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Guidelines

The 1st EoETALY Consensus on the Diagnosis and Management of Eosinophilic Esophagitis–Current Treatment and Monitoring ☆

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ABSTRACT

The present document constitutes Part 2 of the EoETALY Consensus Statements guideline on the diagnosis and management of eosinophilic esophagitis (EoE) developed by experts in the field of EoE across Italy (i.e., EoETALY Consensus Group). Part 1 was published as a different document, and included three chapters discussing 1) definition, epidemiology, and pathogenesis; 2) clinical presentation and natural history and 3) diagnosis of EoE. The present work provides guidelines on the management of EoE in two final

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chapters: 4) treatment and 5) monitoring and follow-up, and also includes considerations on knowledge gaps and a proposed research agenda for the coming years. The guideline was developed through a Delphi process, with grading of the strength and quality of the evidence of the recommendations performed according to accepted GRADE criteria.This document has received the endorsement of three Italian national societies including the Italian Society of Gastroenterology (SIGE), the Italian Society of Neurogastroenterology and Motility (SINGEM), and the Italian Society of Allergology, Asthma, and Clinical Immunology (SIAAIC). The guidelines also involved the contribution of members of ESEO Italia, the Italian Association of Families Against EoE.

1. Introduction

The present manuscript constitutes Part 2 of the EoETALY Consensus Statements on the diagnosis and management of eosinophilic esophagitis (EoE) formulated by the EoETALY Consensus Group. Part 1 of the EoETALY Consensus Statements included three chapters: 1) definition, epidemiology, and pathogenesis; 2) clinical presentation and natural history and 3) diagnosis of EoE [1]. The present document includes two final chapters: 4) treatment and 5) monitoring and follow-up of EoE (Table 1). The full methodology of Part 1 and 2 of the EoETALY Consensus Statements is reported in Part 1 and its supplementary materials [1].

2. CHAPTER 4: TREATMENT

Fig. 1 provides a summary of the therapeutic algorithm of EoE.

STATEMENT 24

Improvement in histology, endoscopy, symptoms, and EoE-specific quality of life all represent treatment endpoints in patients with EoE.

Level of evidence: High
Recommendation: Strong
Agreement: 96.7% [D + (0%); D (0%); D – (0%); A- (3.3%); A (10%); A + (86.7%)]

Summary of evidence

RCTs in patients with EoE are heterogeneous in terms of outcome assessment, with 66.7% of RCTs investigating histologic response, and 28.8% clinical response as primary outcome [2]. However, EoE is a complex disease with clinical, endoscopic, and histologic biomarkers of disease activity [3,4]. The COREOS collaborators group developed a core outcome set for EoE, including histopathology, endoscopy, patient-reported symptoms, and EoE-specific quality of life. With regards to histology, the number of eosinophils per high-power field (400x magnification) should be assessed, and histologic remission should be defined on the basis of a peak eosinophil count of $<$15/HPF in all biopsies. Endoscopic findings should be assessed based on the EoE endoscopic reference score (EREFS) and should be scored from 0 to 8, scoring the most severe grade of esophageal EoE-associated features; the endoscopic EREFS-based remission should be defined as an EREFS score of $\leq$2 [5]. It is proposed that, in RCTs, symptoms severity should be assessed using the Dysphagia Symptom Questionnaire (DSQ) [6] and the Eosinophilic Esophagitis Activity Index (EEsAI) with a 7-day recall period for adults [7], and the Pediatric Eosinophilic Esophagitis Symptom Score v2.0 (PESS v2.0) for children [8]. In adults with EoE the terms 'trouble swallowing' and/or 'delayed or slow passage of food' should be used when querying dysphagia. Quality of life should be measured with the EoE-QoL-A questionnaire for adults [9], and the PedsQL for children [10].

STATEMENT 25

Proton pump inhibitors (PPIs) treatment can achieve clinical and histological remission in a significant proportion of patients with EoE. However, PPI treatment is currently off-label in EoE.

Agreement: 100%% [D + (0%); D (0%); D – (0%); A- (0%); A (16.7%); A + (83.3%)]
Level of evidence: Moderate
Recommendation: Strong

Summary of evidence

PPIs treatment has shown efficacy in a proportion of patients with EoE. Several retrospective studies demonstrated that patients with clinical, endoscopic and histological features compatible with EoE achieved clinicopathological response to PPI therapy [11–15]. Subsequently, a large prospective study and then several randomized controlled trials (RCTs) supported these findings [16–19].

A systematic review with meta-analysis published in 2016, including 33 studies with 619 patients with EoE, summarized available evidence and concluded that PPI therapy can lead to a clinical response in 60.8% (95% CI, 48.38%–72.2%) and histologic remission in 50.5% (95% CI, 42.2%–58.7%) of patients. No significant differences were noted according to patients' age, study design, and type of PPI assessed. The authors demonstrated that PPIs were non significantly more effective in prospective studies (52.6% vs 39.1%) administered twice daily compared with once daily (55.9% vs 49.7%), or in patients with abnormal pH monitoring (65.4% vs 49.3%) [20]. Based on available evidence, recommended PPI doses to induce EoE remission in adults are omeprazole 20–40 mg twice daily or equivalent, and in children 1–2 mg/kg of omeprazole daily or equivalent.

STATEMENT 26

PPI treatment can maintain clinical and histological remission in patients with EoE, although long-term maintenance data have a low level of evidence.

Agreement: 100% [D + (0%); D (0%); D – (0%); A- (0%); A (40%); A + (60%)]
Level of evidence: Low
Recommendation: Strong

Summary of evidence

An old long-term retrospective multicenter study of 75 patients with PPI-responsive esophageal eosinophilia who had at least 12 months of follow up and in whom PPI therapy was tapered to the lowest dose, a sustained histological response was demonstrated in the majority of patients[20]. Among those who relapsed, most regained histological remission after dose escalation, suggesting that some patients require high-dose PPI for maintenance of remission. Gomez-Torrijos et al. observed that 31 out of 38 patients remained in remission when the dose of PPI was reduced to once daily, and 15 out of 18 remained in remission when daily high-dose PPI was reduced to regular dose PPI [21]. Another study reported that 17

Table 1
Summary of EoETALY consensus statements chapters 4 and 5.

CHAPTER 4: TREATMENT

Statement	Level of Agreement	Recommendation and quality of evidence
24. Improvement in histology, endoscopy, symptoms, and EoE-specific quality of life all represent treatment endpoints in patients with EoE.	96.7%	*Strong recommendation - High quality of evidence*
25. PPI treatment can achieve clinical and histological remission in a significant proportion of patients with EoE. However, PPI treatment is currently off-label in EoE	100%	*Strong recommendation - Moderate quality of evidence*
26. PPI treatment can maintain clinical and histological remission in patients with EoE, although long-term maintenance data have a low level of evidence.	100%	*Strong recommendation - Low quality of evidence*
27. PPI treatment is safe and well-tolerated.	93.3%	*Strong recommendation - Moderate quality of evidence*
28. Topical steroids are effective for inducing histological and clinical remission in eosinophilic esophagitis.	100%	*Strong recommendation - High quality of evidence*
29. Clinical and histological relapse is high after withdrawal of topical steroid treatment. Following clinical review, maintenance treatment should be recommended.	100%	*Strong recommendation - High quality of evidence*
30. Systemic steroids are not recommended as a standard of care in eosinophilic esophagitis.	100%	*Strong recommendation - High quality of evidence*
31. Topical steroids have a good safety profile for induction and maintenance of remission in the medium term. Longer term data are lacking.	100%	*Conditional recommendation - Moderate quality of evidence*
32. Elemental diet induces histologic remission in the majority of EoE patients.	90%	*Conditional recommendation - Low quality of evidence*
33. Empiric food elimination diets can induce clinical and histologic remission in a significant proportion of EoE patients when instructed by a dedicated professional figure. A step-up approach starting from a one-food elimination diet of animal milk is reasonable to reduce unnecessary dietary restrictions and endoscopies.	100%	*Strong recommendation - Moderate quality of evidence*
34. Dietary elimination of identified food trigger categories can maintain remission in patients with EoE, although long term compliance may be challenging for patients.	96.7%	*Conditional recommendation - Low quality of evidence*
35. Allergy testing should not be used for guiding dietary elimination treatment in patients with EoE.	96.7%	*Conditional recommendation - Low quality of evidence*
36. Elimination diets are generally safe, but their use can increase the risk of nutritional deficiencies. Accordingly, patients undergoing elimination diet should be supervised by an experienced dietician.	96.7%	*Strong recommendation - Low quality of evidence*
37. Endoscopic dilatation of strictures can effectively relieve dysphagia in patients with EoE.	96.7%	*Strong recommendation - Low quality of evidence*
38. Endoscopic dilatation is safe in patients with EoE	93.3%	*Conditional recommendation - Low quality of evidence*
39. Topical steroids, proton pump inhibitors, elimination diets, and dupilumab can be considered for the treatment of EoE. The first line approach should be accurately defined in each single patient, according to patients' characteristics, preferences, and available resources.	96.7%	*Strong recommendation –* - *High quality of evidence (EoE-specific topical steroids and dupilumab)* - *Moderate quality of evidence (Elimination diets and inhaled/swallowed topical steroids),* - *Low quality of evidence (PPIs)*
40. Monoclonal antibodies without regulatory approval for EoE should not be used outside of randomized controlled trials.	100%	*Strong recommendation - High quality of evidence*
41. Immunomodulators (azathioprine, 6-mercaptopurine) are not recommended in patients with EoE	100%	*Strong recommendation - Low quality of evidence*
42. Anti-allergic drugs are not recommended for the treatment of EoE.	96.7%	*Strong recommendation - Low quality of evidence*

CHAPTER 5: MONITORING AND FOLLOW UP

Statement	Level of Agreement	Recommendation and quality of evidence
43. - Endoscopy with esophageal biopsies is currently the gold standard for monitoring EoE because symptoms do not correlate well with the histologic activity. - Endoscopy with biopsy 8–12 weeks after initiation of therapy and after every therapeutic modification should be performed to assess treatment response in patients with EoE	96.7%	*Strong recommendation - High quality of evidence*
44. The natural history of EoE is associated with a high rate of disease relapse after any treatment withdrawal.	100%	*Recommendation not applicable - High quality of evidence*
45. - Patients with EoE in clinical and histological remission should be regularly followed-up with symptomatic, endoscopic and histologic assessment to prevent disease progression. - Patients with EoE and proven clinical and histological remission who experience symptoms relapse should undergo endoscopy with histologic assessment as soon as possible.	86.7%	*Conditional recommendation - Very low quality of evidence*

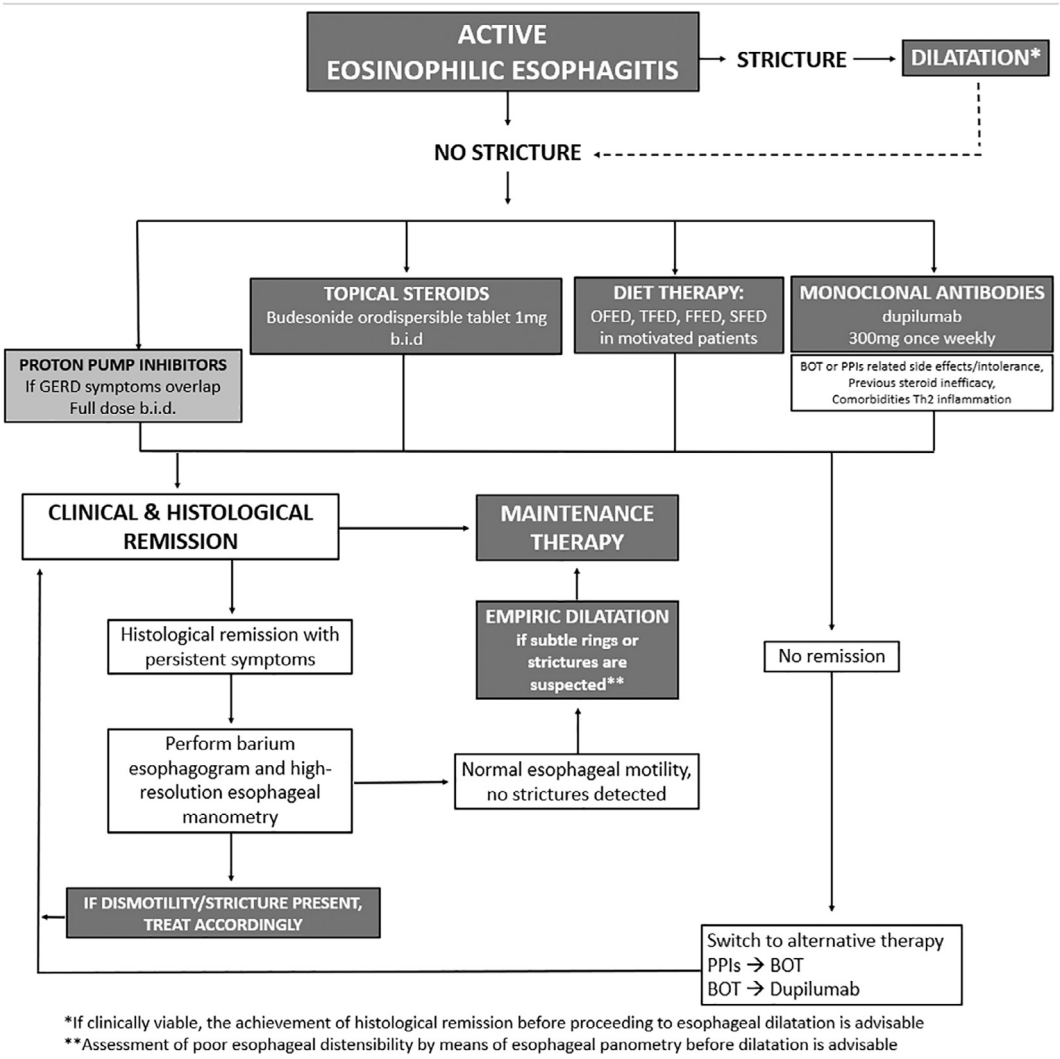

Fig. 1. Therapeutic algorithm for eosinophilic esophagitis.
Abbreviations of Figure 1: BOT, budesonide orally disintegrating tables; PPIs, proton pump inhibitors; GERD, gastroesophageal reflux disease.

out of 57 failed to maintain remission over a 1-year period on 1 mg/kg per dose twice daily of PPI [22]. Finally, a recent retrospective study suggested that PPIs could maintain histological remission following topical steroids-induced remission up to 12 weeks in adults with EoE who had previously failed induction of remission with PPIs [23].

STATEMENT 27

PPI treatment is safe and well-tolerated.

Agreement: 93.3% [D + (0%); D (0%); D – (0%); A- (6.7%); A (20%); A + (73.3%)]
Level of evidence: Moderate
Recommendation: Strong

Summary of evidence

Like any other drug, PPIs have known common minor adverse effects such as headaches and gastrointestinal problems [24]. Some studies found local effects of long term PPIs use including atrophic gastritis due to prolonged acid suppression, hypergastrinemia, chronic H. pylori infection, and development of gastric polyps [25]. A double-blind trial published in 2019 by Moayyedi et al. that randomly assigned 8791 patients receiving rivaroxaban with aspirin or rivaroxaban or aspirin alone to 40 mg of pantoprazole daily and 8807 patients to placebo, found no statistically significant difference between the two groups in safety events, except for enteric infections (1.4% vs 1.0% in the placebo group; odds ratio, 1.33; 95% confidence interval, 1.01–1.75) [26]. Regarding patients with EoE, a recent observational study demonstrated that the risk of fracture in EoE taking PPIs was not statistically significantly elevated compared to non-EoE reference individuals [27]. In conclusion, at present, there are no reported safety concerns for PPI therapy in EoE.

STATEMENT 28

Topical steroids are effective for inducing histological and clinical remission in eosinophilic esophagitis.

Agreement: 100% [D + (0%); D (0%); D – (0%); A- (0%); A (13.3%); A + (86.7%)]
Level of evidence: High
Recommendation: Strong

Summary of evidence

In a recent network meta-analysis, topical steroids have been shown to rank high among other drugs for the induction of remission in EoE [28]. In addition, EoE-specific steroid formulations

ranked higher than off-label topical steroids for induction of remission in active EoE [28].

Historically, off-label topical steroids adapted from the treatment of asthma have been used in patients with EoE but novel EoE-specific topical steroids are being investigated [28]. Of these, orally disintegrating budesonide (BOT) has been recently approved for EoE in Europe [29], based on a RCT showing a clinico-histological remission rate of up to 57.6% after six weeks of treatment and of 85% after 12 weeks of treatment[30], and based on an open-label induction study showing a clinic-histological remission rate of 69.9% after six weeks of treatment [30]. Other steroidal preparations, which are currently under investigation, include budesonide oral suspension (BOS), oral viscous budesonide, and fluticasone orally disintegrating tablet [31]. Topical steroids designed for the treatment of asthma and used off label in patients with EoE include nebulized/swallowed budesonide and fluticasone preparations. These drugs have shown efficacy of for the treatment of EoE compared to placebo [32]. However, since EoE-specific steroid formulations are now available for EoE and rank higher than off-label topical steroids in terms of induction of remission [28], the use of off-label topical steroids should be avoided and limited to those situations in which EoE-specific treatments are unavailable.

STATEMENT 29

Clinical and histological relapse is high after withdrawal of topical steroid treatment. Following clinical review, maintenance treatment should be recommended.

Agreement: 100% [D + (0%); D (0%); D – (0%); A- (0%); A (23.3%); A + (76.7%)]
Level of evidence: High
Recommendation: Strong

Summary of evidence

EoE is a chronic disease with a high recurrence rate after cessation of therapy [33]. Accordingly, we would recommend maintenance treatment for patients who respond to induction treatment. However, solid long-term data on the efficacy of topical steroids are currently lacking. In a phase-3 double blind RCT comparing maintenance treatment with BOT either 0.5 mg two times per day or 1.0 mg two times per day, remission was maintained in 73.5% and 75% of patients, respectively, compared to 4.4% in the placebo group after 48 weeks of treatment [34]. In another randomized treatment withdrawal study enrolling patients in clinic-histological remission while on BOS 2 mg per day, following randomization to BOS 2 mg two times per day or placebo, after 36 weeks of treatment, disease remission was maintained in 83.3% of patients randomized to BOS 2 mg two times per day compared to 50% of those randomized to placebo [35].

STATEMENT 30

Systemic steroids are not recommended as a standard of care in eosinophilic esophagitis.

Agreement: 100% [D + (0%); D (0%); D – (0%); A- (0%); A (16.6%); A + (83.4%)]
Level of evidence: High
Recommendation: Strong

Summary of evidence

In a RCT, 80 children were randomized to either prednisolone (1 mg/kg two times per day) or swallowed fluticasone (220 mg or 440 mg four times per day according to age) for 12 weeks. Histological remission was non-significantly different in the two groups at week four. However, adverse events were significantly more common among patients randomized to prednisolone[37]. Another retrospective study on 22 patients, systemic steroids were administered to children with stricturing EoE [36]. Post-treatment, 95% of patients showed resolution of the strictures, 67% had normal eosinophilic counts, and all patients improved clinically. Reported transient adverse events included hyperphagia, weight gain, hyperactivity, and acne [37]. Of note, there are no data on the use of systemic steroids for the management of EoE in adults. Based on the available evidence, systemic steroids have been shown to induce remission of EoE. Based on the incidence of adverse events and the vailability of alternatives (i.e., topical steroids), we do not recommend the use of systemic steroids in the management non-stricturing EoE.

STATEMENT 31

Topical steroids have a good safety profile for induction and maintenance of remission in the medium term. Longer term data are lacking.

Agreement: 100% [D + (0%); D (0%); D – (0%); A- (0%); A (23.3%); A + (76.7%)]
Level of evidence: Moderate
Recommendation: Conditional

Summary of evidence

RCTs investigating different preparations of topical steroids have generally shown a good safety profile in the short and medium term, without significantly higher incidence of serious adverse events among patients taking active drugs compared to placebo [30,31,34, 38–43]. Esophageal candidiasis has been reported in up to 15% of patients undergoing topical steroidal treatment [34, 38,39, 41,42,44]. In such instances, antifungal treatment is recommended to resolve the fungal infection. A recent study [45] summarized the safety data up to 208 weeks coming from six clinical trials (phases 1–3) conducted on BOS. Most of the adverse events were of mild or moderate severity and did not lead to study drug discontinuation . In up to 43%, 27% and 17% of patients taking BOS 2 mg twice a day, infections (esophageal candidiasis, oral candidiasis, upper respiratory tract infection, nasopharyngitis, sinusitis or influenza), gastrointestinal, and central nervous system adverse events were reported. However, the rate of all adverse events was similar for participants receiving BOS 2.0 mg twice a day, BOS any dose, and placebo. In contrast, adrenal adverse events were more frequent among those taking BOS [45]. Long-term RCT and real-life prospective studies are needed to assess the rate and severity of possible adverse events related to topical steroidal treatment and provide a basis for which follow-up strategy should be put in place for patients taking long term topical steroids. The EoETALY Consensus Group suggests careful clinical monitoring of possible treatment-related adverse events in patients taking long-term topical steroids [46].

STATEMENT 32

Elemental diet induces histologic remission in the majority of EoE patients.

Agreement: 90% [D + (3.3%); D (0%); D – (3.3%); A- (3.3%); A (33.3%); A + (56.7%)]
Level of evidence: Low
Recommendation: Conditional

Summary of Evidence

The elemental diet involves the replacement of all types of table food with elemental or amino-acid based formulas. Paediatric series have shown an overall >90% histologic remission in EoE using amino acid formulas[47]. Two prospective adult studies of elemental diet reported a lower histologic response of approximately 75%,

however both trials were limited by a 4-week treatment period and high patient nonadherence and drop out due to poor palatability. In a recent systematic review of six single group observational studies with 431 patients, adults less frequently achieved histologic remission compared to children [47]. Significant obstacles limit the use of amino acid formula, including palatability problems, limited meal variety, lack of reimbursement, and number of endoscopies required to identify specific triggers during food reintroduction. In addition, food reintroduction may be associated with the de novo development of IgE-mediated food allergies [48].

STATEMENT 33

Empiric food elimination diets can induce clinical and histologic remission in a significant proportion of EoE patients when instructed by a dedicated professional. A step-up approach starting from a one-food elimination diet of animal milk is reasonable to reduce unnecessary dietary restrictions and endoscopies.

Agreement: 100% [D + (0%); D (0%); D – (0%); A- (0%); A (23.3%); A + (76.7%)]
Level of evidence: Moderate
Recommendation: Strong

Summary of evidence

The six-food elimination diet (SFED) is one of the first type of empiric diet proposed for the treatment of EoE[50]. A meta-analysis by Arias A. et al. published in 2014 showed an efficacy of 71.3% (95% CI 61.7–80) for the induction of histological remission in patients undergoing a SFED [49]. Lower rates of histological remission are reported by studies in which patients were not routinely instructed by an expert [50]. More recently, a retrospective study showed that the response to the SFED may be lower during pollen season in adults with EoE sensitized to pollens compared to patients that are not sensitized to seasonal pollens [51]. Accordingly, seasonal pollens may account for a proportion of the failures of SFED regimens.

Most patients responsive to SFED have only one or two trigger categories of foods identified after the six-food challenge [52–54]. In a multicentre study, the elimination of food started from two food categories (dairy and gluten containing grains; i.e., TFED) and then progressively increases to FFED and SFED in case of lack of response. In this case series, a progressive histological remission rate of 44% for TFED, 60% for FFED and 80% for SFED in the adult cohort of patients was reported [54]. Compared with the initial SFED, a step-up strategy reduced endoscopic procedures and diagnostic process time by 20% and 30%, respectively. Finally, a recently published RCT comparing the efficacy of an animal milk elimination diet compared to a SFED showed that the two dietary regimens had similar efficacy (34% vs 40%, respectively), questioning the utility of large dietary restrictions in patients with EoE [55]. Accordingly, to improve patients' compliance to dietary regimens, it is reasonable to propose a step-up empiric elimination diet, starting from the elimination of animal milk, before proceeding to larger dietary restrictions.

STATEMENT 34

Dietary elimination of identified food trigger categories can maintain remission in patients with EoE, although long term compliance may be challenging for patients.

Agreement: 96.7% [D + (0%); D (0%); D – (0%); A- (3.3%); A (26.7%); A + (70%)]
Level of evidence: Low
Recommendation: Conditional

Summary of evidence

The long-term avoidance of trigger foods identified during the reintroduction process of a food elimination diet can maintain remission in patients with EoE. In a prospective, at one-year follow-up, all 25 patients who had responded to the SFED were asymptomatic and on complete histological remission while on the diet. Persistent clinical and histological remission was also described after two and three years in all patients that were able to maintain the follow up (15 and four patients, respectively) [56]. Efficacy of long-term food elimination diets was also confirmed by the prospective study by Philpott et al. The study reported that 56% of responders to SFED (10 patients) were still in histological remission after nine months. However, the remaining 44% of patients ceased the diet during the follow-up period[51]. To date, there are no data about long term efficacy after induction of remission with four, two or one food elimination diets.

STATEMENT 35

Allergy testing should not be used for guiding dietary elimination treatment in patients with EoE.

Agreement: 96.7% [D + (0%); D (0%); D – (0%); A- (3.3%); A (23.3%); A + (73.3%)]
Level of evidence: Low
Recommendation: Conditional

Summary of evidence

The exposure to environmental allergens in patients with EoE triggers a chronic inflammatory response in the esophagus [57,58]. Based on this evidence, several studies have investigated the role of allergy testing to inform targeted elimination diets based on individual food sensitization profiles, as opposed to empiric elimination diets [3]. However, a meta-analysis showed that dietary restrictions based on food sensitization profiles have lower histological remission rates compared to empiric elimination or elemental diets [49]. In particular, it was estimated that one third of adults and less than a half of children achieved histological remission of EoE following targeted elimination diets. It must be noted, however, that the studies included in the meta-analysis used heterogeneous methodology to investigate possible trigger foods, including skin prick test (SPT), atopy patch test (APT), and serum-specific IgE testing. Accordingly, further prospective studies are required to improve the quality of available evidence and increase the strength of recommendation on targeted elimination diets, which currently seem to be less effective than both empiric elimination and elemental diets [48].

STATEMENT 36

Elimination diets are generally safe, but their use can increase the risk of nutritional deficiencies. Accordingly, patients undergoing elimination diet should be supervised by an experienced dietician.

Agreement: 96.7% [D + (0%); D (0%); D – (0%); A- (3.3%); A (23.3%); A + (73.3%)]
Level of evidence: Low
Recommendation: Strong

Summary of evidence

Food elimination diets and elemental diets can increase the risk of delayed onset of oral-motor skills, failure to thrive, malnutrition, and impaired growth in children, as well as nutritional imbalances and unintended weight loss in adults [3]. In this regard, a recent systematic review showed that food restrictions may increase the risk of nutritional deficiencies in children with EoE [59]. In a study comparing GERD and EoE patients, although serum nutritional markers were normal in both groups, food diaries showed

suboptimal dietary calcium and vitamin D intake in those with EoE [60]. Given the complexity of food elimination diets, the involvement of an experienced dietitian can help providing personalized education and practical guidance on how to maintain a nutritionally balanced and palatable diet, and mitigate risks of elimination dietary regimens [48,61].

STATEMENT 37

Endoscopic dilatation of strictures can effectively relieve dysphagia in patients with EoE.

Agreement: 96.7% [D + (0%); D (0%); D – (0%); A- (3.3%); A (20%); A + (76.7%)]
Level of evidence: Low
Recommendation: Strong

Summary of evidence

Two recent systematic reviews and metanalysis [62,63] have looked at effectiveness of dilatation in EoE. Seventeen and nine studies were included in the two meta-analyses, respectively, accounting for a total of 536 and 504 patients undergoing dilatation either with bougie or hydrostatic balloon dilatators. Most included studies were retrospective or case series. Clinical improvement occurred in 95% [62] and 85% [63] of patients over a median follow-up of 12 months and clinical response was similar between children and adults, although the paediatric group was much smaller[62]. The median number of dilatations was two and the mean post-dilatation esophageal diameter was 16 mm. The main limitations of included studies, derived by their observational retrospective nature, was the variable use of concomitant medical treatment. In the two reports with the biggest cohorts of 207 and 164 patients, respectively [64,65], effectiveness of dilatation was similar in patients on dietary or topical steroid therapy and in those who were not receiving medical treatment. In addition, a recent study [66] suggested that the need of repeat dilatation is decreased by maintenance pharmacological or dietary treatment. Finally, after dilatation there is a long-lasting dissociation of esophageal eosinophilia and symptoms. The implication for patients' care is that symptoms should not be used to monitor therapy response for at least one year after dilatations [67]. Finally, in view of the low sensitivity of endoscopy for identification of strictures [68–70] and the possibility of reduced esophageal distensibility at esophageal panometry (FLIP) despite histological remission [71,72], empiric esophageal dilatation may potentially be offered to patients on drug/diet treatment with residual trouble in swallowing, who are in histological remission and have an apparently stricture free esophagi at endoscopy and at barium esophagogram, provided that other possible causes of dysphagia, such as esophageal dysmotility [73,74], have been ruled out first [68,70].

STATEMENT 38

Endoscopic dilatation is safe in patients with EoE.

Agreement: 93.3% [D + (0%); D (0%); D – (0%); A- (6.7%); A (33.3%); A + (60%)]
Level of evidence: Low
Recommendation: Conditional

Summary of evidence

Three recent systematic reviews with meta-analysis [62,63, 75] have looked at safety of dilatation. The meta-analyses have included 37, 27 and 14 studies, respectively (12 studies included in all 3 systematic reviews) for a total of 977, 845 and 809 patients who underwent 2034, 1831 and 1543 dilatations. Most studies were retrospective or case series. No procedure-related deaths occurred. Pooled perforation rates ranged from 0.033% to 0.61% in the three metanalysis, GI haemorrhage rates from 0.028% to 0.05% and hospitalization from 0.67% to 0.74%. Significant heterogeneity among studies was found for perforation and for hospitalization. Chest pain not requiring hospitalization occurred in a median of 9.3% of patients with a wide variation of rates among studies, ranging from 0.63% to 50% [62,63, 75]. A trend was seen toward lower frequency of perforation and chest pain for the minority of pediatric patients compared with the adult ones. The estimated perforation rate for bougie was similar to that of balloons (0.022% vs 0.059%) [75]. The recently developed BougieCap has shown to be safe in a cohort of 50 patients, the only adverse event being a slipped device which could be retrieved [76]. Finally, although there are no data supporting that dilatation is safer when patients are in histological remission [62,63], if clinically viable, the achievement of histological disease control is advisable before performing esophageal dilatations in patients with EoE.

STATEMENT 39

Topical steroids, proton pump inhibitors, elimination diets, and dupilumab can be considered for the treatment of EoE. The first line approach should be accurately defined in each single patient, according to patients' characteristics, preferences, and available resources.

Agreement: 96.7% [D + (0%); D (0%); D – (0%); A- (3.3%); A (36.7%); A + (60%)]
Level of evidence: high (EoE-specific topical steroids and dupilumab), moderate (Elimination diets and inhaled/swallowed topical steroids), low (PPIs)
Recommendation: Strong

Summary of evidence

Topical steroids, proton pump inhibitors, and elimination diets have shown efficacy in terms of induction of remission in active EoE [28], and are currently recommended by international clinical guidelines as possible first line treatments for EoE [77–80]. The European Medicines Agency recently approved dupilumab for the treatment of EoE in adults and adolescents of 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medical therapy [81]. Although a recent network meta-analysis has investigated the comparative efficacy of available treatments for EoE [28], heterogeneous quality of evidence hampers strong recommendations regarding the positioning of the different treatments in the therapeutic algorithm of EoE. It must be noted, however, that currently approved drugs for EoE (BOT and dupilumab) rank high among other drugs for the induction of remission in active EoE and are superior to placebo in terms of histological remission, symptom response, end endoscopy findings improvement [28]. We therefore stress that the choice on which treatment should be the first line approach should be defined in each single patient according to patients' characteristics, preferences, and availability of resources.

BOT is the only topical steroid currently approved for the treatment of EoE in the European Union [29]. BOT has demonstrated superiority compared to placebo in terms of induction and maintenance of histological, clinical, and endoscopic remission in EoE [30,34,38]. With regards to food elimination diets, prospective non-randomized and RCTs support their use for the treatment of EoE [2,54]. Although the evidence is of moderate quality, food elimination diets have shown efficacy for induction of remission in active EoE [54]. With regards to PPIs, data coming from observational studies have shown efficacy for induction of histological remission in around 50% of patients with active EoE [19,20, 82], although one RCT showed that esomeprazole 40 mg once daily induced histological remission in 33% of patients after 8 weeks of

treatment [18]. Finally, dupilumab, a fully human monoclonal antibody that blocks the IL-4 receptor, inhibiting both IL-4 and IL-13 signaling, has shown efficacy for induction of remission in EoE patients aged 12 years or older [83]. Of note, in the dupilumab EoE trials, all patients had PPI-refractory EoE, and 73% of patients had already tried additional management including elimination diets or topical steroids, suggesting that dupilumab could be considered a second line treatment following a trial of other available treatments. In addition, a recent post-hoc analysis found that the efficacy of dupilumab is not affected by prior topical steroids treatment [84,85]. There are some scenarios in which dupilumab could be considered a first line approach in EoE. For instance, in EoE patients with concomitant asthma, atopic dermatitis, or nasal polyposis that are candidate to biologic therapy according to current management guidelines [86–88], dupilumab could be used as a first-line approach to treat both EoE and other concomitant atopic comorbidities [88]. In this regard, a retrospective study recently showed that dupilumab therapy initiated for asthma, atopic dermatitis, nasal polyposis or for compassionate use, induced symptomatic and histologic remission of EoE and reduced the need for EoE-directed therapy in a significant proportion of patients [89].

STATEMENT 40

Monoclonal antibodies without regulatory approval for EoE should not be used outside of randomized controlled trials.

Agreement: 100% [D + (0%); D (0%); D – (0%); A- (0%); A (16.6%); A + (83.4%)]
Level of evidence: High
Recommendation: Strong

Summary of evidence

Investigational biological therapies that have not gained regulatory approval for use in EoE should not be used outside of EoE RCTs, although some biologics may be a treatment option in patients with other allergic diseases[77].

Cendakimab, a monoclonal antibody against IL-13, has shown promising results in two phase II EoE RCTs [90,91]. In a 16-week double blind, randomized trial of 99 adults with active EoE, patients receiving weekly injections of Cendakimab (180 mg weekly or 360 mg weekly) were found to have a significant reduction of esophageal eosinophils count, EoE endoscopic features, and dysphagia scores compared with the placebo group [90,92]. Currently, two phase III trials (CC-93,538-EE-001 and CC-93,538-EE-002) are investigating the use of Cendakimab for induction and maintenance of remission in both adults and adolescents with active EoE.

In recent years, several RCTs have tested anti-IL5 therapies for the management of EoE[93, 94]. However, to date, none of these anti-IL5 agents adequately fulfilled the expected endpoints. In particular, Mepolizumab and Reslizumab both significantly reduced esophageal eosinophil counts in children and adolescents with EoE, but the treatments were not superior to placebo in terms of histologic remission and symptoms improvement [93,94]. In addition, results from a phase III trial investigating the use of Benralizumab, an anti-IL-5 receptor monoclonal antibody effective for the treatment of eosinophilic asthma [95], showed failure to achieve symptoms improvement at week 24 compared to placebo and was terminated. A novel target for investigational biologic therapies in EoE is TSLP. Tezepelumab is a human monoclonal antibody that binds to TSLP and blocks the interaction with its receptor [96]. Tezepelumab was approved by the Food and Drug Administration as an add-on maintenance treatment in adult and adolescents aged 12 years and older with severe asthma. A phase III trial is currently recruiting to evaluate the efficacy and safety of Tezepelumab in patients with active EoE.

STATEMENT 41

Immunomodulators (azathioprine, 6-mercaptopurine) are not recommended in patients with EoE.

Agreement: 100% [D + (0%); D (0%); D – (0%); A- (0%); A (10%); A + (90%)]
Level of evidence: Low
Recommendation: Strong

Summary of evidence

In 2007, Netzer at al. reported clinical and histological remission to azathioprine (AZA) or 6-mercaptopurine in three steroid-refractory patients with EoE [97]. However, this study lacked an internal control group and based on the low quality of evidence. To date, there are several ongoing phase 1 and 2 placebo-controlled studies aiming at assessing the efficacy of new immunomodulators on histological and clinical response in this group of patients [2]. There is currently insufficient evidence to recommend immunomodulators in active EoE.

STATEMENT 42

Anti-allergic drugs are not recommended for the treatment of EoE.

Agreement: 96.7% [D + (0%); D (0%); D – (0%); A- (3.3%); A (6.7%); A + (90%)]
Level of evidence: Low
Recommendation: Strong

Summary of evidence

Sixty-eight adult or paediatric EoE patients (19 in prospective studies, 8 in a retrospective study, 41 in a RCT) were treated with Montelukast, a leukotriene D4 antagonist. The use of Montelukast showed improvement in symptoms but failed to maintain remission induced by topical steroid therapy [98–100]. Twenty-six adults with histologically proven EoE were treated in a double-blind, placebo-controlled RCT with OC000459, a selective antagonist of CRTH2, that compared to placebo led to a modest clinical improvements [101]. Finally, in a RCT, 16 children with histologically proven EoE were treated with viscous oral cromolyn sodium, a mast-cell stabilizer, without improvements in esophageal eosinophilia or symptoms [102]. Accordingly, anti-allergic drugs are not currently recommended for clinical use in patients with EoE.

3. CHAPTER 5: MONITORING AND FOLLOW UP

STATEMENT 43

- Endoscopy with esophageal biopsies is currently the gold standard for monitoring EoE because symptoms do not correlate well with the histologic activity.
- Endoscopy with biopsy 8–12 weeks after initiation of therapy and after every therapeutic modification should be performed to assess treatment response in patients with EoE

Agreement: 96.7% [D + (0%); D (0%); D - (0%); A- (3.3%); A (16.7%); A + (80%)]
Level of evidence: High
Recommendation: Strong

Summary of evidence

Symptoms alone are not a reliable indicator of disease activity. A systematic review with meta-analysis [103] including 23 adult and paediatric studies (8 RCTs, 7 prospective and 8 retrospective

Table 2
Summary of the research agenda.

Area of research	Research need	Rationale
Pathogenesis	Improve knowledge of the pathophysiology of EoE	Role of genetic predisposition and environmental trigger factors to prevent disease onset
Diagnosis	Develop predictive model to improve the recognition of EoE and reduce diagnostic delay	Predictive models might be a useful instrument for clinicians and general practitioners to select patients for endoscopy and esophageal biopsies
	Find potential non-invasive or minimally-invasive biomarkers in EoE	Non-biopsy-based biomarkers could make less cumbersome the diagnosis and monitoring of the disease
Natural history	Improve the knowledge of natural history in treated and untreated patients	The knowledge of natural history of the disease would help in the management of the disease by identifying which patients are at higher risk of disease complications
Management	Improve knowledge on confounding factors affecting the correlation between symptom perception and histological disease activity	The assessment of confounding factors might improve disease management by allowing to reliably assess disease activity without the need for esophageal biopsies
	Assess what is the best first line therapeutic approach	Available data do not allow to establish a therapeutic hierarchy in EoE
	Role of combination treatment	Whether a combination of different treatments may have a positive impact on patients' outcomes.
	Assess the role of biologics in treatment-naïve patients	Whether biologics in treatment-naïve patients provide better outcomes than those provided in patients who failed previous treatments is unknown
	Long term management in responsive patients	Efficacy and safety data in the long term in treatment responsive patients are needed. Intervals and necessity of histological assessment in long-term clinically-responsive patients are unclear.

studies, 1202 patients) found a modest correlation ($\beta_1 = 0.64$) of symptomatic and histologic response to any therapy, with high heterogeneity. Moreover, the correlation between symptoms and histology is lower when patients undergo esophageal dilatation [67,104].

In prospective studies and RCTs, the EREFS score has been shown to be responsive to treatment in both adults and children [5,105, 106]. In a secondary analysis of a RCT involving 111 patients treated with topical steroids, Cotton at al. reported that an EREFS threshold of ≤2 was 80% sensitive and 83% specific for histologic response (AUC 0.793), and consistent with clinical response (AUC 0.547) [5]. Furthermore, a recent study has not found significant differences in reliability and responsiveness between original EREFS and its modifications (simplified and expanded versions) [107].

Since less invasive technologies and non-invasive biomarkers for EoE are not yet available in clinical practice [108], endoscopy with biopsy after 8–12 weeks after every therapeutic modification is always advised in order to assess treatment response.

STATEMENT 44

The natural history of EoE is associated with a high rate of disease relapse after treatment withdrawal.

Agreement: 100% [D + (0%); D (0%); D – (0%); A- (0%); A (20%); A + (80%)]
Level of evidence: High
Recommendation: Not Applicable

Summary of evidence

Recurrence of EoE following therapy withdrawal usually occurs within one year according to RCTs and observational studies [33, 35,109,110,111]. In a RCT, the overall rate of recurrence after withdrawal was 57%, with a median time of 244 days. Symptoms were also associated with histological relapse in 78% of the patients[34]. EoE clinical relapse also occurred in 80% of the cases after a median time of 22.4 weeks after withdrawal of other swallowed topical corticosteroids[109]. According to a retrospective, multicentre study including 75 patients taking PPI, 16 discontinued this medication due to unwillingness to take it, and 14 had symptom recurrence within one year[20].

STATEMENT 45

- Patients with EoE in clinical and histological remission should be regularly followed-up with symptomatic, endoscopic and histologic assessment to prevent disease progression.
- Patients with EoE and proven clinical and histological remission who experience symptoms relapse should undergo endoscopy with histologic assessment as soon as possible.

Agreement: 86.7% [D + (0%); D (0%); D – (0%); A- (3.3%); A (26.7%); A + (70%)]
Level of evidence: Very low
Recommendation: Conditional

Summary of evidence

There are limited data on specific follow-up intervals for reassessing EoE patients on maintenance therapy [77,79, 112]. One early natural history study in patients with EoE included 30 adults followed up for a mean period of 7.2 years [113]. Untreated EoE patients had high rates of persistent dysphagia, esophageal inflammation and remodeling resulting in stricture formation and functional abnormalities [113]. A large retrospective review of pediatric EoE followed-up over a 3.3 year period found that EoE had a chronic and relapsing course, despite repeated topical steroid treatment [114]. Accordingly, as a proportion of patients may lose long term response to maintenance therapy [50,109,115–118], follow-up, including clinical and endoscopy with histologic assessment may be reasonably indicated. As asymptomatic EoE patients may also experience a fibrotic progression with stricture complications, the follow-up should be suggested irrespectively from the presence of symptoms [73,74,119]. Recent long-term retrospective data from a cohort of 159 EoE patients in steroid maintenance treatment[119] have shown that the frequency of stricture formation was significantly lower in patients adhering to a close follow-up schedule (22.9 vs. 33.6%, p = 0.038). The absence of a close follow-up was a significant risk factor for stricture development [120].

Patients who experience symptoms relapse may have histologically active disease, supporting the recommendation to perform an EGDS with multiple esophageal biopsies in all EoE patients who experience symptoms relapse regardless of any ongoing treatment. With regards to patients in clinical remission who were in histological remission at their last EGDS and are on a stable treatment, although the absence of symptoms makes it difficult to justify an EGDS with multiple biopsies, long-term loss of response to therapy remains a concern [121]. In this regard, a retrospective study conducted on 701 patients with EoE, showed that a gap in care longer than 2 years was associated with increased disease activity and fi-

brostenotic complications, especially in those who did not receive regular follow up [122]. Based on available evidence, it is proposed that patients with EoE who are on a stable maintenance treatment and in clinical remission, with histological remission confirmed at their last EGDS, should undergo a clinical assessment after 12–18 months from their last EGDS to assess symptoms status and possible treatment-related side effects. In addition, repeat EGDS with esophageal biopsies to assess histological disease activity should be performed on a case-to-case basis when clinically indicated and based on patients' risk of asymptomatic recurrent disease.

4. RESEARCH AGENDA

Despite EoE being a relatively new disease, it has become a significant health concern, particularly in the gastroenterology and immunology community. Accordingly, the healthcare burden of EoE already exceeds that of inflammatory bowel diseases and celiac disease [123,124]. The amount of research on EoE has nearly doubled every year over the last ten years, and this is largely due to the advocacy efforts of both patients and researchers. With the advent of artificial intelligence [125,126], new tools to improve the diagnosis of EoE have become available [127]. Current standard of care treatment options may not provide an optimal disease management in the long term. In addition, it must be acknowledged that patients with EoE are burdened with a poor QoL. It is therefore our duty, together with the EoE patients' associations, to work hard to improve our knowledge and, subsequently, patients' well-being. The future research agenda should aim at filling the gap in the setting of pathogenesis, diagnosis, natural history, and management of EoE. Table 2 provides a summary of the research needs proposed by the EoETALY Consensus Group.

Data availability

No additional data available.

Author contributions

NdB, PV, RP, GB, BB, SO, MG, EVS, BA, FBS, OB, EB, ADS, LD, MF, MFu, AI, PI, MVL, EM, GM, AM, MP, ACP, IP, MR, SR, GS, ST, FZ contributed to writing, review, editing and voting. PDA, GP, FR, ER, PZ, contributed to review and editing.

Declaration of interests

Nicola de Bortoli: Advisory board member for: AlfaSigma, Sanofi Genzyme, Dr.Falk; Lecture grants from Reckitt-Benkiser, Malesci, Dr. Flak, Sofar, Alfa-Sigma, Pharma-Line.

Pierfrancesco Visaggi: Has served as speaker for Dr. Falk, JB Pharmaceuticals, Malesci.

Roberto Penagini: Has served as speaker for Dr Falk, Sanofi.

Edda Battaglia: has served as consultant for NZP, GUNA

Gaia Pellegatta has served as speaker for Dr. Falk, Sanofi Genzyme, , Malesci.

Paola Iovino: Has served as consultant for Dr. Falk

Giovanni Marasco: Served as an advisory board member for AlfaSigma, EG Pharma, Monteresearch srl, Recordati, Cineca. Received lecture grants from Agave, AlfaSigma, Bromatech, Clorofilla, Echosens, Ferring, Mayoly Spindler, Menarini and Schwabe Pharma.

Salvatore Oliva: Has served as speaker for Sanofi, Medtronic; Has served as consultant for: Sanofi, Medtronic, Brystol; Has received research support from Alfa Sigma, Medtronic.

Francesca Racca: has served as speaker for Sanofi; has served as consultant for Dr.Falk, Sanofi, GSK

Erminia Ridolo: has served as consultant for Dr Falk

Edoardo Vincenzo Savarino: has served as speaker for Abbvie, Agave, AGPharma, Alfasigma, Aurora Pharma, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Fresenius Kabi, Galapagos, Janssen, JB Pharmaceuticals, Innovamedica/Adacyte, Malesci, Mayoly Biohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr. Falk, Fenix Pharma, Fresenius Kabi, Janssen, JB Pharmaceuticals, Merck & Co, Nestlè, Reckitt Benckiser, Regeneron, Sanofi, SILA, Sofar, Synformulas GmbH, Takeda, Unifarco; he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco, Zeta Farmaceutici.

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Supplementary materials

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