

Current hurdles in the management of eosinophilic oesophagitis: The next steps

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Author contributions: Attwood SEA and Wilson MSJ made substantial contributions to the conception, design, drafting and final approval of the final version of the manuscript to be published.

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Received: August 23, 2012 Revised: October 26, 2012

Accepted: January 17, 2013

Published online: February 14, 2013

Abstract

Eosinophilic oesophagitis (EoE) is a chronic, antigen mediated disease of the disease of the oesophagus that may present in both adults and children. It is characterised by intermittent dysphagia, food bolus obstruction and weight loss. The pathogenesis is incompletely understood but is thought to culminate in poor compliance, or reduced distensibility. The condition is being reported and studied in the literature with increasing incidence, although equally it is highly likely that the diagnosis is being missed altogether with alarming frequency. Diagnosis of the condition requires at least one oesophageal biopsy with an eosinophil count greater than 15 per high power field. Endoscopic features include trachealisation, furrows, white exudate, narrowing and in the most severe cases stricture formation although none are pathognomonic of the condition. Therapy is often not required, but in the acute setting may take the form of dietary therapy or topical steroids. Long term maintenance therapy is usually only required in the most severe cases and the most effective treatment is the subject of ongoing research. There are a number of hurdles to be overcome in the management of patients with EoE. These include; improving our understanding of the aetiology

of the condition, investigating the individual causes, assessing the true disease severity and planning the best long term maintenance therapy. Distinguishing EoE from EoE gastro-oesophageal reflux disease is also a hurdle because the two conditions, both being common, can co-exist. In order to overcome these hurdles, a multifaceted approach is required. The management of food bolus obstruction requires a management algorithm that is accepted and endorsed by a number of specialties. National and international disease registers should be established in order to facilitate future research but more importantly to address areas where further education or increased diagnostic capabilities may be required. Assessment of disease severity should become a key goal, and the development of specific biomarkers for EoE should also be a priority. Finally, randomised controlled trials of new agents are required to assess the best treatment in both the acute and long term setting.

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Key words: Eosinophil oesophagitis; Dysphagia; Food bolus obstruction; Therapy; Gastroscopy

Attwood SEA, Wilson MSJ. Current hurdles in the management of eosinophilic oesophagitis: The next steps. *World J Gastroenterol* 2013; 19(6): 790-796 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i6/790.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i6.790>

INTRODUCTION

Eosinophilic oesophagitis (EoE) is an increasingly common cause of dysphagia or food bolus obstruction. EoE is a chronic antigen mediated disease of the oesophagus. It is characterised symptomatically by oesophageal dysfunction and histologically by eosinophil predominant inflammation. The condition was first described almost 30

years ago in a cohort of patients with > 20 intraepithelial eosinophils (IEE) per high power field seen on oesophageal biopsy, with 11 of the 12 demonstrating normal oesophageal acid exposure on 24 pH monitoring^[1]. A further cohort of 10 patients with recurrent dysphagia and high concentrations of IEE at endoscopic biopsy was reported in 1994^[2].

Until 2007 only 212 cases had been reported in the literature^[3]. Since that time, the reporting of cases of EoE has increased dramatically. More than 750 articles incorporating several thousand patients have been published on the subject since being first described with seventy five per cent being published in the last five years.

EoE is sometimes described as “oesophageal asthma” on account of its association with atopy. Up to 50% of patients also have bronchial asthma or allergic rhinitis, and 20% have atopic dermatitis^[4]. Males are affected three times more often than females, and patients typically present either in childhood or during the third or fourth decades of life.

The typical presenting features of this condition include intermittent dysphagia, food bolus obstruction and weight loss. In the paediatric population, patients may also present with nausea, vomiting, weight loss and failure to thrive.

Recent consensus guidelines state that histological evidence of at least 15 intraepithelial eosinophils per high power field (eos/hpf) in at least one oesophageal mucosal biopsy stained with haematoxylin and eosin is required for the diagnosis. However, in the correct clinical setting, patients may be considered to have EoE with < 15 eos/hpf. An example would be an atopic male on a proton pump inhibitor (PPI) at the time of diagnostic endoscopy with typical endoscopic findings. Gastro-oesophageal reflux disease (GORD) should be excluded by demonstrating a lack of response to high dose proton pump inhibitor therapy or normal oesophageal pH monitoring^[5,6].

Not only is oesophageal biopsy essential in all patients with food bolus obstruction or dysphagia, regardless of the endoscopic appearance, the number of biopsies taken is also important. A minimum of six biopsies should be taken; two each from the upper, mid and lower oesophagus. Using a benchmark of 15 eos/hpf, it has been shown that the diagnostic sensitivity for EoE is 84%, 97% and 100% when 2, 3 and 6 biopsies are taken respectively^[7]. A further study demonstrated 100% sensitivity when 5 biopsies were taken^[8].

Estimates of the prevalence of EoE in the general population vary in the literature. In Switzerland, the adult prevalence has been estimated to be 0.02%^[9], 0.44% in the United States^[10] and 1% in Sweden^[11]. In more targeted populations, such as those undergoing oesophageal endoscopy the prevalence is significantly greater and in the region of 6%-15%^[12,13].

The current hurdles in the management of patients with EoE include; improving our understanding of the aetiology of the condition, investigating the individual causes, assessing the true disease severity and planning

the best long term maintenance therapy. Distinguishing EoE from GORD is also a hurdle because the two conditions, both being common, can co-exist.

AETIOLOGY AND PATHOPHYSIOLOGY

The pathophysiology of this condition is incompletely understood and is the subject of ongoing research and debate. Expert consensus has concluded that the condition arises as a result of an antigen mediated immunologic process resulting in oesophageal inflammation. The specific allergen(s) is yet to be identified but a number of theories have been postulated. Skin prick testing has been shown to have a poor predictive value for the identification of specific food allergens in patients with EoE^[14]. Given that the condition is being reported with increasing frequency this raises the possibility of an environmental allergen being involved in the pathogenesis. The “hygiene hypothesis” or declining incidence of *Helicobacter pylori* have both been proposed to play a role given that they have coincided with increased incidence of EoE^[15,16].

Acid reflux (GORD) is not usually present in patients with EoE. However, it is standard practice to perform diagnostic biopsies while patients are on PPI to exclude the contribution of reflux injury^[5]. When symptoms are atypical, or if there is a mixture of reflux symptoms and dysphagic EoE symptoms then 24 h pH monitoring should be employed to guide therapy. There is a subgroup of symptomatically typical EoE patients, with normal pH profiles who seem to respond to PPI, and these PPI responsive patients will benefit from with maintenance therapy^[17].

Oesophageal biopsy specimens from patients with EoE compared to normal controls or patients with GORD show increased levels of the T helper 2 (Th2) cytokines, principally interleukin-5 (IL-5) and IL-13^[18-20], with increased levels of the eosinophil chemoattractants eotaxin-1 and eotaxin-3 also reported^[20-23]. Other studies have also demonstrated increased levels of other cytokines such as tumour necrosis factor- β 1 and fibroblast growth factor-9^[24,25]. GORD can be distinguished from EoE by its high level of COX-2 activation, while both show high rates of proliferation (Ki-67)^[26].

It is thought that long standing oesophageal inflammation results in remodelling of the oesophageal wall in a similar manner to the airway remodelling seen in patients with bronchial asthma. A potential sequela is a fragile mucosa that is likely to tear easily as demonstrated by reported cases of spontaneous or procedure induced oesophageal rupture.

ASSESSING THE TRUE DISEASE SEVERITY

EoE can present at any age, but is more prevalent in childhood or during the third and fourth decades of life^[5]. Adult patients typically present with a long history of intermittent, often severe dysphagia. In the most se-

vere cases the dysphagia may be continuous and associated with odynophagia and chest pain. EoE is also prevalent in the paediatric population, and is often associated with other atopic conditions. The clinical presentation varies with age. Infants and toddlers may present with prolonged feeding time or frank denial of food, whereas older children may present with vomiting and odynophagia. Adolescents, like adults tend to present with dysphagia. Less frequently, the child may present with failure to thrive and weight loss^[27,28].

EoE is associated with a number of abnormalities of the oesophagus at endoscopy. These include; oesophageal rings (or trachealisation), furrows, white exudate, narrowing and in the most severe cases stricture formation. The pathogenesis of dysphagia in EoE is believed to be poor compliance, or reduced distensibility. If this affects the esophagus diffusely then a narrow bore oesophagus that fails to distend will result. If there is focal fibrosis, a stricture will be evident. The distinction is important when considering interventions such as dilation^[29]. However, normal endoscopic findings do not exclude the diagnosis and neither are the above endoscopic findings pathognomonic of the condition. A number of studies have demonstrated histopathological evidence of EoE in patients with normal appearance of the oesophagus at endoscopy. This highlights the importance of oesophageal biopsy for all patients presenting with food bolus obstruction or dysphagia, even in the presence of a normal looking oesophagus^[12,30].

Recent research has also shown that up to half of patients who present acutely with food bolus obstruction have underlying EoE. In a prospective series of 43 patients presenting with food bolus obstruction, of whom 29 had biopsies taken from the proximal and distal oesophagus, 14 (50%) fulfilled the histological criteria for EoE^[31]. A further study reported that 17 of 31 (55%) patients presenting with food bolus obstruction fulfilled the histological criteria for EoE^[32]. It is for these reasons that the most recent consensus guidelines stress the need for oesophageal biopsy of all patients presenting with dysphagia. In patients presenting with acute food bolus obstruction, oesophageal biopsies should also be taken at the time of disimpaction with arrangements made for appropriate clinical follow up^[33]. In countries where the management of acute food bolus obstruction is principally managed by non EoE specialists, efforts should be made to raise awareness of the condition in order to avoid missed diagnoses^[34].

A disease specific EoE health related quality of life questionnaire has also been developed^[35]. This may be useful in identifying those who may benefit from treatment and in the assessment of response to therapy both in the clinical and research setting. There is a need to identify overall disease severity and to establish if symptoms, endoscopy or pathology can predict therapeutic outcomes.

Attention has also turned towards identifying potential biomarkers of the disease. Serum eosinophil derived

neurotoxin has recently been highlighted as a potential diagnostic biomarker for EoE that may also be valid in assessing response to therapy and relapse of symptoms^[36].

THERAPY

The acute management of EoE has a fairly well established pattern of treatment algorithms. In the paediatric setting, diet and topical steroids are the mainstay of treatment in the acute phase. In adults non obstructive disease is usually treated with topical steroids as the first line therapy, along with avoidance of known food precipitants. For obstructive EoE dilatation is worthwhile. Long term maintenance therapy is believed to be valuable but there is no evidence in controlled studies with long term follow up. Disease severity is both difficult to score and not predictive of long term natural history. The lack of long term therapy does not necessarily lead to the development of long term complications^[37].

Dietary therapy in the acute setting can take on a number of forms. The introduction of an elemental diet has been used effectively to induce remission of symptoms and oesophageal inflammation particularly in the paediatric setting^[38], with some recent success reported in adult^[39]. In adults, the role of dietary therapy is being assessed but is not well established. The major drawback of this approach is the unpalatable nature of the diet. Some diets are intolerable in the long term, and recurrence of symptoms after cessation of the elemental diet is common. An alternative approach has been attempted, again with some success. This involved the introduction of a six-food elimination diet (wheat, milk, eggs, soya, nuts and rice) over a 6-12 wk period and improved patients' symptoms^[40,41]. Further work by the same group highlighted the major drawback of dietary therapy in terms of compliance with the avoidance of particular food groups that are so common in western societies^[42]. In the paediatric setting there has been some success with single food introduction following the six food elimination diet, with milk being identified as the most common causative food antigen^[43].

Topical steroids in the acute setting are usually very effective with 60%-80% symptom resolution^[44]. For long term maintenance topical corticosteroids have demonstrated some efficacy^[44,45] although there is a risk of candida infection with long term use. Traditionally, topical steroid therapy is in widespread use for the management of bronchial asthma. In EoE the topical steroid is swallowed as opposed to inhaled. The most frequently employed topical steroid is fluticasone propionate at a dose of 300 to 500 micrograms twice daily, but doses of up to 880 micrograms twice daily have also been reported. The aim is to maximise exposure to the oesophagus and therefore spraying the back of the throat and swallowing the agent coats the oesophagus. This should be undertaken twice daily (morning and night time) to maximise the exposure of topical steroid to the oesophagus over a 24-h period. More recently, oral viscous budesonide has

also been shown to be effective^[46,47] and in one case report a superior alternative to swallowed fluticasone^[48]. Studies of clinical response to topical steroids do show variation in clinical outcome and also poor correlation of histological response with clinical improvement^[49]. It is thought that topical corticosteroid therapy acts by reversing the oesophageal remodelling that occurs in EoE^[45]. In a paediatric population fluticasone has been associated with improvements in the endoscopic, histologic and immunological parameters of EoE. However, the improvement was less marked in patients with a history of allergy^[50].

In some patients reflux type symptoms and occasionally dysphagia is improved by PPI therapy. It is useful to measure the degree of acid reflux in these patients with 24 h pH monitoring to help gauge the need for combinations of PPI and topical steroid therapy.

Monteleukast, a leukotriene receptor antagonist has been proposed as a long term treatment. In an observational study of twelve patients, monteleukast was associated with a good symptomatic response (dysphagia scores and frequency of bolus obstruction) with an inconsistent reduction in the associated concentration of eosinophils^[51]. A similar response has been demonstrated in a small cohort of paediatric patients^[52]. The use of monteleukast has been criticised in some quarters on account of the lack of a placebo controlled group in the original paper reporting its use, and a further study has shown that monteleukast is inefficient in maintaining steroid reduced remission in EoE^[53].

Oesophageal dilatation has been shown to be a safe and effective therapy in EoE, particularly in the presence of strictures^[54]. However, mucosal tears are a worrisome occurrence but may be acceptable if an effective dilatation is achieved. Oesophageal perforation is a recognised complication of this procedure, but rare^[55]. As a result, this intervention gained an adverse reputation somewhat prematurely. A recent systematic review has estimated a 0.1% risk of oesophageal perforation as a direct result of oesophageal dilatation^[56,57], and this is no different to the risk of perforation when dilating a peptic stricture^[58].

EoE may cause a stiffening of the oesophageal wall and produce poor compliance. Subsequent attempts to regurgitate or dislodge a food bolus may then cause a tear (usually partial) in the oesophagus^[59-61]. The frequency of perforation seems to be greater from the food bolus itself than with dilatation. Management needs careful assessment because if the perforation is only a dissection, with a contained leak and no free fluid in the chest cavity, then non surgical management may be sufficient. The majority of such perforations heal with such a conservative approach^[5].

More recently, attention has turned towards potential monoclonal antibody therapies against specific cytokines. Mepolizumab, a monoclonal antibody against IL-5 has been shown in a small randomised controlled trial to reduce the peak oesophageal eosinophil count, but with no improvement in clinical symptoms^[62]. Similarly reslizumab (anti IL-5)^[63], infliximab (anti-tumor necro-

sis factor- α)^[64] and omalizumab (anti-IgE)^[65] have been shown to reduce peak oesophageal eosinophil counts with no improvement in clinical symptoms. Results from larger randomised trials are awaited.

With thoughts towards the future, potential targets for therapy are being evaluated. One candidate currently in phase II clinical trials is the chemoattractant receptor expressed on Th2 cells (CRTH2) antagonist^[66]. CRTH2 is a receptor expressed on Th2 cells that is known to bind to prostaglandin in asthmatics. By developing a drug with the ability to block this receptor it is hoped that a key component of the inflammatory response in patients with EoE will be disabled with a subsequent clinical improvement for the patient.

FUTURE CHALLENGES

In order to facilitate future clinical research into this condition then the largest centres should collaborate closely. Both national and international disease registers should be established in order to better understand the epidemiology of this novel condition. National and international registers will enable the identification of the largest centres with the highest incidence and prevalence, but more importantly identify those centres with low or zero prevalence. This will enable targeted education to be focused upon these centres as undoubtedly this represents missed or misinterpreted diagnoses.

With recent research highlighting that up to half of patients presenting with acute food bolus obstruction fulfil the diagnostic criteria for EoE, formal protocols should be implemented to ensure that patients undergo oesophageal biopsy at the time of disimpaction to exclude EoE. In a number of countries where the management of acute food bolus obstruction is managed by specialties with little or no knowledge of the existence of this condition this will require collaborative links to be forged between gastroenterology, ENT and surgical colleagues as appropriate. Ensuring these patients undergo oesophageal biopsy is likely to result in a significant increase in the incidence of EoE and sufficient resources should be in place in order to cope. This will require dissemination of the existence of this condition into primary care.

REFERENCES

- 1 **Attwood SE**, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993; **38**: 109-116 [PMID: 8420741]
- 2 **Straumann A**, Spichtin HP, Bernoulli R, Loosli J, Vögtlin J. [Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings]. *Schweiz Med Wochenschr* 1994; **124**: 1419-1429 [PMID: 7939509]
- 3 **Pasha SF**, DiBaise JK, Kim HJ, De Petris G, Crowell MD, Fleischer DE, Sharma VK. Patient characteristics, clinical, endoscopic, and histologic findings in adult eosinophilic esophagitis: a case series and systematic review of the medical literature. *Dis Esophagus* 2007; **20**: 311-319 [PMID: 17617880 DOI: 10.1111/j.1442-2050.2007.00721.x]

- 4 **Attwood SE**, Lamb CA. Eosinophilic oesophagitis and other non-reflux inflammatory conditions of the oesophagus: diagnostic imaging and management. *Best Pract Res Clin Gastroenterol* 2008; **22**: 639-660 [PMID: 18656822 DOI: 10.1016/j.bpg.2007.12.003]
- 5 **Liacouras CA**, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, Burks AW, Chehade M, Collins MH, Dellon ES, Dohil R, Falk GW, Gonsalves N, Gupta SK, Katzka DA, Lucendo AJ, Markowitz JE, Noel RJ, Odze RD, Putnam PE, Richter JE, Romero Y, Ruchelli E, Sampson HA, Schoepfer A, Shaheen NJ, Sicherer SH, Spechler S, Spergel JM, Straumann A, Wershil BK, Rothenberg ME, Aceves SS. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011; **128**: 3-20.e6; quiz 21-22 [PMID: 21477849 DOI: 10.1016/j.jaci.2011.02.040]
- 6 **Furuta GT**, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, Bonis P, Hassall E, Straumann A, Rothenberg ME. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; **133**: 1342-1363 [PMID: 17919504 DOI: 10.1053/j.gastro.2007.08.017]
- 7 **Shah A**, Kagalwalla AF, Gonsalves N, Melin-Aldana H, Li BU, Hirano I. Histopathologic variability in children with eosinophilic esophagitis. *Am J Gastroenterol* 2009; **104**: 716-721 [PMID: 19209168 DOI: 10.1038/ajg.2008.117]
- 8 **Gonsalves N**, Policarpio-Nicolas M, Zhang Q, Rao MS, Hirano I. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc* 2006; **64**: 313-319 [PMID: 16923475 DOI: 10.1016/j.gie.2006.04.037]
- 9 **Straumann A**, Simon HU. Eosinophilic esophagitis: escalating epidemiology? *J Allergy Clin Immunol* 2005; **115**: 418-419 [PMID: 15696105 DOI: 10.1016/j.jaci.2004.11.006]
- 10 **Kapel RC**, Miller JK, Torres C, Aksoy S, Lash R, Katzka DA. Eosinophilic esophagitis: a prevalent disease in the United States that affects all age groups. *Gastroenterology* 2008; **134**: 1316-1321 [PMID: 18471509 DOI: 10.1053/j.gastro.2008.02.016]
- 11 **Ronkainen J**, Talley NJ, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, Vieth M, Stolte M, Walker MM, Agréus L. Prevalence of oesophageal eosinophils and eosinophilic oesophagitis in adults: the population-based Kalixanda study. *Gut* 2007; **56**: 615-620 [PMID: 17135307 DOI: 10.1136/gut.2006.107714]
- 12 **Prasad GA**, Talley NJ, Romero Y, Arora AS, Kryzer LA, Smyrk TC, Alexander JA. Prevalence and predictive factors of eosinophilic esophagitis in patients presenting with dysphagia: a prospective study. *Am J Gastroenterol* 2007; **102**: 2627-2632 [PMID: 17764492 DOI: 10.1111/j.1572-0241.2007.01512.x]
- 13 **Veerappan GR**, Perry JL, Duncan TJ, Baker TP, Maydonovitch C, Lake JM, Wong RK, Osgard EM. Prevalence of eosinophilic esophagitis in an adult population undergoing upper endoscopy: a prospective study. *Clin Gastroenterol Hepatol* 2009; **7**: 420-426, 426.e1-2 [PMID: 19162236 DOI: 10.1016/j.cgh.2008.10.009]
- 14 **Kamdar TA**, Ditto AM, Bryce PJ. Skin prick testing does not reflect the presence of IgE against food allergens in adult eosinophilic esophagitis patients: a case study. *Clin Mol Allergy* 2010; **8**: 16 [PMID: 21083924 DOI: 10.1186/1476-7961-8-16]
- 15 **Bonis PA**. Putting the puzzle together: epidemiological and clinical clues in the etiology of eosinophilic esophagitis. *Immunol Allergy Clin North Am* 2009; **29**: 41-52, viii [PMID: 19141340 DOI: 10.1016/j.iac.2008.09.005]
- 16 **Dellon ES**, Peery AF, Shaheen NJ, Morgan DR, Hurrell JM, Lash RH, Genta RM. Inverse association of esophageal eosinophilia with *Helicobacter pylori* based on analysis of a US pathology database. *Gastroenterology* 2011; **141**: 1586-1592 [PMID: 21762663 DOI: 10.1053/j.gastro.2011.06.081]
- 17 **Molina-Infante J**, Ferrando-Lamana L, Ripoll C, Hernandez-Alonso M, Mateos JM, Fernandez-Bermejo M, Dueñas C, Fernandez-Gonzalez N, Quintana EM, Gonzalez-Nuñez MA. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011; **9**: 110-117 [PMID: 20920599 DOI: 10.1016/j.cgh.2010.09.019]
- 18 **Straumann A**, Bauer M, Fischer B, Blaser K, Simon HU. Idiopathic eosinophilic esophagitis is associated with a T(H)2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001; **108**: 954-961 [PMID: 11742273 DOI: 10.1067/mai.2001.119917]
- 19 **Mishra A**, Hogan SP, Brandt EB, Rothenberg ME. IL-5 promotes eosinophil trafficking to the esophagus. *J Immunol* 2002; **168**: 2464-2469 [PMID: 11859139]
- 20 **Lucendo AJ**, De Rezende L, Comas C, Caballero T, Bellón T. Treatment with topical steroids downregulates IL-5, eotaxin-1/CCL11, and eotaxin-3/CCL26 gene expression in eosinophilic esophagitis. *Am J Gastroenterol* 2008; **103**: 2184-2193 [PMID: 18844613 DOI: 10.1111/j.1572-0241.2008.01937.x]
- 21 **Mishra A**, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by an IL-5, eotaxin-1, and STAT6-dependent mechanism. *Gastroenterology* 2003; **125**: 1419-1427 [PMID: 14598258]
- 22 **Konikoff MR**, Blanchard C, Kirby C, Buckmeier BK, Cohen MB, Heubi JE, Putnam PE, Rothenberg ME. Potential of blood eosinophils, eosinophil-derived neurotoxin, and eotaxin-3 as biomarkers of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006; **4**: 1328-1336 [PMID: 17059896 DOI: 10.1016/j.cgh.2006.08.013]
- 23 **Bhattacharya B**, Carlsten J, Sabo E, Kethu S, Meitner P, Tavares R, Jakate S, Mangray S, Aswad B, Resnick MB. Increased expression of eotaxin-3 distinguishes between eosinophilic esophagitis and gastroesophageal reflux disease. *Hum Pathol* 2007; **38**: 1744-1753 [PMID: 17900656 DOI: 10.1016/j.humpath.2007.05.008]
- 24 **Mulder DJ**, Pacheco I, Hurlbut DJ, Mak N, Furuta GT, MacLeod RJ, Justinich CJ. FGF9-induced proliferative response to eosinophilic inflammation in oesophagitis. *Gut* 2009; **58**: 166-173 [PMID: 18978176 DOI: 10.1136/gut.2008.157628]
- 25 **Aceves SS**, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2007; **119**: 206-212 [PMID: 17208603 DOI: 10.1016/j.jaci.2006.10.016]
- 26 **Lewis CJ**, Lamb CA, Kanakala V, Pritchard S, Armstrong GR, Attwood SE. Is the etiology of eosinophilic esophagitis in adults a response to allergy or reflux injury? Study of cellular proliferation markers. *Dis Esophagus* 2009; **22**: 249-255 [PMID: 19207551 DOI: 10.1111/j.1442-2050.2008.00896.x]
- 27 **Aceves SS**, Newbury RO, Dohil MA, Bastian JF, Dohil R. A symptom scoring tool for identifying pediatric patients with eosinophilic esophagitis and correlating symptoms with inflammation. *Ann Allergy Asthma Immunol* 2009; **103**: 401-406 [PMID: 19927538 DOI: 10.1016/S1081-1206(10)60359-6]
- 28 **Mukkada VA**, Haas A, Maune NC, Capocelli KE, Henry M, Gilman N, Petersburg S, Moore W, Lovell MA, Fleischer DM, Furuta GT, Atkins D. Feeding dysfunction in children with eosinophilic gastrointestinal diseases. *Pediatrics* 2010; **126**: e672-e677 [PMID: 20696733 DOI: 10.1542/peds.2009-2227]
- 29 **Kwiatk MA**, Hirano I, Kahrilas PJ, Rothe J, Luger D, Pandolfino JE. Mechanical properties of the esophagus in eosinophilic esophagitis. *Gastroenterology* 2011; **140**: 82-90 [PMID: 20858491 DOI: 10.1053/j.gastro.2010.09.037]
- 30 **Mackenzie SH**, Go M, Chadwick B, Thomas K, Fang J, Kuwada S, Lamphier S, Hilden K, Peterson K. Eosinophilic oesophagitis in patients presenting with dysphagia--a prospective analysis. *Aliment Pharmacol Ther* 2008; **28**: 1140-1146 [PMID: 18624788 DOI: 10.1111/j.1365-2036.2008.03795.x]

- 31 **Kerlin P**, Jones D, Remedios M, Campbell C. Prevalence of eosinophilic esophagitis in adults with food bolus obstruction of the esophagus. *J Clin Gastroenterol* 2007; **41**: 356-361 [PMID: 17413601 DOI: 10.1097/01.mcg.0000225590.08825.77]
- 32 **Desai TK**, Stecevic V, Chang CH, Goldstein NS, Badizadegan K, Furuta GT. Association of eosinophilic inflammation with esophageal food impaction in adults. *Gastrointest Endosc* 2005; **61**: 795-801 [PMID: 15933677]
- 33 **Hurtado CW**, Furuta GT, Kramer RE. Etiology of esophageal food impactions in children. *J Pediatr Gastroenterol Nutr* 2011; **52**: 43-46 [PMID: 20975581 DOI: 10.1097/MPG.0b013e3181e67072]
- 34 **Bergquist H**, Bove M. Eosinophilic esophagitis in adults: An ear, nose, and throat perspective. *Laryngoscope* 2009; **119**: 1467-1471 [PMID: 19504557 DOI: 10.1002/lary.20255]
- 35 **Taft TH**, Kern E, Kwiatek MA, Hirano I, Gonsalves N, Keefer L. The adult eosinophilic oesophagitis quality of life questionnaire: a new measure of health-related quality of life. *Aliment Pharmacol Ther* 2011; **34**: 790-798 [PMID: 21806649 DOI: 10.1111/j.1365-2036.2011.04791.x]
- 36 **Subbarao G**, Rosenman MB, Ohnuki L, Georgelas A, Davis M, Fitzgerald JF, Molleston JP, Croffie JM, Pfefferkorn MD, Corkins MR, Lim JR, Steiner SJ, Schaefer E, Gleich GJ, Gupta SK. Exploring potential noninvasive biomarkers in eosinophilic esophagitis in children. *J Pediatr Gastroenterol Nutr* 2011; **53**: 651-658 [PMID: 21694637 DOI: 10.1097/MPG.0b013e318228cee6]
- 37 **Kanakala V**, Lamb CA, Haigh C, Stirling RW, Attwood SE. The diagnosis of primary eosinophilic oesophagitis in adults: missed or misinterpreted? *Eur J Gastroenterol Hepatol* 2010; **22**: 848-855 [PMID: 20453656 DOI: 10.1097/MEG.0b013e32832c7709]
- 38 **Spergel JM**, Andrews T, Brown-Whitehorn TF, Beausoleil JL, Liacouras CA. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005; **95**: 336-343 [PMID: 16279563 DOI: 10.1016/S1081-1206[10]61151-9]
- 39 **Peterson K**, Clayton F, Vinson L, Fang J, Boynton K, Gleich G, Byrne K. Utility of an elemental diet in adult eosinophilic esophagitis. *Gastroenterology* 2011; **140**: 180
- 40 **Gonsalves N**, Yang G-Y, Doerfler B. A prospective clinical trial of six food elimination diet and reintroduction of causative agents in adults with eosinophilic oesophagitis. *Gastroenterology* 2009; **136**: 280
- 41 **Gonsalves N**, Yang GY, Doerfler B, Ritz S, Ditto AM, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 2012; **142**: 1451-1459.e1; quiz e14-15 [PMID: 22391333 DOI: 10.1053/j.gastro.2012.03.001]
- 42 **Gonsalves N**, Hirano I. Quality of Life Assessment in Adults with EoE At Baseline and After Treatment with Dietary Therapy: Is the Treatment Worse Than the Disease? *Gastroenterology* 2009; **136**: 137
- 43 **Kagalwalla AF**, Shah A, Li BU, Sentongo TA, Ritz S, Manuel-Rubio M, Jacques K, Wang D, Melin-Aldana H, Nelson SP. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr* 2011; **53**: 145-149 [PMID: 21788754 DOI: 10.1097/MPG.0b013e31821cf503]
- 44 **Arora AS**, Perrault J, Smyrk TC. Topical corticosteroid treatment of dysphagia due to eosinophilic esophagitis in adults. *Mayo Clin Proc* 2003; **78**: 830-835 [PMID: 12839078]
- 45 **Aceves SS**, Newbury RO, Chen D, Mueller J, Dohil R, Hoffman H, Bastian JF, Broide DH. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy* 2010; **65**: 109-116 [PMID: 19796194 DOI: 10.1111/j.1398-9995.2009.02142.x]
- 46 **Dohil R**, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology* 2010; **139**: 418-429 [PMID: 20457157 DOI: 10.1053/j.gastro.2010.05.001]
- 47 **Straumann A**, Conus S, Degen L, Felder S, Kummer M, Engel H, Bussmann C, Beglinger C, Schoepfer A, Simon HU. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010; **139**: 1526-1537, 1537.e1 [PMID: 20682320 DOI: 10.1053/j.gastro.2010.07.048]
- 48 **Krishna SG**, Kakati BR, Olden KW, Brown DK. Treatment of eosinophilic esophagitis: is oral viscous budesonide superior to swallowed fluticasone spray? *Gastroenterol Hepatol (NY)* 2011; **7**: 55-59 [PMID: 21346855]
- 49 **Alexander JA**, Jung KW, Arora AS, Enders F, Katzka DA, Kephart GM, Kita H, Kryzer LA, Romero Y, Smyrk TC, Talley NJ. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012; **10**: 742-749.e1 [PMID: 22475741 DOI: 10.1016/j.cgh.2012.03.018]
- 50 **Noel RJ**, Putnam PE, Collins MH, Assa'ad AH, Guajardo JR, Jameson SC, Rothenberg ME. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2004; **2**: 568-575 [PMID: 15224281]
- 51 **Attwood SE**, Lewis CJ, Bronder CS, Morris CD, Armstrong GR, Whittam J. Eosinophilic oesophagitis: a novel treatment using Montelukast. *Gut* 2003; **52**: 181-185 [PMID: 12524397]
- 52 **Stumphy J**, Al-Zubeidi D, Guerin L, Mitros F, Rahhal R. Observations on use of montelukast in pediatric eosinophilic esophagitis: insights for the future. *Dis Esophagus* 2011; **24**: 229-234 [PMID: 21073625 DOI: 10.1111/j.1442-2050.2010.01134.x]
- 53 **Lucendo AJ**, De Rezende LC, Jiménez-Contreras S, Yagüe-Compadre JL, González-Cervera J, Mota-Huertas T, Guagnozzi D, Angueira T, González-Castillo S, Arias A. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. *Dig Dis Sci* 2011; **56**: 3551-3558 [PMID: 21674173 DOI: 10.1007/s10620-011-1775-y]
- 54 **Schoepfer AM**, Gschossmann J, Scheurer U, Seibold F, Straumann A. Esophageal strictures in adult eosinophilic esophagitis: dilation is an effective and safe alternative after failure of topical corticosteroids. *Endoscopy* 2008; **40**: 161-164 [PMID: 18253909 DOI: 10.1055/s-2007-995345]
- 55 **Straumann A**, Bussmann C, Zuber M, Vannini S, Simon HU, Schoepfer A. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. *Clin Gastroenterol Hepatol* 2008; **6**: 598-600 [PMID: 18407800 DOI: 10.1016/j.cgh.2008.02.003]
- 56 **Cohen MS**, Kaufman AB, Palazzo JP, Nevin D, Dimarino AJ, Cohen S. An audit of endoscopic complications in adult eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2007; **5**: 1149-1153 [PMID: 17683993 DOI: 10.1016/j.cgh.2007.05.017]
- 57 **Jacobs JW**, Spechler SJ. A systematic review of the risk of perforation during esophageal dilation for patients with eosinophilic esophagitis. *Dig Dis Sci* 2010; **55**: 1512-1515 [PMID: 20238250 DOI: 10.1007/s10620-010-1165-x]
- 58 **Riley SA**, Attwood SE. Guidelines on the use of oesophageal dilatation in clinical practice. *Gut* 2004; **53** Suppl 1: i1-i6 [PMID: 14724139]
- 59 **Liguori G**, Cortale M, Cimino F, Sozzi M. Circumferential mucosal dissection and esophageal perforation in a patient with eosinophilic esophagitis. *World J Gastroenterol* 2008; **14**: 803-804 [PMID: 18205276]
- 60 **Quiroga J**, Prim JM, Moldes M, Ledo R. Spontaneous circumferential esophageal dissection in a young man with eosinophilic esophagitis. *Interact Cardiovasc Thorac Surg* 2009; **9**: 1040-1042 [PMID: 19752151 DOI: 10.1510/icvts.2009.208975]

- 61 **Shim LS**, Grehan M. Education and Imaging. Gastrointestinal: oesophageal perforation during endoscopy for food impaction in eosinophilic oesophagitis. *J Gastroenterol Hepatol* 2010; **25**: 428 [PMID: 20136991 DOI: 10.1111/j.1440-1746.2009.06181.x]
- 62 **Straumann A**, Conus S, Grzonka P, Kita H, Kephart G, Bussmann C, Beglinger C, Smith DA, Patel J, Byrne M, Simon HU. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut* 2010; **59**: 21-30 [PMID: 19828470 DOI: 10.1136/gut.2009.178558]
- 63 **Spergel JM**, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G, O’Gorman MA, Abonia JP, Young J, Henkel T, Wilkins HJ, Liacouras CA. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2012; **129**: 456-463, 463.e1-3 [PMID: 22206777 DOI: 10.1016/j.jaci.2011.11.044]
- 64 **Straumann A**, Bussmann C, Conus S, Beglinger C, Simon HU. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. *J Allergy Clin Immunol* 2008; **122**: 425-427 [PMID: 18678345 DOI: 10.1016/j.jaci.2008.06.012]
- 65 **Fang J**, Hilden K, Gleich G, Emerson L, Ogorman M, Lo-wichik A, Peterson KA. A Pilot Study of the Treatment of Eosinophilic Esophagitis With Omalizumab. *Gastroenterology* 2011; **140**: 235
- 66 **Pettipher R**, Hansel TT, Armer R. Antagonism of the prostaglandin D2 receptors DP1 and CRTH2 as an approach to treat allergic diseases. *Nat Rev Drug Discov* 2007; **6**: 313-325 [PMID: 17396136 DOI: 10.1038/nrd2266]

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