Oesinophilic Oesophagitis: Current Evidence and Strategies of Management

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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[1]. EoE is now considered as a systemic disorder and not only a local condition with an important immunological background[2]. 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[3] 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[4]. 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[5].

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[6]. The histological diagnosis of EoE requires demonstration of at least 15 eosinophils per high power field on esophageal histology[7]. Topical corticosteroids and elimination of diets, and esophageal dilation for stricture is widely agreed as treatment options[8-10]. However, special groups of patients are showing no response to these modalities and represent a real challenge to the gastroenterologists, surgeons, dietitians, paediatricians and immunologists. Management of EoE depends on practice location, EoE patient load, and participation in educational activities[11]. 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 esophageal 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.

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[12-14]. 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[15]. Gluten is implicated in 78% of cases[16]. 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[17]. Interleukin (IL)-4 and IL-13, Th2 cytokines transforming growth factor (TGF)-β1 overproduced in allergic disorders, have direct profibrotic and remodeling effects in EoE[18]. The triggering materials are stimulating T-helper (Th-2) to induce cascades of inflammatory responses[19]. Recent study showed genetic underpinnings that implicate EoE susceptibility caused by polymorphisms in the thymic stromal lymphopoietin protein gene[20-23]. 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[24]. Mast cell is involved to promote muscle cell hyperplasia and hypertrophy and may have a significant role in promoting esophageal functional abnormalities in EoE[25]. There is inverse relationship between Barrett’s and EoE[26].

Diagnosis

Peripheral eosinophilia + history of food impaction + PPI refractory heartburn is associated with high prediction of EoE[27]. A significant proportion of patients with Shatzki’s rings (SRs) also have EoE, which may not always be suspected[28]. Association with achalasia (<1%) and cystic fibrosis was also reported[29,30]. At least 15 eosinophils per high power field or a threshold value of approximately 120 eosinophils per mm² was arbitrarily fixed as a diagnostic criterion[31]. 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[32]. Alongside the number of eosinophils further histological features associated with the EoE, such as abscesses of eosinophils or basal layer enlargement, may be of diagnostic help in the borderline cases[33]. On endoscopy, white specks, linear furrows, trachialization and concentric rings (Figure 2) are indicative of EoE[32,33]. Esophageal biopsy specimens should be obtained from all patients with clinical features of EoE, regardless of the endoscopic appearance of the esophagus[34]. Eotaxin-3 and IL-13 have emerged as the most promising advances with respect to sensitivity and degree of positive correlation to disease process[35]. Further research showed Epithelial-derived markers differentially expressed in eosinophilic esophagitis easily detectable by immunohistochemistry with potential diagnostic utility[36]. MicroRNA analysis is identified as a possible noninvasive disease biomarker[37].

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[17,30]. Avoiding the triggering food entities that were highlighted above in the introduction and causes sections was improving the symptoms in majority of patients[34,40]. Additionally there was substantial histologic improvement after 4 weeks on the elemental diet[40].

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\[41\]. 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\[45\]. 50% of patients with an EoE phenotype respond to PPI therapy\[41\]. A trial of PPI therapy was recommended for patients with esophageal eosinophilia and symptoms, even in cases of clear-cut EoE\[46,47\]. The response however was not guaranteed and a group of patients were considered non-responders\[48\].

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\[49,50\]. Although both steroid and PPI are equally effective for histological response, PPI provide better clinical benefit especially in patients with GORD\[51\].

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\[52\]. 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\[53-56\]. Type and size of dilators, number of prior dilations, and age of patient were not associated with complications\[47\]. Swallowed fluticasone inhaler (followed by OGD with dilation if necessary) was the more economical initial strategy when compared with D with dilation first\[48\].

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\[59\]. 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\[40\]. Chronic use of steroid or long term dietary therapy were valuable options in PPI non-responders\[51,62\].

Future studies

Serum biomarkers and genetic testing may play a role in diagnosis\[63\]. Functional probe topography may help in the assessment of EoE and can direct the management options\[64\]. 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\[65\].

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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