

## Oesinophilic Oesophagitis: Current Evidence and Strategies of Management

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### ABSTRACT

The aim of this study is to review the current evidence of etiology, diagnosis and management of oesinophilic oesophagitis. A review of the PubMed literature (2011-2013) was undertaken. Sixty-five papers were selected based on relevance, power, date of publications and the studies that are reporting adult patients. The exclusion criteria were publications before 2011 and studies that were small or pediatric reports. Majority of the studies were reporting EoE etiology, diagnosis and management. The current evidence is supportive of allergic theory and the management by dietary modification, pharmacology and dilatation for strictures. Distinguishing features from gastro-oesophageal reflux disease were suggested and a prediction system was used to diagnose EoE. EoE is increasingly reported pathology, the etiology of which is an allergic reaction by triggering food or ingested allergens that cascades series of inflammatory responses. Dietary modification, topical steroid and PPI are the main lines of current treatment.

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**Key words:** Oesinophilic oesophagitis EoE; Oesophageal dilatation; Gastro-Oesophageal Reflux Disease; Proton Pump Inhibitors

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### INTRODUCTION

Oesinophilic oesophagitis (EoE) has rapidly become a regularly diagnosed problem based on clinical, endoscopy and histopathology tests with a prevalence of approximately 1 in 2000 individuals in the USA and Europe<sup>[1]</sup>. EoE is now considered as a systemic disorder and not only a local condition with an important immunological background<sup>[2]</sup>. Since recognition, it has induced an active research and currently is a hot evolving issue. American Society of Gastroenterology (ASG) has just published the guidelines of diagnosis and management of this condition<sup>[3]</sup> with emphasis on two distinct categories of EoE; oesophageal oesinophilia and proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE). EoE common presentation is dysphagia and food impaction<sup>[4]</sup>. However other symptoms similar to gastro-Oesophageal Reflux disease (GORD) are also reported. Male sex, dysphagia, history of food impaction, absence of pain/heartburn, linear furrowing, and white papules can be used to distinguish EoE from GORD<sup>[5]</sup>. Endoscopic and histopathological examinations are important for the diagnosis but the endoscopy might be normal or showing linear furrows, mucosal rings and white papules, and the narrowed lumen may be appreciated<sup>[6]</sup>. The histological diagnosis of EoE requires demonstration of at least 15 eosinophils per high power field on esophageal histology<sup>[7]</sup>. Topical corticosteroids and elimination of diets, and esophageal dilation for stricture is widely agreed as treatment options<sup>[8-10]</sup>. However, special groups of patients are showing no response to these modalities and represent a real challenge to the gastroenterologists, surgeons, dietitians, pediatricians and immunologists. Management of EoE depends on practice location, EoE patient load, and participation in educational activities<sup>[11]</sup>. The aim of this study is to review the current evidence in the following categories: (1) Causes of EoE; (2) Diagnosis of EoE; (3) Management modalities; (4) Special group of non-responders; (5) New medications and interventions; and (6) Future studies.

### MATERIALS AND METHODS

A review of the PubMed English literatures relevant to EoE was undertaken. The studies were selected based on relevance, power, date of publications (last two years) and the studies that are reporting adult patients. The exclusion criteria were publications before 2011 and studies that were small or pediatric reports. The search words

were: causes of EoE, etiology of EoE, diagnosis of EoE, endoscopy findings in EoE, treatment of EoE, management of EoE, non PPI responders in EoE, pharmacology treatment of EoE and oesophageal dilatation for EoE. The study represents a simple review of the recent research and clinical reports to highlight the current evidence in the etiology, diagnosis and management of EoE.

## RESULTS

Sixty-five papers were published during the window time of 2011-2013 and were selected. The types and number of these studies is depicted in figure 1. Majority of the studies were reporting EoE etiology, diagnosis and management. The current evidence is supportive of allergic theory and the management by dietary modification, pharmacology and dilatation for strictures. Distinguishing features from gastro-oesophageal reflux disease were suggested and a prediction system was used to diagnose EoE.

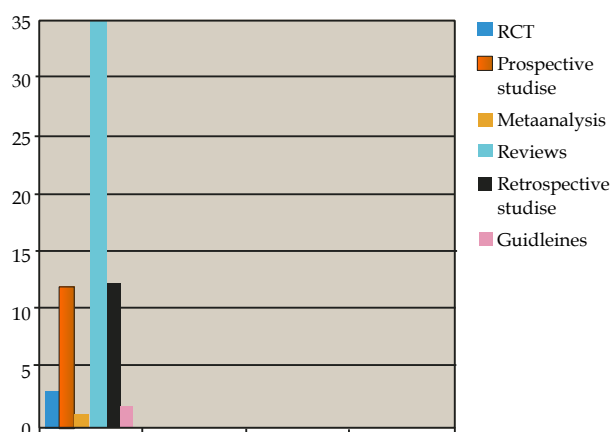


Figure 1 types and number of studies.

## DISCUSSION

### Causes of EoE

The exact etiology of EoE is still not fully understood but the general consensus of specialists considered EoE as allergic disease or oesophageal asthma based on the evidence from majority of the studies to implicate chronic immune reaction secondary to the food or ingested allergens<sup>[12-14]</sup>. Cereals, milk, eggs, fish/seafood, legumes/peanuts, and soy are triggering factors and the cow's milk is associated with more than 60% of allergy<sup>[15]</sup>. Gluten diet is implicated in 78% of cases<sup>[16]</sup>. It is established that the uncontrolled eosinophilic inflammation induces fibrosis, esophageal wall thickening and strictures leading to damage that results in a loss of esophageal function<sup>[17]</sup>. Interleukin (IL)-4 and IL-13, Th2 cytokines transforming growth factor (TGF)- $\beta$ 1 overproduced in allergic disorders, have direct profibrotic and remodeling effects in EoE<sup>[18]</sup>. The triggering materials are stimulating T-helper (Th-2) to induce cascades of inflammatory responses<sup>[19]</sup>. Recent study showed genetic underpinnings that implicate EoE susceptibility caused by polymorphisms in the thymic stromal lymphopoietin protein gene<sup>[20,21]</sup>. Suppressors of Cytokine Signaling (SOCS) proteins probably contribute to EoE pathogenesis by directly or indirectly inducing the Th2 profile, as well as by promoting the production of Th2 cytokines<sup>[22]</sup>. Mast cell is involved to promote muscle cell hyperplasia and hypertrophy and may have a significant role in promoting esophageal functional abnormalities in EoE<sup>[23]</sup>. There is inverse relationship between Barrett's and EoE<sup>[24]</sup>.

### Diagnosis

Peripheral eosinophilia + history of food impaction + PPI refractory heartburn is associated with high prediction of EoE<sup>[25]</sup>. A significant proportion of patients with Shatzki's rings (SRs) also have EoE, which may not always be suspected<sup>[26]</sup>. Association with achalasia (<1%) and cystic fibrosis was also reported<sup>[27,28]</sup>. At least 15 eosinophil per high power field or a threshold value of approximately 120 eosinophils per mm<sup>2</sup> was arbitrarily fixed as a diagnostic criterion<sup>[29]</sup>. Several diagnostic biomechanical changes including pan-esophageal pressurization on manometry, changes in esophageal compliance with decreased distensibility by impedance planimetry, reduced esophageal luminal diameter by esophagograms, and dysfunction in the esophageal longitudinal muscles by endoscopic ultrasound<sup>[30]</sup>. Alongside the number of eosinophils further histological features associated with EoE, such as abscesses of eosinophils or basal layer enlargement, may be of diagnostic help in the borderline cases<sup>[31]</sup>. On endoscopy, white specks, linear furrows, trachialization and concentric rings (Figure 2) are indicative of EoE<sup>[32,33]</sup>. Esophageal biopsy specimens should be obtained from all patients with clinical features of EoE, regardless of the endoscopic appearance of the esophagus<sup>[34]</sup>. Eotaxin-3 and IL-13 have emerged as the most promising advances with respect to sensitivity and degree of positive correlation to disease process<sup>[35]</sup>. Further research showed Epithelial-derived markers differentially expressed in eosinophilic esophagitis easily detectable by immunohistochemistry with potential diagnostic utility<sup>[36]</sup>. MicroRNA analysis is identified as a possible noninvasive disease biomarker<sup>[37]</sup>.

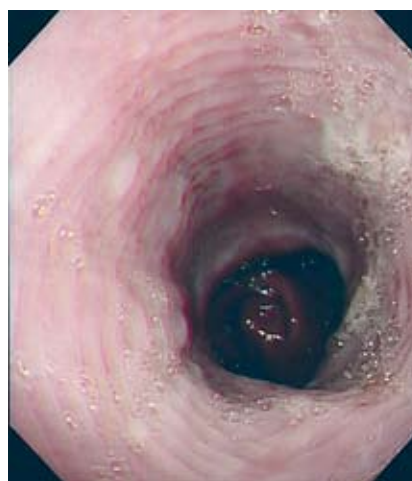


Figure 2 EoE, rings and specks.

### Management

The desired outcome of management would be clinical and pathological improvements or cure. 3 major treatment options for EoE:

**Dietary modification:** the principle of the "the best treatment is avoidance" is applicable in EoE and substantial clinical and histological improvement was reported following dietary modification<sup>[37,38]</sup>. Avoiding the triggering food entities that were highlighted above in the introduction and causes sections was improving the symptoms in majority of patients<sup>[15,40,41]</sup>. Additionally there was substantial histologic improvement after 4 weeks on the elemental diet<sup>[42]</sup>.

**Pharmacologic therapy (topical steroid and proton pump inhibitors PPI, leukotriene modifiers and biologics):**

1. Proton Pump Inhibitor (PPI): Emerging translational research

has evidenced mechanisms by which PPI response in patients with esophageal eosinophilia may be a consequence of PPI effects on the immune pathogenesis of EoE<sup>[43]</sup>. PPIs, in concentrations achieved in the blood with conventional dosing, significantly inhibit IL-4-stimulated eotaxin-3 expression in EoE esophageal cells and block STAT6 binding to the promoter<sup>[44]</sup>. 50% of patients with an EoE phenotype respond to PPI therapy<sup>[45]</sup>. A trial of PPI therapy was recommended for patients with oesophageal eosinophilia and symptoms, even in cases of clear-cut EoE<sup>[46,47]</sup>. The response however was not guaranteed and a group of patients were considered non responders<sup>[48]</sup>.

2. Topical steroids: Both swallowed fluticasone and budesonide in solution have been used as topical therapy for EoE. The course duration could reach 4-8 weeks with recurrence of 50% when the treatment is stopped<sup>[49,50]</sup>. Although both steroid and PPI are equally effective for histological response, PPI provide better clinical benefit especially in patients with GORD<sup>[51]</sup>.

3. New medications: An 8-week treatment with the CRTH2-antagonist, OC000459, exerted modest, but significant, anti-eosinophil and beneficial clinical effects in adult patients<sup>[52]</sup>. Montelukast and Mepolizumab, Tumour Necrosis Factor (TNF), immunotherapy using azothioprine, mercaptopurine are all new concepts but with no effective clinical implications.

3. Endoscopic dilation: Dilatation was effective, safe and provided clinical relieve in majority of patients who developed dysphagia due to EoE<sup>[53-56]</sup>. Type and size of dilators, number of prior dilations, and age of patient were not associated with complications<sup>[57]</sup>. Swallowed fluticasone inhaler (followed by OGD with dilation if necessary) was the more economical initial strategy when compared with D with dilation first<sup>[58]</sup>.

#### Special group of PPI non-responders

Significant number of patients were responding to PPI, however in other group of patients, PPI had no effect and these patients were considered non-responders<sup>[59]</sup>. The case became more complex when GORD was also diagnosed in these patients. Repeat endoscopy and oesophageal biopsy was recommended. Other forms of management such as dietary, steroid, etc was suggested in this group of patients<sup>[60]</sup>. Chronic use of steroid or long term dietary therapy were valuable options in PPI non responders<sup>[61,62]</sup>.

#### Future studies

Serum biomarkers and genetic testing may play a role in diagnosis<sup>[63]</sup>. Functional probe topography may help in the assessment of EoE and can direct the management options<sup>[64]</sup>. Differences between adult and paediatric EoE has been suggested and the most relevant differences were evolutionary changes in the consequences of the disease, including fibrous remodeling, and the ability to express symptoms<sup>[65]</sup>.

## LIMITATIONS OF THE STUDY

1. The papers were selected and assessed by a single author, which may indicate a limited unintentional selection bias.
2. The studies were addressing different issues related to EoE, the pooled data, therefore, were heterogeneous and a simple review was decided.
3. The reported studies had confirmed several issues like etiology, diagnosis and management. Majority of the presented evidence was based on the review and retrospective studies (level 2 and 3). Only 2 relevant Randomized Controlled Trials (RCTs) were published during the last two years and one meta-analysis were included.
4. Some questions were not effectively answered based on the

current evidence. These related to the value of the PPI, topical steroid duration of treatment and further action if patients relapse or show partial improvement. Also how to approach patient who have both GORD and EoE and non-responder to PPI.

5. Prediction of the EoE: few studies showed system of prediction based on eosinophilia, dysphagia and history of atop or allergy. Although these studies were valuable in terms of prediction, the prediction system needs further research to pick up early diagnosis especially in young patients and to prevent the end stigma of stricturing.

## CONCLUSIONS

EoE is increasingly reported pathology, the etiology of which is an allergic reaction by triggering food or ingested allergens that cascades series of inflammatory responses. Dietary modification, topical steroid and PPI are the main lines of current treatment. There were promising advances in the pharmacology treatment of the EoE, however several questions are still without definite answers and further research is suggested to understand the molecular pathology and to develop effective medications and formulate a universal prediction system for diagnosis of EoE.

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## REFERENCES

- 1 Straumann A, Schoepfer AM. Therapeutic concepts in adult and paediatric eosinophilic oesophagitis. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 697-704
- 2 Ferreira CT, Goldani HA. Contribution of endoscopy in the management of eosinophilic esophagitis. *World J Gastrointest Endosc* 2012; **16**(4): 347-55
- 3 Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE). *Am J Gastroenterol* 2013; **108**(5): 679-692
- 4 Roman S, Savarino E, Savarino V, Mion F. Eosinophilic oesophagitis: From physiopathology to treatment. *Dig Liver Dis* 2013; **45**(11): 871-878
- 5 Mulder DJ, Hurlbut DJ, Noble AJ, Justinich CJ. Clinical features distinguish eosinophilic and reflux-induced esophagitis. *J Pediatr Gastroenterol Nutr* 2013; **56**: 263-270
- 6 Remedios M, Jones D, Kerlin P. Eosinophilic oesophagitis: epidemiology, pathogenesis and management. *Drugs* 2011 Mar; **71**(5): 527-540
- 7 Heine RG, Nethercote M, Rosenbaum J, Allen KJ. Emerging management concepts for eosinophilic esophagitis in children. *J Gastroenterol Hepatol* 2011; **26**: 1106-1113
- 8 Segal D, Chande N. The Management of Eosinophilic Esophagitis in Adults. *J Clin Gastroenterol* 2013; **47**(7): 570-577
- 9 Couto M, Rodrigues S, Piedade S, Gaspar A, Morais-Almeida M, Macedo G. Eosinophilic esophagitis. *Acta Med Port* 2011; **24**; Suppl 4: 949-960
- 10 Lieberman JA, Morotti RA, Konstantinou GN, Yershov O, Chehade M. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. *Allergy* 2012; **67**: 1299-1307
- 11 Shaffer CC, Ghaffari G. International survey on evaluation and management of eosinophilic esophagitis. *World Allergy Organ J* 2012; **5**: 95-102
- 12 Al-Hussaini A, Al-Idressi E, Al-Zahrani M. The role of al-

- lergy evaluation in children with eosinophilic esophagitis. *J Gastroenterol* 2013; 11. [Epub ahead of print]
- 13 Kagalwalla AF, Amsden K, Shah A, Ritz S, Manuel-Rubio M, Dunne K, Nelson SP, Wershil BK, Melin-Aldana H. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2012; **55**: 711-716
  - 14 Arora AA, Weiler CR, Katzka DA. Eosinophilic esophagitis: allergic contribution, testing, and management. *Curr Gastroenterol Rep* 2012; **14**: 206-215
  - 15 Lucendo AJ, Arias Á, González-Cervera J, Yagüe-Compadre JL, Guagnozzi D, Angueira T, Jiménez-Contreras S, González-Castillo S, Rodríguez-Domínguez B, De Rezende LC, Tania's JM. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol* 2013; **131**: 797-804
  - 16 Abraham JR, Persad R, Turner JM, Huynh HQ. Gluten-free diet does not appear to induce endoscopic remission of eosinophilic esophagitis in children with coexistent celiac disease. *Can J Gastroenterol* 2012; **26**: 521-524
  - 17 Straumann A, Safroneeva E. Eosinophils in the gastrointestinal tract: friends or foes? *Acta Gastroenterol Belg* 2012; **75**: 310-315
  - 18 Cheng E, Souza RF, Spechler SJ. Tissue remodeling in eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G1175-87
  - 19 Gorospe EC, Arora AS. New diagnostic and therapeutic frontiers in eosinophilic esophagitis. *Minerva Gastroenterol Dietol* 2013; **59**: 59-68
  - 20 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
  - 21 Jo Y. Eosinophilic esophagitis: update 2012. *Korean J Gastroenterol* 2012; **60**(1): 3-12
  - 22 Zafra MP, Cancelliere N, Rodríguez Del Río P, Ruiz-García M, Estévez L, Andregnette V, Sánchez-García S, Fiandor A, Collantes E, Sastre J, Quirce S, Ibáñez MD, Del Pozo V. Misregulation of suppressors of cytokine signaling in eosinophilic esophagitis. *J Gastroenterol*. 2013; **48**(8): 910-920
  - 23 Niranjan R, Mavi P, Rayapudi M, Dynda S, Mishra A. Pathogenic role of mast cells in experimental eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 2013; **304**(12): G1087-94
  - 24 Saboorian MH, Genta RM, Marcus PB, Lindberg GM, Neumann WL. Inverse association of esophageal eosinophilia and Barrett esophagus. *J Clin Gastroenterol* 2012; **46**: 752-757
  - 25 von Arnim U, Wex T, Röhl FW, Neumann H, Küster D, Weigt J, Mönkemüller K, Malfertheiner P. Identification of clinical and laboratory markers for predicting eosinophilic esophagitis in adults. *Digestion* 2011; **84**: 323-327
  - 26 Müller M, Eckardt AJ, Fisseler-Eckhoff A, Haas S, Gockel I, Wehrmann T. Endoscopic findings in patients with Schatzki rings: evidence for an association with eosinophilic esophagitis. *World J Gastroenterol* 2012; **21**: 6960-6966
  - 27 Mandaliya R, DiMarino AJ, Cohen S. Association of achalasia and eosinophilic esophagitis. *Indian J Gastroenterol* 2013 **32**: 54-57
  - 28 Goralski JL, Lercher DM, Davis SD, Dellon ES. Eosinophilic esophagitis in cystic fibrosis: a case series and review of the literature. *J Cyst Fibros* 2013; **12**: 9-14
  - 29 Bussmann C, Straumann A. Eosinophilic esophagitis: The diagnostic contribution of pathology. *Pathologe* 2013; **34**: 110-117
  - 30 Read AJ, Pandolfino JE. Biomechanics of esophageal function in eosinophilic esophagitis. *J Neurogastroenterol Motil* 2012; **18**: 357-64
  - 31 Bussmann C. [Eosinophilic esophagitis. Role of the pathologist in the diagnosis]. *Pathologe* 2012 ; **33** Suppl 2: 228-230
  - 32 Caetano AC, Gonçalves R, Rolanda C. Eosinophilic esophagitis-endoscopic distinguishing findings. *World J Gastroenterol* 2012; **21**; **18**: 4221-4223
  - 33 Hori K, Watari J, Fukui H, Tanaka J, Tomita T, Sakurai J, Kondo T, Oshima T, Toyoshima F, Yamasaki T, Okugawa T, Miwa H. Do endoscopic features suggesting eosinophilic esophagitis represent histological eosinophilia? *Dig Endosc* 2013; **14**. doi: 10.1111/den.12091. [Epub ahead of print]
  - 34 Kim HP, Vance RB, Shaheen NJ, Dellon ES. The prevalence and diagnostic utility of endoscopic features of eosinophilic esophagitis: a meta-analysis. *Clin Gastroenterol Hepatol* 2012; **10**: 988-996
  - 35 Bhardwaj N, Ghaffari G. Biomarkers for eosinophilic esophagitis: a review. *Ann Allergy Asthma Immunol* 2012; **109**: 155-159
  - 36 Matoso A, Mukkada VA, Lu S, Monahan R, Cleveland K, Noble L, Mangray S, Resnick MB. Expression microarray analysis identifies novel epithelial-derived protein markers in eosinophilic esophagitis. *Mod Pathol* 2013; **15**. doi: 10.1038/modpathol.2013.41. [Epub ahead of print].
  - 37 Sicherer SH, Leung DY. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2012. *J Allergy Clin Immunol*. 2013 ; **131**: 55-66.
  - 38 Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, Liacouras CA. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012; **130**: 461-467
  - 39 Straumann A. Eosinophilic esophagitis: rapidly emerging disorder. *Swiss Med Wkly* 2012; **142**: w13513
  - 40 Roman S, Savarino E, Savarino V, Mion F. Eosinophilic oesophagitis: From physiopathology to treatment. *Dig Liver Dis* 2013; **29**. pii: S1590-8658(13)00090-X. doi: 10.1016/j.dld.2013.02.015. [Epub ahead of print]
  - 41 DeBrosse CW, Franciosi JP, King EC, Butz BK, Greenberg AB, Collins MH, Abonia JP, Assa'ad A, Putnam PE, Rothenberg ME. Long-term outcomes in pediatric-onset esophageal eosinophilia. *J Allergy Clin Immunol*. 2011 ; **128**: 132-8.
  - 42 Peterson KA, Byrne KR, Vinson LA, Ying J, Boynton KK, Fang JC, Gleich GJ, Adler DG, Clayton F. Elemental Diet Induces Histologic Response in Adult Eosinophilic Esophagitis. *Am J Gastroenterol* 2013; **5**. doi: 10.1038/ajg.2012.468. [Epub ahead of print]
  - 43 Hirano I. Editorial: Should patients with suspected eosinophilic esophagitis undergo a therapeutic trial of proton pump inhibition? *Am J Gastroenterol*. 2013 ; **108**: 373-5.
  - 44 Zhang X, Cheng E, Huo X, Yu C, Zhang Q, Pham TH, Wang DH, Spechler SJ, Souza RF. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. *PLoS One* 2012; **7**: e50037
  - 45 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
  - 46 Cheng E. Proton pump inhibitors for eosinophilic oesophagitis. *Curr Opin Gastroenterol* 2013; **27**: 416-420

- 47 O'Donnell S, Kelly OB, O'Morain CA. Drug treatment of eosinophilic oesophagitis. *Curr Drug Metab* 2012; **13**: 1323-1326
- 48 Galindo G, Vassalle J, Marcus SN, Triadafilopoulos G. Multimodality evaluation of patients with gastroesophageal reflux disease symptoms who have failed empiric proton pump inhibitor therapy. *Dis Esophagus* 2012; **226**: 443-450
- 49 Remedios M, Jones D, Kerlin P. Eosinophilic oesophagitis: epidemiology, pathogenesis and management. *Drugs* 2011; **26**: 527-540
- 50 Zur E. Eosinophilic esophagitis: treatment with oral viscous budesonide. *Int J Pharm Compd* 2012; **16**: 288-293
- 51 Moawad FJ, Veerappan GR, Dias JA, Baker TP, Maydonovitch CL, Wong RK. Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia. *Am J Gastroenterol* 2013; **108**: 366-372
- 52 Straumann A, Hoesli S, Bussmann Ch, Stuck M, Perkins M, Collins LP, Payton M, Pettipher R, Hunter M, Steiner J, Simon HU. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. *Allergy* 2013; **68**: 375-385
- 53 Dellon ES. Diagnosis and management of eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012; **10**: 1066-1078
- 54 Lucendo AJ, Arias A, Molina-Infante J, Rodríguez-Sánchez J, Rodrigo L, Nantes O, Pérez-Arellano E, de la Riva S, Pérez-Aisa A, Barrio J; The ACAD Group of Researchers. Diagnostic and therapeutic management of eosinophilic oesophagitis in children and adults: Results from a Spanish registry of clinical practice. *Dig Liver Dis* 2013; **22**. pii: S1590-8658
- 55 Carr S, Watson W. Eosinophilic esophagitis. *Allergy Asthma Clin Immunol*. 2011; **10**; 7 Suppl 1: S8. doi: 10.1186/1710-1492-7-S1-S8.
- 56 Attwood SE, Wilson MS. Current hurdles in the management of eosinophilic oesophagitis: the next steps. *World J Gastroenterol* 2013; **14**: 790-796
- 57 Ally MR, Dias J, Veerappan GR, Maydonovitch CL, Wong RK, Moawad FJ. Safety of dilation in adults with eosinophilic esophagitis. *Dis Esophagus* 2013; **26**: 241-245
- 58 Kavitt RT, Penson DF, Vaezi MF. Eosinophilic esophagitis: dilate or medicate? A cost analysis model of the choice of initial therapy. *Dis Esophagus* 2012; **4**. doi: 10.1111/j.1442-2050.2012.01409.x. [Epub ahead of print]
- 59 Schoepfer AM, Simon D, Straumann A. Eosinophilic oesophagitis: latest intelligence. *Clin Exp Allergy* 2011; **41**: 630-639
- 60 Abe Y, Iijima K, Ohara S, Koike T, Ara N, Uno K, Asano N, Imatani A, Kato K, Shibuya D, Shimosegawa T. A Japanese case series of 12 patients with esophageal eosinophilia. *J Gastroenterol* 2011; **46**: 25-30
- 61 Abonia JP, Rothenberg ME. Eosinophilic esophagitis: rapidly advancing insights. *Annu Rev Med* 2012; **63**: 421-434
- 62 Abonia JP, Rothenberg ME. Eosinophilic esophagitis: rapidly advancing insights. *Annu Rev Med* 2012; **63**: 421-434
- 63 Dellon ES. Eosinophilic esophagitis: diagnostic tests and criteria. *Curr Opin Gastroenterol* 2012; **28**: 382-388
- 64 Lin Z, Kahrilas PJ, Xiao Y, Nicodème F, Gonsalves N, Hirano I, Pandolfino JE. Functional luminal imaging probe topography: an improved method for characterizing esophageal distensibility in eosinophilic esophagitis. *Therap Adv Gastroenterol* 2013; **6**: 97-107
- 65 Lucendo AJ, Sánchez-Cazalilla M. Adult versus pediatric eosinophilic esophagitis: important differences and similarities for the clinician to understand. *Expert Rev Clin Immunol* 2012; **8**: 733-45.

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