



Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

Best Practice & Research Clinical Gastroenterology



11

Medical therapy in eosinophilic oesophagitis

Alex Straumann, MD, Prof., Chairman *

Swiss EoE Clinic and EoE Research Network, Roemerstrasse 7, 4600 Olten, Switzerland



Keywords:

Natural history
Oesophageal remodelling
Food impaction
Indications for treatment
Corticosteroids
Immunosuppressants
Biologicals
Unmet needs

A B S T R A C T

Eosinophilic oesophagitis (EoE) is a chronic-inflammatory disease of the oesophagus. If left untreated, eosinophilic inflammation induces fibrosis, angiogenesis and stricture formation, resulting finally in a so called remodelling with structural and functional damage of the organ. In addition, patients with untreated EoE are permanently at risk of experiencing food impactions. It is therefore widely accepted that active EoE should be treated. Any treatment applied in EoE should ideally achieve two therapeutic goals: first, resolution of symptoms, and, second, control of inflammation. Avoidance of food allergens by elimination diets as well as anti-inflammatory drugs have both the ability to achieve these goals. Among the pharmacological options, only corticosteroids have documented efficacy, whereas alternatives have shown rather disappointing results or are still under evaluation. Of note, swallowed topical corticosteroids are at least as efficient as systemically administered corticosteroids but have fewer side effects. As such topical corticosteroids are widely used as first-line drug in the treatment of EoE, even though this compound is currently not approved for this indication by regulatory authorities. Unfortunately, complete resolution of symptoms can be achieved with swallowed topical corticosteroids only in approximately 70% of patients despite appropriate dosing and despite correct administration of these compounds. Control of inflammation is even harder to achieve, as only in approximately 50% of patients tissue eosinophilia disappears completely under this anti-inflammatory medication. For this group of “difficult to treat” patients, therapeutic alternatives are urgently needed. Fortunately several anti-allergic drugs and several biologicals are currently under investigation.

© 2015 Elsevier Ltd. All rights reserved.

* Tel.: +41 62 212 55 77; fax: +41 62 212 55 64.

E-mail address: alex.straumann@hin.ch.

Introduction

Eosinophilic oesophagitis (EoE), a distinct clinico-pathologically defined syndrome, was first recognized and described in the early 1990s [1,2]. Dysphagia and food impaction are the typical manifestations in adults, whereas in children, food refusal and failure to thrive are the predominant symptoms [3–5]. Prior to those first papers describing EoE as its own distinct entity, single case reports attributed oesophageal eosinophilia to a variety of already described disorders, such as gastro-oesophageal reflux, achalasia or eosinophilic gastroenteritis [5]. EoE was originally regarded as something of a curiosity. However, due to increasing incidence of EoE in westernized countries [6,7], it has now reached a prevalence comparable to that of Crohn's disease and is likely to be the most common cause of both dysphagia resulting from ingestion of solid food and spontaneous perforation of the oesophagus [6]. Two decades of intense research has uncovered many molecular, immunological and clinical aspects of this chronic-inflammatory disorder. In addition, EoE experts have been instrumental in establishing diagnostic and therapeutic recommendations [4].

In this article, we will focus exclusively on the pharmacologic treatment of EoE, in particular on indications for treatment, therapeutic goals, the currently available options and the practical performance of pharmacotherapy.

Indications for treatment of eosinophilic oesophagitis

When scientific community is confronted with a new disease, the understanding of its natural course is crucial before any treatment modality can be considered. The first natural history study has demonstrated that EoE is a chronic disease, and that symptoms as well as inflammation persist over the years [8]. As such, the quality of life of EoE patients is substantially impaired as long as EoE is not properly treated [3–5]. Improvement of quality of life is therefore a first indication for treatment.

In addition, basic science research and clinical studies have accordingly confirmed that an ongoing active eosinophilic oesophageal inflammation leads to deposition of subepithelial fibrous tissue in the oesophageal wall [9–11]. This so-called “remodelling” induces alterations that finally result in a rigid and fragile oesophagus with impaired function [3–5]. It is well documented, that this process can be prevented or even reversed by an efficient anti-eosinophil treatment [11,12]. Organ preservation can therefore be regarded as a second, important indication for treatment.

Finally, EoE patients frequently experience long-lasting food-impactions requiring endoscopic interventions [13]. This complication harbours a risk for oesophageal injury, either caused by retching or by improperly performed endoscopic intervention. Food impactions are mostly observed in non-adequately treated patients. A recently published retrospective study has confirmed this observation and shown that patients treated with an anti-eosinophil medication experience significantly less long-lasting food impactions when compared to non-treated patients [14]. Prevention of this unforeseeable EoE complication is therefore a further indication for treatment.

In summary, clinically and histologically active EoE should be treated with anti-eosinophil medication because this measure has potential: first, to diminish symptoms and to improve therefore the quality of life of EoE patients; second, to prevent oesophageal damage caused by tissue remodelling due to unbridled eosinophilic inflammation; and third, to reduce the risk of severe oesophageal injury by preventing long-lasting food impactions.

Treatment goals in eosinophilic oesophagitis

At present, the target of EoE treatment is still a subject of intensive debate. Should the treatment result in the improvement of symptoms or in the normalisation of altered biologic measures or even in both? In the absence of agreement on meaningful therapeutic endpoints, a uniform treatment algorithm for EoE patients is still lacking [4,5]. In general, as stronger the relationship between an altered biological marker and organ damage is, the more critical it is to include it in the therapeutic concept [15]. It is evident that resolution of symptoms is the first goal of EoE treatment. However, given the fact the ongoing eosinophilic inflammation in EoE results in a long-term organ damage – as is the case in

many other chronic-inflammatory diseases – bringing eosinophilic inflammation under control has to be likely regarded as second therapeutic goal.

In conclusion, the ideal therapeutic intervention in EoE has therefore to improve symptoms and to reduce inflammation.

General principles of pharmacological EoE-treatment

Eosinophilic oesophagitis is a new disease. However, it shares many similarities with gastro-oesophageal reflux disease, atopic diseases, such as asthma and atopic dermatitis, and even inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis. Therefore, evaluation of drugs with proven efficacy in these disorders merits careful consideration. Those pharmacologic therapies that have already been evaluated for the purposes of EoE management will now be discussed.

Proton-pump inhibitors

Currently, PPI are used in EoE patients with co-existing gastro-oesophageal reflux disease (GORD) [4]. Given the high prevalence of GORD in a general population, it is likely that both diseases can co-occur. However, it is also possible that impairment of the lower oesophageal sphincter may lead to gastro-oesophageal reflux as sequela of EoE [16]. Moreover, it is also known that acid exposure in EoE subjects is more painful than in control patients [17]. As such, use of PPI may improve symptoms, such as pain, but may in general not have an effect on the underlying inflammatory process.

Based on the initial assumption that EoE does not respond to treatment with proton-pump inhibitors (PPI), in contrast to reflux oesophagitis, a 2-month trial with double dose PPI was recommended to distinguish patients with EoE from those with GORD [4]. Unexpectedly, the use of this so-called diagnostic PPI-trial has shown that a subset of patients with EoE responds to treatment with PPI [18]. This clinical observation has been confirmed by Molina-Infante and co-workers in a prospective trial, demonstrating that half of patients with a typical EoE phenotype respond to PPI treatment [19]. This so called “PPI-responsive oesophageal eosinophilia” is observed in both adult and paediatric EoE and is characterised by symptoms, endoscopic, histologic and even transcriptional abnormalities comparable with “classic” EoE, but responding to monotherapy with PPI [4,17,20]. A recently presented, retrospective multi-center study has shown that patients diagnosed with PPI-responsive oesophageal eosinophilia remain in clinical and histo-pathological remission when treated with PPI therapy long-term [21]. However, it remains to be determined whether acid suppression in patients diagnosed with PPI-responsive oesophageal eosinophilia can be considered as a long-term therapeutic option, and further studies are needed before PPI can be included in the definitive armamentarium of medical therapies for EoE.

Corticosteroids

The first study demonstrating that corticosteroids are able to bring active EoE into remission was published in 1998. Liacouras and co-workers treated 20 paediatric patients with marked oesophageal eosinophilia and chronic reflux-like symptoms unresponsive to aggressive medical anti-reflux therapy with 1.5 mg/kg oral methylprednisolone per day for 4 weeks [22]. After corticosteroid therapy, all but one patient had dramatic clinical and histological improvement. Shortly afterwards, Faubion and co-workers demonstrated that four paediatric EoE patients responded to treatment with topically-administered corticosteroids [23]. In 2008, Schaeffer and colleagues published a prospective controlled paediatric trial comparing oral prednisone with swallowed topical fluticasone [24]. Following 4 weeks of therapy, topical fluticasone was as effective as systemic corticosteroids in bringing EoE patients into histologic and symptomatic EoE remission. However, treatment with swallowed topical fluticasone had fewer side effects. This study provided the first strong evidence that EoE can be controlled without the use of systemic corticosteroids. Meanwhile, a number of controlled clinical trials performed in adult and paediatric EoE patients has demonstrated that swallowed corticosteroids (budesonide, fluticasone and ciclesonide) deposited on the oesophageal surface are highly effective in resolving symptoms, endoscopic and histologic alteration of EoE [25–28]. The results of

these studies are difficult to compare, because different compounds, different formulations, different dosages and different treatment periods were used. Overall, the response rates to treatment with swallowed topical corticosteroids were between 50% and 87% [24–27]. The main drawback of systemic and topical corticosteroid treatment is that almost all patients relapse rapidly after cessation of therapy [24,29]. Therefore, corticosteroids are able to control, but not to cure EoE. The main side effect of swallowed topical corticosteroids is infection of the oro-pharyngeal cavity or the oesophagus with *Candida albicans*. This occurs in 10–15% of the patients [4]. This infection is often asymptomatic and can be treated with topically administered anti-fungal drugs in the majority of patients. Fortunately, systemic side effects of the swallowed topical corticosteroids occur but rarely. However, it is still prudent to exercise caution, when treating children and adults with high doses of swallowed topical corticosteroids. Table 1 summarizes design and findings of the nine already performed Randomized Clinical Trials (RCT's) with swallowed topical corticosteroids in the short-term treatment of EoE.

Since EoE is a chronic disease, a long-term therapeutic management strategy is required. In a first controlled long-term study, adult EoE patients were treated for one year with low dose budesonide. The treatment with 0.25 mg twice daily swallowed budesonide was effective in keeping 50% of EoE patients in complete or partial histologic remission, whereas none of the placebo patients was in remission at the end of the study period [29]. However, the optimal maintenance regimen has not yet been determined, and further studies are necessary to evaluate the optimal dose of swallowed topical corticosteroids for maintenance therapy in adult and paediatric EoE patients.

Leukotriene inhibitors

In an open label study, Attwood and colleagues showed that montelukast, a leukotriene receptor antagonist, is able to induce symptomatic relief in adult patients with EoE. However, its use has not been shown to have any effect on oesophageal eosinophilia [30]. Unfortunately, neither this symptom relief nor the anti-inflammatory effect could later on be confirmed in a prospective trial of this medication [31]. Therefore, the use of leukotriene inhibitors for treatment of EoE is not recommended [4].

Immunosuppressants

As mentioned above, in up to 70% of patients symptom resolution can be achieved with properly performed treatment with swallowed topical corticosteroids. However, approximately 30% of patients remain symptomatic and suffer therefore from steroid-refractory EoE. In analogy to steroid-refractory inflammatory bowel disease, immunosuppressants have been evaluated in these patients. Indeed, purin-analogues have shown to be effective in a small series of adult patients with refractory EoE [32]. Surprisingly, this promising treatment modality has not been further evaluated and is currently almost neglected.

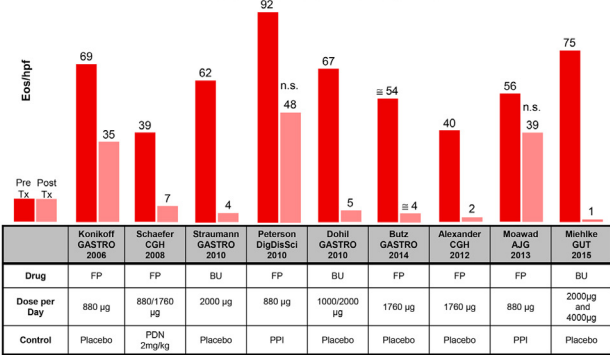
Prostaglandin D₂ receptor antagonists

EoE has many characteristics of a T_H2 type inflammatory response [33]. Prostaglandin D₂ receptor 2, also known as CRTH2, is a chemoattractant receptor expressed by eosinophils and T_H2 cells. This receptor mediates activation of lymphocytes in response to prostaglandin D₂. OC000459 is a first generation selective prostaglandin D₂ receptor 2 antagonist that blocks the ability of prostaglandin D₂ to recruit and activate eosinophils and T_H2 cells. The efficacy and safety of OC000459 monotherapy was evaluated in adult patients with active EoE in a randomised placebo-controlled trial. An 8-week treatment with this compound led to a reduction of the eosinophil load in the oesophageal tissue by approximately 36% [34]. EoE-related symptoms improved, and the appearance of EoE-associated endoscopic alterations was diminished. These findings demonstrate that patients with EoE respond to treatment with OC000459. The drug had an excellent safety profile. However, the overall effect was only moderate. The value of a CRTH2 blockade in the treatment of EoE needs to be further evaluated, preferably with new generation compounds.

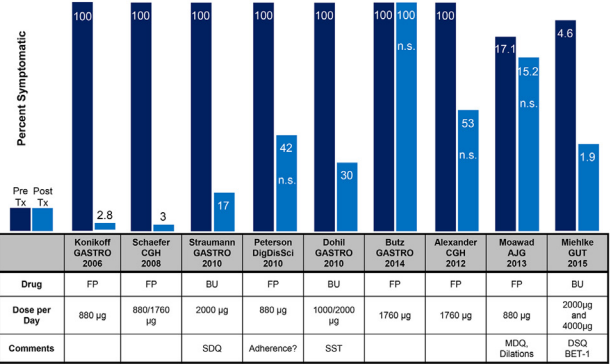
Table 1
(A–D) Randomized controlled trials with corticosteroids in EoE.

Overview									
	Konikoff GASTRO 2006	Schaefer CGH 2008	Straumann GASTRO 2010	Peterson DigDisSci 2010	Dohil GASTRO 2010	Butz GASTRO 2014	Alexander CGH 2012	Moawad AJG 2013	Miehke GUT 2015
Cohort	36 Ped 21/15	80 Ped 40/40	36 Adults 18/18	30 Adults 15/15	24 Ped 15/9	42 Ped 28/14	42 (36) Adults 21/15	42 Adults 21/21	76 Adults 19/19/19/19
Drug	FP	FP	BU	FP	BU	FP	FP	FP	BU
Dose per Day	880 µg	880/1760 µg	2000 µg	880 µg	1000/2000 µg	1760 µg	1760 µg	880 µg	2000µg and 4000µg
Control	Placebo	PON 2mg/kg	Placebo	PPI	Placebo	Placebo	Placebo	PPI	Placebo
Tx Period	12 wks	4 wks	2 wks	8 wks	12 wks	12 wks	6 wks	8 wks	2 wks
Blinding	DB	Open	DB	Open	DB	DB	DB	SB	DB
Particularity		ICS vs sCS	Induction Principle	ICS vs PPI Drop Outs	Dosing age- adjusted	Weaning Schedule		ICS vs PPI	Tx1 vs Sup Dif Doses

Effect on Tissue Eosinophilia

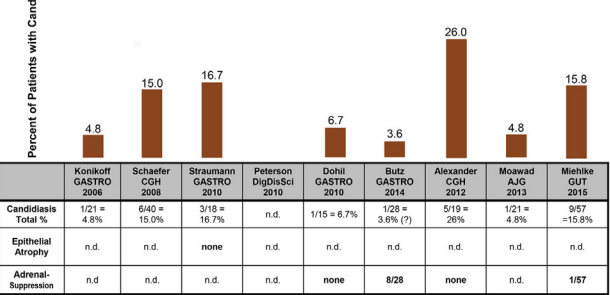


Effect on Symptoms (PRO's)



Side Effects

Overall Rate of Candidiasis 27/219 = 12.3%



Biologic agents

Interleukin 5 (IL-5) is critically important in the maturation, differentiation, activation and tissue recruitment of eosinophils [35]. Mepolizumab and reslizumab – humanized anti-IL-5 antibodies – are therefore highly specific anti-eosinophil drugs. One trial performed with anti-IL-5 monoclonal antibodies in adult and two in paediatric EoE have demonstrated a significant reduction of eosinophils in the oesophageal tissue and in the peripheral blood [36–38]. Unfortunately, mepolizumab as well as reslizumab exerted only minimal clinical improvement in all three studies [36–38].

In active EoE, the pro-inflammatory cytokine *tumour necrosis factor α* (TNF- α) is up-regulated and highly expressed in the squamous epithelium [39]. Unfortunately, an open-label proof of mechanism treatment with the anti-TNF monoclonal antibody infliximab had neither been proven to be effective in reducing eosinophilic tissue infiltration nor in improving EoE-related symptoms [39].

More than 70% of EoE patients have markedly increased total *immunoglobulin E* (IgE) serum levels [4]. In addition, the number of IgE + cells – most likely mast cells – is increased in the oesophageal mucosa of patients with active EoE [4,33]. Therefore, it was tempting to evaluate the efficacy of IgE-blocking agents. One prospective, randomised, placebo-controlled trial with omalizumab evaluated the effect of an IgE blockade in 30 adults with eosinophilic oesophagitis [40]. Unfortunately, omalizumab did neither reduce symptoms of EoE nor tissue eosinophil counts when compared with placebo. In contrast, Alpan and co-workers found in a non-blinded study of 15 EoE patients that tissue eosinophils, as well as tryptase- and IgE-positive cells decreased after a 12-week treatment with omalizumab. In addition, endoscopy and symptom scores improved significantly [41]. However, given the design limitation of the second study and the fact, that IgE likely does not play a key role in the immune-pathogenesis of EoE [40], the blocking of IgE does not appear to be very promising approach.

It has been demonstrated that a large number of EoE-associated genes are directly induced by *interleukin 13* (IL-13) in oesophageal epithelial cells, confirming that IL-13 is a major regulator of the pathways involved in EoE. IL-13 mRNA is indeed overexpressed 16 fold in patients with EoE [42]. In a recently published, double-blind, placebo-controlled trial using QAX576, the effect of an IL-13 blocking approach was evaluated in a series of 23 adult patients with active EoE [43]. After a 12-week course of treatment with intravenous QAX576, the eosinophil load decreased by 60% (17 patients), whereas an increase of 23.3% was observed in the placebo group (eight patients).

In conclusion, among the already evaluated biologic agents, anti-IL-13 monoclonal antibody holds most promise as a novel therapeutic approach for management of EoE.

Pharmacological EoE treatment in clinical practice

Following a discussion of currently available options for the pharmacological treatment of EoE, we would like to discuss the way these therapies can be used in a routine clinical practice.

Once clinician is confronted with a patient with clinically and histologically active EoE, it is prudent to evaluate whether this patient should be treated with an anti-eosinophil drug or with food elimination diet. Since no studies directly comparing the efficacy of these two completely different modalities have been carried out to date [4], the treatment decision taken is not an evidence-based one and should be based on the individual preference of the patient. Physicians in EoE centers should therefore be adept in treating patients choosing either pharmacological or dietary therapy. Given the fact that not a single pharmacological therapy for management of EoE has been approved by regulatory authorities in USA and Europe [44], patients should be carefully instructed on how to administer these drugs, originally designed for the delivery into the airway and not into the oesophagus. Indeed, the improper administration of these drugs is believed to be one of the main causes of refractory EoE [45]. The dietary treatment has the drawback that more than one staple food is removed from the diet. As such, the patients should be encouraged to seek the professional advice of both allergists and dieticians familiar with the particularities of EoE [46–48]. Lastly, the recommendations that follow pertain to management of adult EoE, and pediatricians may have to adapt some of these recommendations.

Given the data on efficacy of swallowed topical corticosteroids in bringing active EoE into remission [4], we recommend that EoE patients should be put on an *induction treatment* with 1 mg bid fluticasone or budesonide for a period of two–four weeks. Of note, it has been demonstrated by Dellon and co-workers that the effect of the compound strongly depends on contact time of the compound with the oesophageal surface [49]. Therefore, viscous syrup, melting tablet or powder are preferable formulations for swallowed topical corticosteroids. Patients should be instructed to avoid eating and drinking for at least half an hour after administration of the drug [4]. The best time for application of the drug is at bedtime and after breakfast. A 2-week induction treatment is able to bring approximately 70% of EoE patients into clinical and histological remission [27].

After achieving a remission, a patient should be put on a *maintenance treatment*, because if EoE is left untreated, the flare-up episodes occur after approximately three months on average [24,29]. The long-term regimens are still not well defined. A daily 0.5 mg dose of budesonide might be likely too low for some patients, as approximately one third of the patients had experienced a flare-up episode when being treated with this dose in a one-year trial [29]. Using doses higher than 2 mg daily has the drawback of lacking safety data regarding systemic side effects. Therefore, the optimal dose might lay somewhere in-between 0.5 and 2.0 mg. So long that many uncertainties regarding the evolution of the disease and the long-term side effects of pharmacologic treatment still exist, we strongly recommend that EoE patients are seen by gastroenterologist on an annual basis for clinical, endoscopic and histologic work-up.

Patients that do not achieving a remission after an induction-treatment with swallowed topical corticosteroids need to be re-evaluated in order to distinguish between those patients, in whom both symptoms and inflammation persist and those, in whom only symptoms remain. If inflammation is under control, symptoms might be caused by fibro-stenosis and a gently performed dilation might be appropriate [50]. In contrast, if inflammation is not under control, either a repeated induction treatment with swallowed topical corticosteroids, a combination of swallowed topical corticosteroids with a single-food elimination diet or a treatment with immunosuppressants should be considered. However, it is generally recommended to refer patients with refractory EoE to specialized centers. The proposed treatment algorithm is shown in Fig. 1.

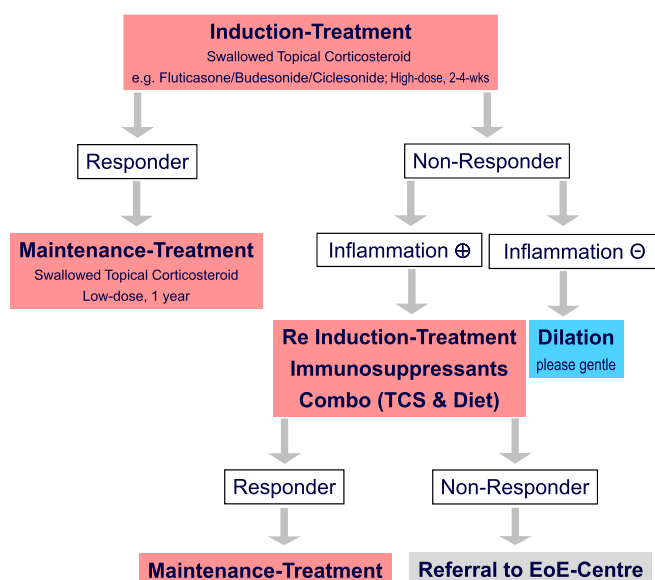


Fig. 1. Algorithm illustrating the current treatment strategy in eosinophilic oesophagitis.

Practice points

- Clinically and histologically active eosinophilic oesophagitis must be treated, even when patients effectively cope with their symptoms
- Because eosinophilic oesophagitis is a chronic disease a long-term follow-up and a long-term therapeutic strategy is needed
- Swallowed topical corticosteroids have proven efficacy, a good safety profile and are currently used as first-line drugs for treatment of eosinophilic oesophagitis

Research agenda

- Evaluation of swallowed topical corticosteroid maintenance treatment with respect to dosage, tolerance and side effects
- Evaluation of alternative medications for patients suffering from steroid-refractory eosinophilic oesophagitis
- Comparison of medical (swallowed topical corticosteroids) with dietary (empiric elimination diets) modality

Conflict of interest

Alex Straumann has consultant contracts with Actelion, Falk, Novartis, Receptos, Regeneron and Roche-Genentech.

References

- [1] Attwood SE, Smyrk TC, Demeester TR, Jones JB. Esophageal eosinophilia with dysphagia, a distinct clinicopathologic syndrome. *Dig Dis Sci* 1993;38:109–16.
- [2] Straumann A, Spichtin HP, Bernoulli R, Loosli J, Voegtlin J. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings [in German with English abstract]. *Schweiz Med Wochenschr* 1994;124:1419–29.
- [3] Furuta GT, Liacouras C, Collins MH, Gupta S, Justinich C, Putnam P, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007;133:1342–63.
- [4] Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3–20.
- [5] Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I, et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy* 2012;67:477–90.
- [6] Hruz P, Straumann A, Bussmann Ch, Heer P, Simon HU, Zwahlen M, et al. Escalating incidence of eosinophilic esophagitis: a 20 year prospective, population-based study in Olten county Switzerland. *J Allergy Clin Immunol* 2011;128:1349–50.
- [7] Van Rhijn BD, Verheij J, Smout AJ, Bredenoord AJ. Rapidly increasing incidence of eosinophilic esophagitis in a large cohort. *Neurogastroenterol Motil* 2013;25:47–52.
- [8] Straumann A, Spichtin HP, Grize L, Bucher KA, Beglinger C, Simon HU. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. *Gastroenterology* 2003;125:1660–9.
- [9] Mishra A, Wang M, Pemmaraju VR, Collins MH, Fulkerson PC, Abonia PJ, et al. Esophageal remodeling develops as a consequence of tissue specific IL-5-induced eosinophilia. *Gastroenterology* 2008;134:204–14.
- [10] Aceves SS, Newbury RO, Dohil R, Bastian JF, Broide DH. Esophageal remodeling in pediatric eosinophilic Esophagitis. *J Allergy Clin Immunol* 2007;119:206–12.
- [11] Lucendo AJ, Arias A, De Rezende LC, Yague-Compadre JL, Mota-Huertas T, Gonzalez-Castillo S, et al. Subepithelial collagen deposition, profibrogenic cytokine gene expression, and changes after prolonged fluticasone propionate treatment in adult eosinophilic esophagitis: a prospective study. *J Allergy Clin Immunol* 2011;128:1037–46.
- [12] Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 2013;145:1230–6.
- [13] Straumann A, Bussmann C, Zuber M, Vannini S, Simon HU, Schoepfer AM. Eosinophilic esophagitis: analysis of food impaction and perforation in 251 adolescent and adult patients. *Clin Gastroenterol Hepatol* 2008;6:598–600.
- [14] Kuchen T, Straumann A, Safroneeva E, Romero Y, Bussmann C, Vavricka S, et al. Swallowed topical corticosteroids reduce the risk for long-lasting bolus impactions in eosinophilic esophagitis. *Allergy* 2014;69:1248–54.
- [15] Straumann A, Safroneeva E, Schoepfer AM. Placebo and other interventions in asthma. *N Engl J Med* 2011;365:1446–8.

- [16] Spechler SJ, Genta RM, Souza RF. Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol* 2007;102:1301–6.
- [17] Krarup AL, Villadsen GE, Mejlgaard E, Olesen SS, Drewes AM, Funch-Jensen P. Acid hypersensitivity in patients with eosinophilic oesophagitis. *Scand J Gastro* 2010;45:273–81.
- [18] Ngo P, Furuta GT, Antonioli DA, Fox VL. Eosinophils in the esophagus – peptic or allergic eosinophilic esophagitis? Case series of three patients with esophageal eosinophilia. *Amer J Gastroenterol* 2006;101:1666–70.
- [19] Molina-Infante J, Ferrando-Lamana L, Ripoll C, Hernandez-Alonso M, Mateos JM, Fernandez-Bermejo M, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011;9:110–7.
- [20] Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol* 2015;135:187–97.
- [21] Molina-Infante, UEGW-2014 Poster.
- [22] Liacouras CA, Wenner WJ, Brown K, Ruchelli E. Primary eosinophilic esophagitis in children: successful treatment with oral corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;26:380–5.
- [23] Faubion WA, Perrault J, Burgart LJ, Zein NN, Clawson ML, Freese DK. Treatment of eosinophilic esophagitis with inhaled corticosteroids. *J Pediatr Gastroenterol Nutr* 1998;27:90–3.
- [24] Schaefer ET, Fitzgerald JF, Molleston JP, Croffie JM, Pfefferkorn MD, Corkins MR, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clin Gastroenterol Hepatol* 2008;6:165–73.
- [25] Konikoff MR, Noel RJ, Blanchard C, Kirby C, Jameson SC, Buckmeier BK, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic Esophagitis. *Gastroenterology* 2006;131:1381–91.
- [26] 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;139:418–29.
- [27] Straumann A, Conus S, Degen L, Felder S, Kummer M, Engel HJ, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010;139:1526–37.
- [28] Schroeder S, Fleischer DM, Masterson JC, Gelfand E, Furuta GT, Atkins D. Successful treatment of eosinophilic esophagitis with ciclesonide. *J Allergy Clin Immunol* 2012;129:1419–21.
- [29] Straumann A, Conus S, Degen L, Frei C, Bussmann Ch, Beglinger Ch, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2011;9:400–9.
- [30] Attwood SEA, Lewis CJ, Bronder CS, Morris CD, Armstrong GR, Whittam J. Eosinophilic oesophagitis: a novel treatment using montelukast. *Gut* 2003;52:181–5.
- [31] Lucendo AJ, De Rezende LC, Jimenez-Contreras S, Yague-Compadre JL, Gonzalez-Cervera J, Mota-Huertas T, et al. Montelukast was inefficient in maintaining steroid-induced remission in adult eosinophilic esophagitis. *Dig Dis Sci* 2011;56:3551–8.
- [32] Netzer P, Gschossmann JM, Straumann A, Sendensky A, Weimann R, Schoepfer AM. Corticosteroid-dependent eosinophilic esophagitis: azathioprine and 6-Mercaptopurine can induce and maintain long-term remission. *Eur J Gastroent Hepatol* 2007;19:865–9.
- [33] Straumann A, Bauer M, Fischer B, Blaser K, Simon H-U. Idiopathic eosinophilic esophagitis is associated with a T_H 2-type allergic inflammatory response. *J Allergy Clin Immunol* 2001;108:954–61.
- [34] Straumann A, Hoesli S, Bussmann Ch, Stuck M, Perkins M, Payton M, et al. Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. *Allergy* 2013;68:375–85.
- [35] Horie S, Gleich GJ, Kita H. Cytokines directly induce degranulation and superoxide production from human eosinophils. *J Allergy Clin Immunol* 1996;98:371–81.
- [36] Straumann A, Conus S, Grzonika P, Kita H, Kephart G, Bussmann Ch, et al. Anti-Interleukin-5 antibody treatment (Mepolizumab) in active eosinophilic esophagitis: a randomized, placebo-controlled. Double Blind Trial *Gut* 2010;59:21–30.
- [37] Assa'ad AH, Gupta SK, Collins MH, Thomson M, Heath AT, Smith DA, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology* 2011;141:1593–604.
- [38] Spergel JM, Rothenberg ME, Collins MH, Furuta GT, Markowitz JE, Fuchs G, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2012;129:456–63.
- [39] Straumann A, Bussmann Ch, Conus S, Beglinger Ch, Simon HU. Anti-TNF-alpha (infliximab) therapy for severe adult eosinophilic esophagitis. *J Allergy Clin Immunol* 2008;122:425–7.
- [40] Clayton F, Fang JC, Gleich GJ, Lucendo AL, Olalla JL, Vinson LA, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology* 2014;147:602–9.
- [41] Loizou D, Enav B, Komlodi-Pasztor E, Hider P, Kim-Chang J, Noonan L, et al. The effect of omalizumab treatment on allergic tissue inflammation and clinical outcomes in patients with eosinophilic esophagitis; an open label, single arm study. *PLOS One* 2015;10:e113483.
- [42] Blanchard C, Mingler MK, Vicario M, Abonia JP, Wu YY, Lu TX, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol* 2007;120:1292–300.
- [43] Rothenberg ME, Wen T, Greenberg A, Alpan O, Enav B, Hirano I, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2015;135:500–7.
- [44] Straumann A, Schoepfer A. Update on basic and clinical aspects of eosinophilic oesophagitis. *Gut* 2014;63:1355–63.
- [45] Mikkada VA, Furuta GT. Management of refractory eosinophilic esophagitis. *Dig Dis* 2014;32:134–8.
- [46] Kagalwalla AF, Sutongo TA, Ritz S, Hess T, Nelson SP, Emerick KM, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006;4:1097–102.
- [47] Gonsalves N, Yang GY, Doerfler B, Ritz S, Ditto A, Hirano I. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology* 2012;142:1451–9.

- [48] Lucendo AJ, Arias A, Gonzalez-Cervera J, Yague-Compadre JL, Guagnozzi D, Angueira T, et al. 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.
- [49] Dellon ES, Sheikh A, Speck O, Woodward K, Whitlow AB, Hores JM, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology* 2012;143:321–4.
- [50] Schoepfer AM, Gonsalves N, Bussmann Ch, Conus S, Simon HU, Straumann A, et al. Esophageal dilation in eosinophilic esophagitis: effectiveness, safety and impact on the underlying inflammation. *Amer J Gastroenterol* 2010;105:1062–70.