.' This term refers to the easily torn mucosa leading to linear splits sometimes found in EO following the passage of the endoscope.²¹ Another notable endoscopic finding in EO is the presence of oesophageal narrowing, either in the form of diffuse narrowing (narrow calibre oesophagus) or focal strictures that often occur in the proximal oesophagus.^{22,23} Finally, Schatzki's rings can be associated with chronic eosinophilic inflammation. With all of these forms of oesophageal narrowing, there is frequently discordance between what is seen radiographically and endoscopically, raising the question of whether they represent fixed fibrosis or transient dysmotility with isolated



Figure 1. Representative endoscopic view of the esophageal mucosa from a 10 year old boy with EE demonstrating longitudinal furrows and whitish exudate.

or discrete contractions.²⁴ This was reinforced in Liacouras' series, where 24 patients were initially thought to have oesophageal narrowing on barium imaging, but only 1 was subsequently found to have a fixed stricture on endoscopy.⁶

Several series have documented normal endoscopic appearances of the oesophageal mucosa. Two series accounting for 435 children report that approximately 30% have normal appearing mucosa.^{6,8} However, subsequent reports suggest that subtle and non-specific evidence of inflammation is present in most patients with EO.²⁵

HISTOLOGY

A significant amount of discussion concerning the number of eosinophils that characterise EO and GORD has taken place over the last decade.²⁶ It should be noted that the oesophagus is the one area of the GI tract that contains no resident eosinophils. Eosinophils can infiltrate the oesophageal mucosa in a number of pathologic diseases, including GORD, EO, hypereosinophilic syndrome, infections, malignancies, and inflammatory bowel disease. EO is a disease with a patchy distribution, and it is thus imperative that multiple biopsies be obtained from several levels of the oesophagus in order to increase the diagnostic yield. Gonsalves et al reported that in adults with EO, using a cutoff of 15 eosinophils per high-powered field, the sensitivity of a single biopsy was 55%, while when 5 biopsies were obtained, the sensitivity increased to 100%.²⁷ The histological assessment for EO has focused on the number of eosinophils per high-powered field, with reported numbers ranging anywhere from 5 to greater than 24 per high-powered-field. After consideration of this published literature and extensive clinical experience, the consensus statement from the First International Gastrointestinal Eosinophilic Research Symposium determined that a number of greater than or equal to 15 eosinophils per HPF was consistent with a diagnosis of EO in the proper clinical setting.¹

Other pathologic abnormalities can be observed in histological sections from patients with EO. Basal hyperplasia and papillary lengthening are frequent observations.^{18,28–30} Eosinophilic microabscesses (defined as 4 or more eosinophils abutting each other) as well as superficial layering of eosinophils are also seen in EO (Figure 2).^{28,29} Degranulation of eosinophils with subsequent deposition of granule

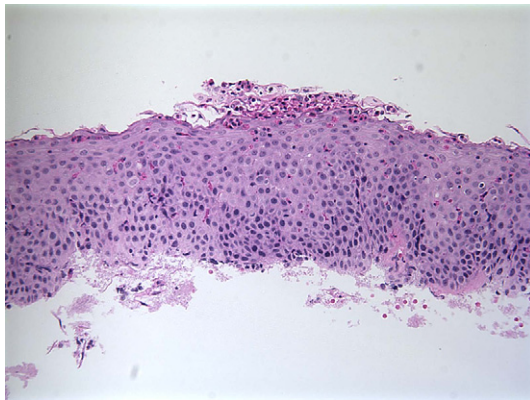


Figure 2. Esophageal mucosa with numerous intraepithelial eosinophils, severe basilar hyperplasia with rete peg elongation and superficial eosinophilic microabscesses.

proteins within the epithelium in biopsy samples from adults with EO indicates the presence and activity of activated eosinophils.^{16,28,31} Mast cells are frequently increased in areas of eosinophilic inflammation and may help distinguish patients with EO from those with GORD.³² Two recent studies identified remodeling of the oesophagus in EO as evidenced by increased subepithelial fibrosis and vascularity.^{28,33}

Endoscopic biopsy forceps do not always allow for assessment of the oesophageal submucosa, but two reports obtained adequate tissue to make interesting observations. The first involved a 26-year-old man who presented with spontaneous oesophageal rupture and had full thickness eosinophilic inflammation in the resected section. In the second patient, minimal eosinophilic infiltrate in the mucosal layer was observed, but greater than 100 eosinophils per HPF were seen in the muscularis propria. Inflammation was concentrated around peripheral nerves and ganglia, suggesting a potential relationship between eosinophils and nerves.^{34,35} These reports raise the speculation that occult eosinophilic infiltration may occur in some patients with significant dysphagia and normal or near-normal epithelial biopsies.

LABORATORY ABNORMALITIES

Standardised non-invasive markers of oesophageal inflammation are lacking. The identification of such a methodology would obviate the need for repetitive endoscopy and biopsies. To address this issue, a study of 47 paediatric patients correlated blood and stool markers with endoscopic and histological findings in patients with active EO compared to those with EO in remission and normal controls. The investigators determined that plasma levels of eosinophil derived neurotoxin, eotaxin-3, and peripheral absolute eosinophil count were elevated compared to controls, and significantly correlated with eosinophil density on biopsy.³⁶ Peripheral eosinophilia occurs in some patients with EO, but is a non-specific finding.^{37,38} Measurements of total IgE levels are very non-specific in patients with EO.^{18,23,38,39}

Several reports have utilised in-vitro testing for specific allergens, including RAST and skin prick testing. Although these tests are often positive, they have unclear significance in EO, and are not always helpful in directing management.^{29,40} Liacouras et al noted that the combination of both skin prick and atopy patch testing was better able to determine food sensitivity, leading to improvement in EO after food removal in 25/26 patients tested.⁴¹

A recent landmark study determined the genetic signature of selected patients with EO. Blanchard et al performed a genome-wide microarray analysis of oesophageal tissues from 13 EO patients compared to 2 control groups (non-EO oesophagitis patients, and normal patients). This analysis identified eotaxin-3 as the most highly upregulated gene in patients with EO. In addition, they isolated a single gene polymorphism in the eotaxin-3 gene which imparted greater disease susceptibility.¹⁴ This finding provides the scientific basis for the development of improved diagnostic testing and targeted treatments.

NATURAL HISTORY

Many questions remain about the natural history of this disease. Since it is a relatively new disease, few long-term studies have been completed. Assa'ad et al reported their 8 years of follow-up of 57 paediatric EO patients. Of this group, 14% had resolution of their disease after treatment, 33% had persistent disease in spite of treatment, and

53% had disease which relapsed after treatment was stopped.⁵ These findings are consistent with clinical experience and previous reports showing that patients often relapse once treatment is discontinued, and that a significant number have worsening symptoms, especially of dysphagia, over time.^{6,42} In contrast, Konikoff et al identified that between nine and 18% of children with EO underwent spontaneous remission of their disease over the course of a placebo treatment. This would indicate that EO may have occasional spontaneous remissions, although it is unclear whether these would be permanent.⁴³

A significant body of literature demonstrates that narrow calibre oesophagus or oesophageal strictures, as well as Schatzki rings with or without food impaction develop in selected patients over time.^{13,21,24,35} In addition to fixed anatomic changes, stationary and long-term oesophageal manometry studies show dysmotility in some patients with EO, which may be a consequence of deeper patterns of inflammation affecting muscles or nerves.^{23,44,45} To date, no cases of progression of EO to Barrett's oesophagus or malignancy have been reported.

TREATMENT

Corticosteroids have been the mainstay of pharmacologic therapy for EO. Systemic corticosteroids have been shown to improve both symptoms and histology, but symptoms and oesophageal eosinophils frequently recur if treatment is stopped.^{6,37} Because of concerns about potential side-effects of chronic systemic steroids, numerous studies demonstrated targeted delivery of steroids via the use of swallowed fluticasone or viscous budesonide.^{4,46–48} The first double-blind, placebo controlled trial of swallowed fluticasone propionate was recently completed. In this study, 50% of patients treated with fluticasone had resolution of their symptoms and oesophageal eosinophilia, as opposed to nine percent of patients treated with placebo. Fluticasone treated patients either responded completely, or had no response, and allergic patients were less likely to respond than patients without any history of atopy, food allergy, or asthma.⁴³ The main complication associated with topical treatment is oral candidiasis.⁴⁷

Since the oesophageal mucosa contains increased numbers of mast cells in EO, mast cell stabilisers such as cromolyn have been administered. Liacouras et al reported that the use of cromolyn in 14 patients provided no improvement in either symptoms or histology.⁶ Patients with EO who used leukotriene receptor antagonists showed improvement in symptoms but not histological abnormalities. Attwood et al determined that 7 of 8 patients treated with montelukast in doses up to 100 mg per day had complete symptom resolution, but oesophageal eosinophilia remained unchanged.⁴⁹ In another report, 2 of 6 EO patients treated with montelukast had complete resolution of their symptoms, while 2 experienced no relief (the other two were non-compliant).⁵⁰ Gupta et al measured similar cysteinyl leukotriene levels in oesophageal biopsies from paediatric EO patients and normal controls, providing some evidence that may explain this lack of clinical effectiveness.⁵¹

Patients with oesophageal strictures may require oesophageal dilation. Adult and paediatric studies report success with balloon and bougie dilatation of strictures and narrow calibre oesophagi. Significant risks associated with this procedure include pain, mucosal tearing, and perforation.^{22,42,52–55} Narrowings can also recur after treatment and may require repeated dilations.

Because of the association with food allergies, nutritional management has also been successfully used. Liacouras et al showed that testing for specific allergens using

a combination of skin prick and patch testing followed by elimination of implicated foods led to histologic and clinical improvement in 77% of a group of 146 patients.³⁹ Similarly, Kagawalla et al empirically eliminated the 6 foods most commonly associated with food allergies from the diets of 35 EO children who had not received any allergy testing. Significant clinical and histological responses were measured in 74% of patients in comparison to 88% improvement in 25 patients treated with an elemental diet alone.⁵⁶ The most effective nutritional management is the exclusive use of elemental, amino acid based formulas, which have a 92–98% success rate in terms of both complete symptom and histologic resolution.^{57,58} Problems associated with this treatment include poor compliance and formula cost.

Based on murine studies showing the IL-5 dependency of oesophageal inflammation, as well as translational studies identifying increased IL-5 expression in human oesophageal biopsies in EO, anti-IL-5 antibody treatment has been used in small series of patients with EO. Four adults with EO responded to anti-IL-5 treatment with significantly decreased peripheral and oesophageal eosinophilia, improved dysphagia, and improved quality of life scores.^{59,60} The utility of such targeted treatments in selected patient populations awaits further study.

Symptom resolution, histological normalcy or both have thus far been used as primary markers of treatment success, but optimal treatment endpoints remain an unresolved issue. Complicating this problem is the fact that clinical experience suggests some patients have asymptomatic oesophageal eosinophilia. Since it is unknown how many patients with persistent oesophageal eosinophilia develop long-term complications such as cancer, strictures, or dysmotility, research studies continue to use clinical and histological criteria as treatment endpoints. Until the natural history of EO becomes clearer (i.e. the incidence of these complications in treated and untreated patients) this will remain an area of controversy in clinical practice.

EOSINOPHILIC GASTROINTESTINAL DISEASES

EGIDs are a rare group of diseases with scattered case reports dating back to 1937. In contrast to EO, there does not appear to be a similar male predominance in patients with EGIDs. All ages are affected, with a peak incidence in the third decade in the largest case series.⁶¹

Murine models suggest differences in mechanisms of eosinophilic inflammation of the oesophagus and the rest of the gastrointestinal tract. For instance, in a murine model of oesophageal inflammation, sensitisation and challenge to aeroallergens induces airway and oesophageal eosinophilia, but not gastric or small intestinal eosinophilia. This response is interleukin-5 dependent. Conversely, in a different murine model, oral antigen exposure leads to significant eosinophil and mast cell accumulation in the small intestine that is eotaxin-1 dependent and only partially dependent on IL-5. These studies allow for the speculation that chemokine signaling is different in EO as opposed to eosinophilic gastroenteritis.^{62,63}

Clinical manifestations of this disease vary greatly depending on the depth of inflammation. The disease is generally classified as mucosal, muscular, or serosal depending on the level of predominant involvement. Mucosal disease (which is the most frequently reported) can have varying non-specific symptoms, such as abdominal pain, weight loss, nausea, vomiting, diarrhoea, intestinal bleeding, or protein losing enteropathy.^{64,65} Muscular EGID tends to present with signs of obstruction, which can be due to either mechanical obstruction or dysmotility with involvement of the myenteric

plexus.^{66–68} In fact, the presentation may mimic hypertrophic pyloric stenosis.⁶⁹ The serosal form presents with eosinophilic ascites.⁷⁰

Endoscopic findings in this disease are non-specific, and include white exudates, erythema, friability, mucosal thickening, polyps, and erosions/ulcerations. Deeper involvement in the muscular or serosal forms occurs without obvious gross mucosal changes.^{61,71}

Histology and diagnostic criteria are not standardised. No guidelines exist defining pathological numbers of GI eosinophils, and involvement may be patchy, similar to EO. Diagnosis of the deeper forms is made even more difficult by the need for thicker biopsies than obtained endoscopically, and in fact may require an open or laparoscopic examination for diagnosis. Eosinophils can be seen in close proximity to the myenteric plexus in the muscular form.⁶⁸ Eosinophils are frequently degranulated at sites of inflammation. In the largest series, the stomach and small intestine are the areas most frequently affected. Serosal disease can be documented with a peritoneal tap of the ascitic fluid.⁷² Peripheral eosinophilia is present in anywhere from 50 to 100% of reported patients.⁶¹

Treatment of this disease is similar to that of EO, but decisions are based on case series since the rarity of patients precludes controlled treatment studies. Several reports showed improvement in symptoms and histology in EGIDs with elimination and elemental diets.^{69,73} Similarly, multiple case series showed the efficacy of systemic corticosteroids, which often have significant side effects.^{65,73,74} Case reports showed improvement in symptoms with the use of leukotriene receptor antagonists.^{65,75,76} EGIDs are chronic illnesses which exhibit a waxing and waning course that can recur once treatments are stopped.

SUMMARY

The past decade has seen an explosion of research into eosinophilic gastrointestinal diseases paralleling the rapid rise in diagnoses. Clinical experience and research studies support the fact that these diseases are chronic and relapsing in nature. Poorly controlled EO may cause progressive dysphagia secondary to fibrosis and/or dysmotility. While treatment with elemental diets or corticosteroids improves symptoms and histology, significant problems with side effects and compliance arise with chronic use.

While our knowledge base is expanding exponentially, many areas are in need of further exploration. Natural history studies will give us a better understanding of how these diseases manifest over time and will guide future treatment plans. Future work will include targeted treatments including anti-IL-5 antibody and better means to monitor disease progression.

Practice points

- Eosinophilic gastrointestinal diseases are a relatively common group of diseases with a wide variety of presentations, with eosinophilic oesophagitis the most well described.
- Patients with eosinophilic oesophagitis present in many different ways, including abdominal pain, failure to thrive, dysphagia, and food impaction.
- A high index of suspicion is needed to look for these diagnoses, as their presentation overlaps with many other diseases.
- Treatment with elemental diets and corticosteroids are effective but relapses are frequent once treatments are discontinued.

Research agenda

- Natural history studies.
- Non-invasive measurements of eosinophilic inflammation.
- Controlled treatment trials of newer therapies, as well as non-pharmacologic means of managing disease.
- Studies of pathogenesis.

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REFERENCES

1. Furuta GT, Liacouras CA, Collins MH et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; **133**: 1342–1363.
2. Ngo P, Furuta GT, Antonioli DA et al. Eosinophils in the esophagus—peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Am J Gastroenterol* 2006; **101**(7): 1666–1670.
3. Liacouras CA. Eosinophilic esophagitis in children and adults. *J Pediatr Gastroenterol Nutr* 2003; **37**(Suppl 1): S23–S28.
4. Noel RJ, Putnam PE, Collins MH et al. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2004; **2**(7): 568–575.
- *5. Assa'ad AH, Putnam PE, Collins MH et al. Pediatric patients with eosinophilic esophagitis: an 8-year follow-up. *J Allergy Clin Immunol* 2007; **119**(3): 731–738.
- *6. Liacouras CA, Spergel JM, Ruchelli E et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005 Dec; **3**(12): 1198–1206.
7. Noel RJ, Putnam PE & Rothenberg MR. Eosinophilic esophagitis. *N Engl J Med* 2004; **351**(9): 940–941.
8. Cherian S, Smith NM & Forbes DA. Rapidly increasing prevalence of eosinophilic oesophagitis in Western Australia. *Arch Dis Child* 2006; **91**(12): 1000–1004.
9. Gill R, Durst P, Rewalt M & Elitsur Y. Eosinophilic esophagitis disease in children from West Virginia: a review of the last decade (1995–2004). *Am J Gastroenterol* 2007; **102**: 1–5.
10. Fox VL, Nurko S & Furuta GT. Eosinophilic esophagitis: it's not just kid's stuff. *Gastrointest Endosc* 2002; **56**(2): 260–270.
11. Patel SM & Falchuk KR. Three brothers with dysphagia caused by eosinophilic esophagitis. *Gastrointest Endosc* 2005; **61**(1): 165–167.
12. Meyer GW. Eosinophilic esophagitis in a father and a daughter. *Gastrointest Endosc* 2005; **61**(7): 932.
13. Zink DA, Amin M, Gebara S et al. Familial dysphagia and eosinophilia. *Gastrointest Endosc* 2007; **65**(2): 330–334.
- *14. 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): 536–547.
15. Baxi S, Gupta SK, Swigonski N & Fitzgerald JF. Clinical presentation of patients with eosinophilic inflammation of the esophagus. *Gastrointest Endosc* 2006; **64**(4): 473–478.
16. Desai TK, Stecevic V, Chang CH et al. Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest Endosc* 2005; **61**(7): 795–801.
17. Lim JR, Gupta SK, Croffie JM et al. White specks in the esophageal mucosa: an endoscopic manifestation of non-reflux eosinophilic esophagitis in children. *Gastrointest Endosc* 2004; **59**(7): 835–838.

18. Sant'Anna AM, Rolland S, Fournet JC et al. Eosinophilic esophagitis in children: symptoms, histology and pH probe results. *J Pediatr Gastroenterol Nutr* 2004; **39**(4): 373–377.
19. Straumann A, Bauer M, Fischer B et al. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001; **108**(6): 954–961.
20. Gupta SK, Fitzgerald JF, Kondratyuk T et al. Cytokine expression in normal and inflamed esophageal mucosa: a study into the pathogenesis of allergic eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2006; **42**(1): 22–26.
21. Straumann A, Rossi L, Simon HU et al. Fragility of the esophageal mucosa: a pathognomonic endoscopic sign of primary eosinophilic esophagitis? *Gastrointest Endosc* 2003; **57**(3): 407–412.
22. Khan S, Orenstein SR, Di Lorenzo C et al. Eosinophilic esophagitis: strictures, impactions, dysphagia. *Dig Dis Sci* 2003; **48**(1): 22–29.
23. Luis AL, Rinon C, Encinas JL et al. Non stenotic food impaction due to eosinophilic esophagitis: a potential surgical emergency. *Eur J Pediatr Surg* 2006; **16**(6): 399–402.
24. Nurko S, Teitelbaum JE, Husain K et al. Association of Schatzki ring with eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr* 2004; **38**(4): 436–441.
25. Croese J, Fairley SK, Masson JW et al. Clinical and endoscopic features of eosinophilic esophagitis in adults. *Gastrointest Endosc* 2003; **58**(4): 516–522.
26. Winter HS, Madara JL, Stafford RJ et al. Intraepithelial eosinophils: a new diagnostic criterion for reflux esophagitis. *Gastroenterology* 1982; **83**(4): 818–823.
27. Gonsalves N, Policarpio-Nicholas M, Zhang Q et al. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc* 2006; **64**(3): 313–319.
- *28. Parfitt JR, Gregor JC, Suskin NG et al. Eosinophilic esophagitis in adults: distinguishing features from gastroesophageal reflux disease: a study of 41 patients. *Mod Pathol* 2006; **19**(1): 90–96.
29. Walsh SV, Antonioli DA, Goldman H et al. Allergic esophagitis in children: a clinicopathological entity. *Am J Surg Pathol* 1999; **23**(4): 390–396.
30. Attwood SE, Smyrk TC, Demeester TR et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993; **38**(1): 109–116.
31. Mueller S, Aigner T, Neureiter D et al. Eosinophil infiltration and degranulation in oesophageal mucosa from adult patients with eosinophilic oesophagitis: a retrospective and comparative study on pathological biopsy. *J Clin Pathol* 2006; **59**(11): 1175–1180.
32. Kirsch R, Bokhary R, Marcon MA et al. Activated mucosal mast cells differentiate eosinophilic (allergic) esophagitis from gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 2007; **44**(1): 20–26.
33. Aceves SS, Newbury RO, Dohil R et al. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2007; **119**(1): 206–212.
34. Riou PJ, Nicholson AG & Patorino U. Esophageal rupture in a patient with idiopathic eosinophilic esophagitis. *Ann Thorac Surg* 1996; **62**(6): 1854–1856.
35. Stevoff C, Rao S, Parsons W et al. EUS and histopathologic correlates in eosinophilic esophagitis. *Gastrointest Endosc* 2001; **54**(3): 373–377.
36. 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): 1328–1336.
37. 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): 380–385.
38. Esposito S, Marinello D, Paracchini R et al. Long-term follow-up of symptoms and peripheral eosinophil counts in seven children with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2004; **38**(4): 452–456.
39. 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): 336–343.
40. Orenstein SR, Shalaby TM, Di Lorenzo C et al. The spectrum of pediatric eosinophilic esophagitis beyond infancy: a clinical series of 30 children. *Am J Gastroenterol* 2000; **95**(6): 1422–1430.
41. Spergel JM, Beausoleil JL, Mascarenhas M et al. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002; **109**(2): 363–368.
- *42. Straumann A, Spichtin HP, Grize L et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003; **125**(6): 1660–1669.

- *43. 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): 1381–1391.
44. Lucendo AJ, Castillo P, Martin-Chavarri S et al. Manometric findings in adult eosinophilic oesophagitis: a study of 12 cases. *Eur J Gastroenterol Hepatol* 2007; **19**(5): 417–424.
45. Lucendo AJ. Motor disturbances participate in the pathogenesis of eosinophilic oesophagitis, beyond the fibrous remodelling of the oesophagus. *Aliment Pharmacol Ther* 2006; **24**(8): 1264–1267.
46. Faubion WA, Perrault J, Burgart LJ et al. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr* 1998; **27**(1): 90–93.
47. Teitelbaum JE, Fox VL, Twarog FJ et al. Eosinophilic esophagitis in children: immunopathological analysis and response to fluticasone propionate. *Gastroenterology* 2002; **122**(5): 1216–1225.
48. Aceves SS, Dohil R, Newbury RO et al. Topical viscous budesonide suspension for treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2005; **116**(3): 705–706.
49. Attwood SE, Lewis CJ, Brondor CS et al. Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut* 2003; **52**(2): 181–185.
50. Shah M, Choo E, Childs F et al. Eosinophilic esophagitis-distinguishing endoscopic features and response to leukotriene receptor antagonist. *Am J Gastroenterol* 2004; **99**: S6.
51. Gupta SK, Peters-Golden M, Fitzgerald JF et al. Cysteinyl leukotriene levels in esophageal mucosal biopsies of children with eosinophilic inflammation: are they all the same? *Am J Gastroenterol* 2006; **101**(5): 1125–1128.
52. Cantu P, Velio P, Prada A et al. Ringed oesophagus and idiopathic eosinophilic oesophagitis in adults: an association in two cases. *Dig Liver Dis* 2005; **37**(2): 129–134.
53. Vasilopoulos S, Murphy P, Auerbach A et al. The small-caliber esophagus: an unappreciated cause of dysphagia for solids in patients with eosinophilic esophagitis. *Gastrointest Endosc* 2002; **55**(1): 99–106.
54. Morrow JB, Vargo JJ, Goldblum JR et al. The ringed esophagus: histological features of GERD. *Am J Gastroenterol* 2001; **96**(4): 984–989.
55. Kaplan M, Mutlu EA, Jakate S et al. Endoscopy in eosinophilic esophagitis: “feline” esophagus and perforation risk. *Clin Gastroenterol Hepatol* 2003; **1**(6): 433–437.
56. 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): 1097–1102.
57. 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): 1503–1512.
58. 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): 777–782.
59. Mishra A, Hogan SP, Brandt EB et al. IL-5 promotes eosinophil trafficking to the esophagus. *J Immunol* 2002; **168**(5): 2464–2469.
60. Stein ML, Collins MH, Villanueva JM et al. Anti-IL-5 (mepolizumab) therapy for eosinophilic esophagitis. *J Allergy Clin Immunol* 2006; **118**(6): 1312–1319.
- *61. Khan S. Eosinophilic gastroenteritis. *Best Pract Res Clin Gastroenterol* 2005; **19**(2): 177–198.
62. Mishra A, Hogan SP, Brandt EB et al. An etiological role for aeroallergens and eosinophils in experimental esophagitis. *J Clin Invest* 2001; **107**(1): 83–90.
63. Hogan SP, Mishra A, Brandt EB et al. A pathological function for eotaxin and eosinophils in eosinophilic gastrointestinal inflammation. *Nat Immunol* 2001; **2**(4): 353–360.
64. Kalantar SJ, Marks R, Lambert JR et al. Dyspepsia due to eosinophilic gastroenteritis. *Dig Dis Sci* 1997; **42**(11): 2327–2332.
65. Friesen CA, Kearns GL, Andre L et al. Clinical efficacy and pharmacokinetics of montelukast in dyspeptic children with duodenal eosinophilia. *J Pediatr Gastroenterol Nutr* 2004; **38**(3): 343–351.
66. Whittington PF & Whittington GL. Eosinophilic gastroenteropathy in childhood. *J Pediatr Gastroenterol Nutr* 1988; **7**(3): 379–385.
67. Zora JA, O’Connell EJ, Sachs MI et al. Eosinophilic gastroenteritis: a case report and review of the literature. *Ann Allergy* 1984; **53**(1): 45–47.
68. Schappi MG, Smith VV, Milla PJ et al. Eosinophilic myenteric ganglionitis is associated with functional intestinal obstruction. *Gut* 2003; **52**(5): 752–755.
69. Khan S & Orenstein SR. Eosinophilic gastroenteritis masquerading as pyloric stenosis. *Clin Pediatr* 2000; **39**(1): 55–57.

70. Barabino AV, Castellano E, Gandullia P et al. Chronic eosinophilic ascites in a very young child. *Eur J Pediatr* 2003; **162**(10): 666–668.
71. Katsumi N, Yamaguchi Y, Yamato T et al. Multiple ulcerative lesions of the stomach: a rare case of eosinophilic gastroenteritis. *Gastrointest Endosc* 2002; **56**(5): 762–764.
72. Talley NJ, Shorter RG, Phillips SF et al. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. *Gut* 1990; **31**(1): 54–58.
73. Chen MJ, Chu CH, Lin SC et al. Eosinophilic gastroenteritis: clinical experience with 15 patients. *World J Gastroenterol* 2003; **9**(12): 2813–2816.
74. Lee CM, Changchien CS, Chen PC et al. Eosinophilic gastroenteritis: 10 years experience. *Am J Gastroenterol* 2003; **88**: 70–74.
75. Neustrom MR & Friesen C. Treatment of eosinophilic gastroenteritis with montelukast. *J Allergy Clin Immunol* 1999; **104**: 506.
76. Vanderhoof JA, Young RJ, Hanner TL et al. Montelukast: use in pediatric patients with eosinophilic gastrointestinal disease. *J Pediatr Gastroenterol Nutr* 2003; **36**: 293–294.