

POSITION STATEMENT

Gastroenterology: Eosinophilic Gastrointestinal Disorders

Diagnosis and management of eosinophilic esophagitis in children: An update from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

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Abstract

Introduction: Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus characterized by symptoms of esophageal dysfunction and histologically by predominantly eosinophilic infiltration of the squamous epithelium. European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published a guideline in 2014; however, the rapid evolution of knowledge about pathophysiology, diagnostic criteria, and therapeutic options have made an update necessary.

Methods: A consensus group of pediatric gastroenterologists from the ESPGHAN Working Group on Eosinophilic Gastrointestinal Diseases (ESPGHAN EGID WG) reviewed the recent literature and proposed statements and recommendations on 28 relevant questions about EoE. A comprehensive electronic literature search was performed in MEDLINE, EMBASE, and Cochrane databases from 2014 to 2022. The Grading of Recommendations Assessment, Development and Evaluation system was used to assess the quality of evidence and formulate recommendations.

For affiliations refer to page 35.

Jorge Amil-Dias, Salvatore Oliva, and Alexandra Papadopoulou are joint first authors.

Disclaimers: These guidelines may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice and are intended to be an educational device to provide information that may assist clinicians in providing care to patients. These guidelines are not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may require taking a course of action that varies from these guidelines.

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Results: A total of 52 statements based on the available evidence and 44 consensus-based recommendations are available. A revision of the diagnostic protocol, options for initial drug treatment, and the new concept of simplified empiric elimination diets are now available. Biologics are becoming a part of the potential armamentarium for refractory EoE, and systemic steroids may be considered as the initial treatment for esophageal strictures before esophageal dilation. The importance and assessment of quality of life and a planned transition to adult medical care are new areas addressed in this guideline.

Conclusion: Research in recent years has led to a better understanding of childhood EoE. This guideline incorporates the new findings and provides a practical guide for clinicians treating children diagnosed with EoE.

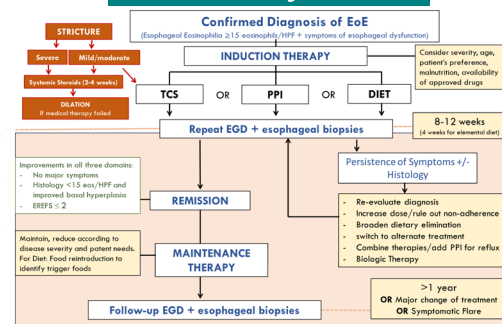
Updated ESPGHAN Guidelines For Diagnosis And Management Of Eosinophilic Esophagitis (EoE) In Paediatrics

● 52 statements ● 44 recommendations

According to the updated Guidelines on

- Simplified protocols for the diagnosis of EoE no longer require failure of a PPI trial.
- Validated tools are available for assessing symptoms and quality of life and should be incorporated in the management of children with EoE.
- The use of endoscopic and histologic scores improves diagnostic efficacy and helps monitor the inflammatory process.
- Systemic steroids may be helpful in the treatment of severe esophageal strictures.
- New biologic agents may be helpful in treating difficult cases that do not respond to or are intolerant of alternative treatments.
- A discrepancy between eosinophil depletion and symptomatic improvement requires reassessment of non-eosinophil-dependent inflammation.
- Quality of life assessment should be part of patient management.
- Implementation of programs for transition to adult care must be considered and started well before patients reach adulthood.

Treatment algorithm



Updated ESPGHAN Guidelines For Diagnosis And Management Of Eosinophilic Esophagitis In Paediatrics
Dias JA et al (2023)

JPGN
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KEYWORDS

biopsies, endoscopy, eosinophilic esophagitis, food sensitivity, histology

1 | INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus characterized by symptoms of esophageal dysfunction and by an eosinophil predominant infiltration of the squamous epithelium on histology. The condition is driven by immune mechanisms, most commonly triggered by food antigens, causing a variety of symptoms ranging from dysphagia and food impaction to growth failure. Although originally described in adults in 1993,¹ the association between EoE and response to dietary modification was reported in a pediatric cohort in 1995 leading to the identification of an entity distinct from gastroesophageal reflux.²

The first coordinated guidelines to address diagnostic criteria and treatment of EoE were published in 2007³ and subsequently revised, refining definitions and recommendations with more precise evidence-based guidance for both pediatric and adult patients.⁴ The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) published its

first pediatric guideline in 2014, with recommendations for the diagnosis and management of EoE in children.⁵ As basic, translational, and clinical research on EoE has since increased immensely, leading to rapidly evolving understanding of disease mechanisms and treatment responses, updated guidance for the diagnosis and treatment of pediatric EoE became necessary. While originally, patients whose esophageal eosinophilia regressed during treatment with proton-pump inhibitors (PPIs) were considered to have an alternative diagnosis, there is now evidence that such patients should be diagnosed with EoE.^{6,7} Some of the recently published guidelines address both adult and pediatric patients.^{7,8} However, we feel that pediatric patients have specific issues, like the predominant inflammatory phenotype and potential benefit of different diagnostic and treatment protocols that may require individual addressing and discussion. Changes to diagnostic algorithms, dietary approaches to treatment and specific management of esophageal strictures in pediatric patients are only some of the issues from the original ESPGHAN guideline that justified revision.

The current update is intended to assist healthcare providers as a framework to aid in the management of pediatric patient with EoE.

2 | METHODS

A revision of the previous guideline on EoE was performed.⁵ The consensus group consisted of pediatric gastroenterologists with expertise in EoE selected from the Eosinophilic Gastrointestinal Diseases Working Group of ESPGHAN.

A list of relevant questions was formulated to address the most relevant issues of diagnosis and management of EoE. The literature search was then performed between October 1, 2014 and December 31, 2021, using PubMed, MEDLINE, EMBASE, Cochrane Library, and Scopus databases. MESH terms are described in File S1. Non-English literature was excluded. The authors were divided into subgroups, and a list of references was built from the search criteria, relevant to each and evaluated by the members of the group according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence (QoE) (high, moderate, low, or very low quality).⁹ Recent important publications were also included to keep this document updated to the state of the art.

Statements and recommendations were discussed in virtual meetings and an electronic vote was held to rate each of them using a 6-point scale (1: *strongly disagree*; 2: *quite disagree*; 3: *somewhat disagree*; 4: *somewhat agree*; 5: *quite agree*; 6: *strongly agree*) with an opportunity to comment. These were approved if more than 80% of the participants agreed with each (Grades 4–6). The statements and recommendations that did not achieve consensus were reformulated and re-voted until agreement was reached.

Statements and recommendations were, whenever possible, based on the available evidence. When evidence from pediatric studies was not available, adult data was sought. Where there was no evidence available from randomized control trials or systematic reviews, consensus among the authors was established.

Each statement is followed with the QoE (high, moderate, low, or very low) and the result of the vote (percent agreement). Each recommendation is followed by the result of the vote (percent agreement) and strength of recommendation (SoR; strong or weak), according to GRADE methodology. In total, 28 questions were agreed upon. From these, 52 statements and 44 recommendations were formulated (Table 1).

What is Known

- There is a discrepancy between symptoms and endoscopic and histologic features.
- Allergy testing is of no value in deciding which foods to eliminate.
- EoE may cause esophageal stenosis even in pediatric patients.
- Maintenance therapy after induction is necessary

What is New

- Validated tools are available for assessing symptoms and quality of life and should be incorporated in the management of children with EoE.
- Systemic steroids may be helpful in the treatment of severe esophageal strictures.
- A discrepancy between eosinophil depletion and symptomatic improvement requires reassessment of non-eosinophil-dependent inflammation.
- Implementation of programs for transition to adult care must be considered and started well before patients reach adulthood.

Currently, patient and family involvement is advocated in the development of disease-specific guidelines to address patient needs and perspectives and to gain a better understanding of how both the disease and treatments impact quality of life. EOS Network—Eosinophilic Diseases Charity, a major patient advocacy group based in the United Kingdom, was involved as the patient advocacy representative in reviewing the manuscript to provide perspectives for patients and families.

Below are the relevant questions followed by statements, summary of evidence and recommendations, where appropriate, as well as practice points related to them.

3 | DEFINITION

Q1: Does the definition of EoE involve exclusion of response to PPI?

Statement 1.1:

EoE is defined as a chronic, local inflammatory disease of the esophagus, which may cause symptoms of esophageal dysfunction, and is characterized histologically by predominantly

TABLE 1 List of statements and recommendations.

Qn	Statement	Recommendation
Section A: Definition		
Q1: Does the definition of EoE involve exclusion of response to PPI?	<p>Statement 1.1: EoE is a chronic, local inflammatory disease of the esophagus, which may cause symptoms of esophageal dysfunction, and characterized histologically by predominantly eosinophilic infiltrates in the absence of alternative causes of eosinophilic inflammation. Agreement: 93%</p> <p>Statement 1.2: Nonresponse to PPI is no longer part of the definition of EoE. Agreement: 100%</p>	
Section B: Risk factors		
Q2: What are the risk factors for EoE?	<p>Statement 2.1: Male gender, atopy, past history of esophageal atresia and family history of EoE are risk factors for the development of EoE. Agreement: 100%</p> <p>Statement 2.2: A genetic predisposition to EoE is supported by evidence of familial clustering as well as twin studies, and susceptibility has been linked to multiple genetic loci. Agreement: 100%</p> <p>Statement 2.3: Early-life environmental factors may be associated with increased risk of developing EoE. Agreement: 90%</p> <p>Statement 2.4: Concomitant atopic diseases are more frequent in children with EoE. Agreement: 100%</p>	<p>Recommendation 2.1: ESPGHAN EGID WG recommends that pediatricians should be aware of the higher incidence of EoE disease in relatives. Agreement: 100%</p> <p>Recommendation 2.2: There is insufficient data to recommend preventive measures to reduce the likelihood of development of EoE. Agreement: 93%</p> <p>Recommendation 2.3: ESPGHAN EGID WG recommends that a high index of suspicion for EoE must be maintained in children with concomitant atopic disease. Agreement: 100%</p>
Section C: Clinical symptoms		
Q3: What are the main symptoms of EoE in pediatric patients?	<p>Statement 3: EoE symptoms vary by age, with young children and infants presenting with symptoms less specific than adolescents (e.g., mimicking reflux or feeding difficulties, and poor weight gain). Agreement: 100%</p>	
Q4: How to assess severity of symptoms suggestive of esophageal dysfunction?	<p>Statement 4: Validated tools are available to assess the severity of symptoms of esophageal dysfunction associated with EoE. Agreement: 93%</p>	<p>Recommendation 4: PEESS v2[®] should be used to assess the severity of pediatric EoE symptoms at diagnosis during disease monitoring, and when evaluating treatment response (see below on clinical monitoring). Agreement: 97%</p>

TABLE 1 (Continued)

Qn	Statement	Recommendation
Section D: Diagnosis		
Endoscopy and other invasive tests		
Q5: Can endoscopy confirm diagnosis of EoE in children?	<p>Statement 5.1: Upper GI endoscopy with biopsies from upper and lower levels of the esophagus (at least two samples from each level) remains the gold standard for diagnosis and follow-up of EoE. Agreement: 100%</p> <p>Statement 5.2: The EoE Endoscopic Reference Score (EREFS) is the most valid and reliable available endoscopic score for assessing EoE, but its use in children with EoE needs further evaluation. Agreement: 100%</p> <p>Statement 5.3: Patients with suspected EoE who underwent endoscopy during treatment with PPIs, may need to repeat endoscopy after stopping that treatment to rule out the diagnosis of EoE. Agreement: 100%</p> <p>Statement 5.4: Eosinophilic involvement of other segments of the GI tract does not exclude the diagnosis of EoE. Agreement: 97%</p> <p>Statement 6: Alternatives to conventional endoscopy under sedation or general anesthesia have been suggested, but their use is not yet standardized. Agreement: 93%</p> <p>Statement 7: The available evidence on the role of esophageal pH/impedance in the diagnostic workup of EoE in childhood is very limited and further studies are needed to establish the role of this test in patient management. Agreement: 100%</p>	<p>Recommendation 5.1: ESPGHAN EGID WG recommends using endoscopic findings as supportive evidence when evaluating suspected EoE. Agreement: 100%</p> <p>Recommendation 5.2 ESPGHAN EGID WG recommends that esophageal biopsies should be performed whenever a diagnosis of EoE is considered, regardless of the endoscopic appearance of the esophagus. Agreement: 100%</p> <p>Recommendation 5.3 ESPGHAN EGID WG recommends upper GI endoscopy with biopsies from the upper and lower levels of the esophagus (at least six, particularly targeting visible lesions) for the diagnosis and follow-up of childhood EoE. Agreement: 100%</p>
Q6: Are there less invasive alternatives to standard upper GI endoscopy?		<p>Recommendation 7: ESPGHAN EGID WG recommends against the use of pH/impedance monitoring in the diagnosis of EoE, however, it may be useful in select cases to identify associated gastroesophageal reflux. Agreement: 97%</p>
Q7: Is an esophageal pH/impedance study necessary to diagnose pediatric EoE?		
Histology		
Q8: How can histology be used for diagnosis and follow-up of EoE in children?	<p>Statement 8.1: A peak eosinophil count of at least 15 eos/HPF in esophageal biopsies is a highly sensitive and specific cutoff value for the diagnosis of EoE in a clinical context. Agreement: 93%</p> <p>Statement 8.2 The size of the HPF area depends on the technical characteristics of the microscope and differs between different microscopes. Agreement: 100%</p>	<p>Recommendation 8.1: ESPGHAN EGID WG recommends the peak value of 15 eos/HPF as the cut-off value in esophageal biopsy specimens, for the histological diagnosis of EoE in an appropriate clinical context. Agreement: 97%</p> <p>Recommendation 8.2: ESPGHAN EGID WG recommends the use of a standardized eosinophil density reporting tool. Agreement: 100%</p>

(Continues)

TABLE 1 (Continued)

Qn	Statement	Recommendation
	<p>Statement 8.3: The histological EoEHSS score is reliable for diagnosis and follow-up, however the clinical necessity of the score needs further evaluation. Agreement: 100%</p>	<p>Recommendation 8.3: ESPGHAN EGID WG recommends converting eos/HPF values to either eos/mm² or to a standardized HPF size (400 × HPF) to enable comparison of eosinophil densities examined under different microscopes and for collaborative research or consultation: eos/HPF × 1/(area of microscope HPF in mm²) = eos/mm². Agreement: 100%</p>
Allergy testing	<p>Statement 9.1: In patients with EoE, specific IgE and skin prick testing (alone or in combination) does not reliably predict triggering antigens in EoE, and the average positive predictive values of these allergy tests are less than 50%. Atopy patch testing has no place in food allergen testing. Agreement: 97%</p> <p>Statement 9.2: Controversy exists regarding the role of serum and tissue IgG4 as a predictor of food specific antigenicity in EoE or for its usefulness for disease management. Agreement: 86%</p>	<p>Recommendation 9: ESPGHAN EGID WG recommends against using available allergy tests to predict dietary triggers of EoE. Agreement: 93%</p>
Biomarkers and non-endoscopic techniques	<p>Statement 10: Several noninvasive or minimally invasive biomarkers and biomarker panels have shown promise in preliminary studies, but they are not accurate enough for routine use in the diagnosis or clinical management of EoE in children. Agreement: 100%</p>	<p>Recommendation 10: The ESPGHAN EGID WG recommends against the use of currently available biomarkers as the sole basis for the diagnosis or management of pediatric EoE patients. Agreement: 100%</p>
Section E: Treatment		
Dietary treatment		
Q11: Elimination diets: Which is the best approach?	<p>Statement 11.1: Six food elimination diet (SFED) induces remission in the majority of patients with EoE. Agreement: 93%</p> <p>Statement 11.2: A step-up approach leads to fewer endoscopies, lower costs, better patient compliance and a decrease in the number of lost school and workdays, as well as better quality of life. Agreement: 97%</p> <p>Statement 11.3:</p>	<p>Recommendation 11.1: ESPGHAN EGID WG recommends empiric elimination diets as the first-line dietary treatment of EoE in childhood; the choice of eliminated foods should be individualized, based on patients' specific needs. Agreement: 100%</p> <p>Recommendation 11.2: ESPGHAN EGID WG recommends that cow's milk, gluten-containing cereals, and eggs should be the first foods to consider for elimination when implementing step-up empirical elimination diet. Agreement: 97%</p> <p>Recommendation 11.3:</p>

TABLE 1 (Continued)

Qn	Statement	Recommendation
	The evidence of targeted elimination diet guided by standard allergy testing (including specific IgE and/or skin prick testing) to induce histologic remission is weak and shows high heterogeneity between studies. Agreement: 100%	ESPGHAN EGID WG recommends against the routine use of TED in the treatment of childhood EoE. Agreement: 97%
Q12: What is the role of Elemental diet in the treatment of EoE?	Statement 12: Amino acid-based formulas (AAF) elemental diets are highly effective in children with EoE and induce histological remission in up to 90% of patients, but drawbacks include high cost, poor compliance and palatability, that limit their use to a second-choice treatment. Agreement: 100%	Recommendation 12: ESPGHAN EGID WG suggests the use of amino-acid formula (AAF) as an option in patients with multiple food allergies, failure to thrive, or those with severe disease who do not respond, or are unable, to follow highly restricted diets. Agreement: 100%
Pharmacological treatment		
Q13: Are all topical steroids effective for induction and maintenance of remission of pediatric EoE?	Statement 13.1: Swallowed topical steroids, such as viscous budesonide and swallowed fluticasone have been shown to induce and maintain remission of EoE in both children and adults. Agreement: 100%	Recommendation 13.1: ESPGHAN EGID WG recommends the use of topical steroids as one of the first line treatment options to induce remission of EoE in children. Agreement: 100%
	Statement 13.2: There is no clear evidence of superiority among the available topical steroids. Agreement: 90%	Recommendation 13.2: ESPGHAN EGID WG recommends considering the use of topical steroids for maintenance in patients who achieve remission with topical steroids, however the optimal maintenance dose and duration need to be defined. Agreement: 100%
Q14: Are topical steroids safe even in long-term use in children?	Statement 14: Use of topical steroids for the treatment of EoE in children is safe. Agreement: 97%	Recommendation 14: ESPGHAN EGID WG recommends that the total steroid burden is calculated and considered (e.g. systemic, topical, nasal or inhaled) when treating EoE with topical steroids, as the combination may lead to increased cumulative steroid exposure and possible adrenal insufficiency. Agreement: 100%
Q15: PPI treatment effective for induction of remission in EoE?	Statement 15: PPIs can induce remission in a proportion of pediatric patients with EoE. Agreement: 100%	Recommendation 15: ESPGHAN EGID WG recommends the use of proton-pump inhibitors as one of the first line treatment options to induce remission of EoE in children. Agreement: 100%
Q16: Is PPI treatment effective in maintenance of remission in EoE?	Statement 16: PPIs at lower doses are effective as maintenance therapy in patients who have achieved remission on these drugs. Agreement: 97%	Recommendation 16: ESPGHAN EGID WG recommends the use of proton-pump inhibitors to maintain remission in PPI-responsive children. Agreement: 100%
Q17: What is the ideal treatment for induction?	Statement 17: PPIs, empiric elimination diets and topical steroids are all options for first-line induction treatments because of their efficacy and safety. Agreement: 100%	Recommendation 17: ESPGHAN EGID WG recommends induction treatment of childhood EoE with either PPI, elimination diet or topical steroids with no evidence of preference. Agreement: 90%

(Continues)

TABLE 1 (Continued)

Qn	Statement	Recommendation
Q18: How long should the induction phase last?	Statement 18: The duration of induction may vary depending on the treatment chosen and disease severity at presentation. Agreement: 93%	Recommendation 18: ESPGHAN EGID WG recommends minimum 8 to 12-weeks of induction for patients on elimination diets, topical steroids or PPIs and not less than 4 weeks on elemental diets before endoscopic reassessment. Agreement: 100%
Q19: Should maintenance treatment be recommended to all patients?	Statement 19: Maintenance treatment is necessary to keep remission after induction treatment. Agreement: 100%	Recommendation 19: ESPGHAN EGID WG recommends maintenance therapy to all patients after achieving histological remission. Agreement: 97%
Q20: How long should maintenance treatment be recommended?	Statement 20.1: Most patients require long-term treatment to maintain clinical and histological remission. Agreement: 100%	Recommendation 20.1: ESPGHAN EGID WG recommends a maintenance period of at least 1 year. Agreement: 90%
	Statement 20.2: Reduction or maintenance of treatment may be guided by disease phenotype and severity, and the specific needs of patients. Agreement: 97%	Recommendation 20.2: ESPGHAN EGID WG suggests that decisions to maintain, reduce, or withdraw treatment should be determined by the severity of the disease and the specific needs of the patient. Agreement: 97%
Q21: How should patients be assessed during the maintenance phase? How often?	Statement 21: There is no evidence on the frequency of follow ups in an asymptomatic patient with EoE Agreement: 97%	Recommendation 21.1: ESPGHAN EGID WG recommends periodic clinical assessment, and individualized endoscopic and histologic evaluations during maintenance phase. Agreement: 97%
		Recommendation 21.2: ESPGHAN EGID WG recommends endoscopic and histological evaluation in case of clinical relapse during maintenance. Agreement: 100%
		Recommendation 21.3: ESPGHAN EGID WG suggests endoscopic and histological re-evaluation after 1-3 years during the maintenance phase in cases of stable clinical remission. Agreement: 100%
Clinical predictors of treatment response		
Q22: What are the predictors of treatment response and risk factors for tissue remodeling in patients with EoE?	Statement 22.1: Duration of noncontrolled EoE disease is an important risk factor for developing fibrostenotic disease, but there are currently no accurate clinical predictors of response to different EoE treatments at the time of diagnosis. Agreement: 97%	Recommendation 22: ESPGHAN EGID WG recommends awareness of disease manifestations and individualized EoE treatment to prevent esophageal tissue remodeling and potential stricture formation. Agreement: 100%
	Statement 22.2: Early diagnosis and effective EoE treatment are important to prevent esophageal remodeling and the risk of stricture formation. Agreement: 100%	

TABLE 1 (Continued)

Qn	Statement	Recommendation
Treatment of refractory EoE		
Q23: Are there other treatment for refractory EoE?	<p>Statement 23.1: Anti-IL-13 and anti-IL-4 receptor antibodies have shown benefit for treatment of adults and teenagers with EoE. Agreement: 100%</p> <p>Statement 23.2: There is limited evidence on treatment with anti-IL-5α and anti-IL-5 antibodies in children with EoE. Agreement: 93%</p> <p>Statement 23.3: Neither the CRTH2 antagonist OC000459 nor the mast cell stabilizer cromolyn sodium are effective in inducing clinical and histological remission in patients with EoE. Agreement: 100%</p> <p>Statement 23.4: Montelukast (a leukotriene receptor antagonist) is not effective in maintaining clinical and histological remission in EoE. Agreement: 100%</p> <p>Statement 23.5: There is no evidence of efficacy of thiopurines in children with EoE. Agreement: 90%</p> <p>Statement 23.6: Omalizumab is not effective in the treatment of pediatric EoE. Agreement: 100%</p>	<p>Recommendation 23.1: ESPGHAN EGID WG recommends that dupilumab can be used in selected cases of children over 1 year old weighing >15 kg with EoE refractory to conventional treatment and in those with concomitant atopic burden with approved indications for biologics. Agreement: 100%</p> <p>Recommendation 23.2: ESPGHAN EGID WG suggests against the routine use of other biologics to treat childhood EoE, but they may be considered in clinical trials or specialized centers until such drugs obtain regulatory agency approvals. Agreement: 97%</p> <p>Recommendation 23.3: ESPGHAN EGID WG recommends against the use of CRTH2 antagonist OC000459 for treatment of pediatric EoE. Agreement: 100%</p> <p>Recommendation 23.4: ESPGHAN EGID WG suggests against the use of cromolyn sodium, or leukotriene receptor antagonists for treatment of pediatric EoE. Agreement: 100%</p> <p>Recommendation 23.5: ESPGHAN EGID WG recommends against the routine use of thiopurines for treatment of children with EoE refractory to first line treatment. Agreement 100%</p> <p>Recommendation 23.6: ESPGHAN EGID WG recommends against the use of omalizumab for the treatment of pediatric EoE. Agreement: 97%</p>
Esophageal strictures—How to treat and follow-up?		
Q24: What is the best method for diagnosing esophageal strictures in pediatric patients with EoE?	<p>Statement 24.1: Endoscopic assessment and barium swallow are complementary for the evaluation of suspected strictures or narrow-caliber esophagus in patients with EoE. Agreement: 100%</p> <p>Statement 24.2: Endoscopy has the advantage of being able to assess inflammatory aspects of EoE, while barium studies can assess the length, severity and positioning of a narrow caliber esophagus. Agreement: 100%</p>	<p>Recommendation 24.1: ESPGHAN-EGID WG recommends a barium swallow before dilation if the anatomy or caliber of the esophagus cannot be clearly defined by upper GI endoscopy. Agreement: 97%</p> <p>Recommendation 24.2: Patient characteristics such as age, symptoms and chronicity of symptoms should be considered when devising a diagnostic plan. Agreement: 97%</p>

(Continues)

TABLE 1 (Continued)

Qn	Statement	Recommendation
Q25: Is esophageal dilation necessary and safe for of strictures in pediatric EoE?	Statement 25.1: Inflammatory esophageal strictures may regress with standard medical/dietary treatment. Agreement: 97%	Recommendation 25.1: ESPGHAN-EGID WG recommends esophageal dilatation in highly selected cases with severe esophageal narrowing that persists despite other forms of treatment or in cases where a rapid symptomatic improvement in required. Agreement: 100%
	Statement 25.2: Esophageal dilation is safe and can rapidly improve symptoms of dysphagia, without affecting the ongoing inflammatory process. Agreement: 97%	Recommendation 25.2: ESPGHAN EGID WG suggests that a short course of systemic steroids be considered as an alternative to dilation in the presence of moderate to severe esophageal strictures with severe symptoms. Agreement: 93%
	Statement 25.3: Treatment with short term systemic steroids can significantly reduce the need for mechanical esophageal dilation in moderate to severe strictures associated with pediatric EoE. Agreement: 93%	
	Statement 26: Both hydrostatic balloon dilatation and Savary-Gilliard bougies are effective and safe in children with EoE, with very low complication rates. Agreement: 100%	Recommendation 26: ESPGHAN-EGID WG suggests the use of either hydrostatic balloons or Savary-Gilliard bougies for esophageal dilation as both are safe and effective. The choice of technique should be based on the experience of physician. Agreement: 100%
Section F: Quality of life—How to assess?		
Q27: How is health related quality of life (HRQoL) defined and best assessed in children with EoE and parent proxy?	Statement 27.1: Health related quality of life in children with EoE and in their parent proxies can be assessed accurately with validated questionnaires. Agreement: 97%	Recommendation 27: ESPGHAN EGID WG recommends the use of validated HRQoL questionnaires in the care of patients with EoE as one of the composite outcome measures evaluating treatment response, following translation and validation in different languages. Agreement: 93%
	Statement 27.2: Health related quality of life assessed with validated questionnaires, correlates inversely with clinical and histological disease activity, as well as with the use of an elimination diet.	
Section G: Transition in eosinophilic esophagitis		
Q28: How should transition of care be addressed in pediatric patients with EoE?	Statement 28: A multidisciplinary team of pediatric and adult gastroenterologist, dietitian and a transition coordinator is optimal for a successful transition to adult care, as well as a joint review of the medical records and disease course, followed by a joint visit with patient, parents and team present. Agreement: 93%	Recommendation 28: The ESPGHAN EGID WG recommends that a multidisciplinary team engaging pediatric and adult specialists (physician, dietitian, nurse and psychologist) work closely in a individualized process of handing-over the care of patients at the end of adolescence. Agreement: 97%

eosinophilic infiltrates in the absence of alternative causes of eosinophilic inflammation.

QoE: Moderate → Agreement: 93%

Statement 1.2:

Non-Response to PPI is no longer part of the definition of EoE.

QoE: High → Agreement: 100%.

Summary of evidence:

Changes to the case definition of EoE revolve around the role of PPIs in the disease. Historically, EoE was thought to present similarly to gastrointestinal reflux disease (GERD), which was also thought to be a major cause of esophageal eosinophilia and distinguishing between the two represented a diagnostic challenge. Therefore, the original EoE guidelines recommended either 24-h pH monitoring or a 2-month trial with high-dose PPIs to rule out GERD as a cause of symptoms and eosinophilic infiltrates before diagnosing EoE.³ However, it soon became clear that the two conditions could coexist, and it has been suggested that each condition could aggravate or lead to development of the other.¹⁰ GERD could potentially cause epithelial dysfunction allowing antigenic stimulation, while the dysmotility associated with EoE could exacerbate pathologic GERD. Consequently, the exclusion of GERD was no longer a prerequisite for the diagnosis of EoE. Subsequently, studies showed that a significant proportion of patients with clinicopathologic features of EoE but no evidence of pathologic esophageal acid exposure respond to treatment with PPIs.^{11–15} In addition, several anti-inflammatory and barrier-protective mechanisms of action of PPIs have been recognized independently of their antisecretory effects.^{16–18} This led to the establishment of a new disease entity distinct from EoE, termed PPI-responsive esophageal eosinophilia (PPI-REE). Diagnostic guidelines from 2011, 2013, and 2014 called for the exclusion of PPI-REE through an 8-week trial of high-dose PPIs and repeat endoscopy before diagnosing EoE.^{4,5,19} Nevertheless, further studies showed that PPI-REE could not be distinguished clinically, endoscopically, or histologically from EoE, and even the esophageal transcriptomes of the esophagus were virtually indistinguishable between the two entities, in contrast to the significantly different transcriptome in GERD.^{11–13,20–26} Moreover, PPI-responsive patients could also respond to topical steroids or elimination diets.^{27,28} Consistently with these recent findings, the 2017 guidelines and the 2018 international consensus from the AGREE conference classified all patients with symptoms of esophageal dysfunction with eosinophil-predominant esophagitis lacking an alternative diagnosis, as EoE.^{6,7} According to these new definitions, which have been incorporated into the current guideline, patients who achieve clinical and histological remission with PPI

therapy are diagnosed with EoE, and therapeutic trials of PPIs have been removed from the diagnostic algorithm. The role of PPIs is now a treatment option rather than an exclusionary criterion for the disease. Medical or dietary interventions performed at the time of a diagnostic endoscopy must be considered when interpreting endoscopy and biopsy results.

4 | RISK FACTORS

Q2: What are the risk factors for EoE?

Statement 2.1:

Male gender, atopy, past history of esophageal atresia and family history of EoE are risk factors for the development of EoE.

QoE: Moderate → Agreement: 100%.

Statement 2.2:

NA genetic predisposition to EoE is supported by evidence of familial clustering as well as twin studies, and susceptibility has been linked to multiple genetic loci.

QoE: Moderate → Agreement: 100%.

Statement 2.3:

Early-life environmental factors may be associated with increased risk of developing EoE.

QoE: Moderate → Agreement: 90%.

Statement 2.4:

Concomitant atopic diseases are more frequent in children with EoE.

QoE: High → Agreement: 100%.

Summary of evidence:

Male gender is a risk factor for developing EoE with an odds ratio of 2.01, as found in several studies and one systematic review.^{28,29} Twin and family studies have shown that genetic factors are important, but that the environment also plays an important role.²⁹

Three approaches have been used to identify possible genetic factors associated with EoE: Association of EoE with Mendelian disorders, identification of candidate genes, and genome-wide association studies (GWAS). Only a minority of patients develop EoE in association with genetic syndromes such as connective tissue disorders, PTEN-hamartoma tumor syndromes, severe dermatitis, multiple allergies, and metabolic wasting syndrome (SAM syndrome).³⁰ Genetic variants with candidate genes at Chemokine (C-C motif) ligand 26 (CCL26), Filaggrin (FLG), cytokine receptor-like

factor 2 (CRLF2), and Desmoglein 1 (DSG1) have been identified with increased risk for EoE. GWAS approaches have identified and replicated the association of genetic variants at loci encoding Thymic stromal lymphopoietin/WD Repeat Domain 36 (TSLP/WD36), Calpain 14 (CAPN14), Leucine Rich Repeat Containing 32 LRRC32/C11orf30, Signal transducer and activator of transcription 6 (STAT6), and Ankyrin Repeat Domain 27 (ANKRD27) with EoE risk.³¹ Some of these genetic variants have been associated with other allergic diseases. To determine whether EoE risk loci are independently associated with EoE from other allergic diseases, a logistic regression strategy was applied to each of the published EoE GWAS loci and found that loci 5q22, 11q13, and 12q13 are the most specific risk loci for developing EoE.³²

Early-life environmental factors have been associated with the development of EoE. Jensen et al. observed positive associations between early life factors and EoE, including prenatal factors (maternal fever: adjusted odds ratio [OR]: 3.18, 95% confidence interval [CI]: 1.27–7.98; preterm labor: OR: 2.18, 95% CI: 1.06–4.48), intrapartum (cesarean section: OR: 1.77, 95% CI: 1.01–3.09), and postnatal factors (antibiotic use: OR: 2.30, 95% CI: 1.21–4.38; use of PPI: OR: 6.05, 95% CI: 2.55–14.40).³³ At least two other case-control studies confirmed the proposed associations.^{34,35} In the latter study, erythema toxicum neonatorum was mentioned as a possible predisposing factor for the development of EoE, possibly mediated through epigenetic changes caused by environmental factors that could lead to the development of EoE later in life. While some of the above environmental factors in early childhood are preventable, currently available evidence does not yet support a recommendation for specific preventive measures. Early antibiotic and PPI use should, in any case, be limited to necessary and proven indications for their use.

An increased prevalence (9.5%–17%) of EoE has been reported in children following repair of congenital esophageal atresia (EA).^{36,37} EoE should be considered in EA patients with persistent symptoms on standard reflux treatment.³⁸

Atopic conditions such as asthma, atopic rhinitis, IgE mediated food allergy and eczema are more common in pediatric patients with EoE. Three recent retrospective studies examined differences in the prevalence of comorbidities in children with and without EoE.^{39–41} The studies consistently reported significantly higher frequencies of comorbid atopic conditions in children with EoE. An association between atopic diseases and EoE was also demonstrated in a prospective pediatric study in which demographic, clinical, serologic, endoscopic, and atopic characteristics of patients with EoE were analyzed to identify atopic and digestive comorbidities (35 EoE, mean age

9.6 years. The main atopic comorbidities in this group of patients were asthma (48%) and allergic rhinitis (37%).⁴²

A protective role for *Helicobacter pylori* infection against the development of EoE has been suggested, however evidence is conflicting. The rationale behind this association is that the immunomodulatory properties of *H. pylori*, polarizing the immune system towards Th-1 response, may confer protection against Th-2 mediated allergic disorders. Therefore, an inverse association between increasing EoE prevalence and declining rate of *H. pylori* infection has been reported in two retrospective studies in children.^{43,44} In contrast, more recent results of a large prospective case-control study conducted in 23 centers enrolling more than 800 participants reported an overall prevalence of *H. pylori* infection 38%.⁴⁵ According to the authors, the prevalence of *H. pylori* infection was not different between EoE cases and controls (37% vs. 40%, OR: 0.97, 95% CI: 0.73–1.30, $p = 0.3$), neither in children (42% vs. 46%, $p = 0.1$) nor in adults (36% vs. 38%, $p = 0.4$).

It has been suggested that the prevalence of EoE is higher in patients with other diseases such as celiac disease (5.6% of EoE, 0.9% of non-EoE, $p < 0.0001$); connective tissue diseases (1.4% of EoE, 0.1% of non-EoE, $p < 0.0001$); cystic fibrosis (0.9% of EoE, 0.05% of non-EoE, $p < 0.0001$); inflammatory bowel disease (0.7% of EoE, 0.2% of non-EoE, $p = 0.03$) and type 1 diabetes mellitus (1.2% of EoE, 0.3% of non-EoE, $p = 0.0069$).³⁹ In contrast, Lucendo et al. did not find definitive evidence for an association between EoE and celiac disease⁴⁶ as individual reports may have been the subject of selection bias towards patients with celiac disease who are subject to endoscopy.

Recommendation 2.1:

ESPGHAN EGID WG recommends that pediatricians should be aware of the higher incidence of EoE in relatives.

SoR: Strong → Agreement: 100%.

Recommendation 2.2:

There is insufficient data to recommend preventive measures to reduce the likelihood of development of EoE.

SoR: Weak → Agreement: 93%.

Recommendation 2.3:

ESPGHAN EGID WG recommends that a high index of suspicion for EoE must be maintained in children with concomitant atopic disease.

SoR: Strong → Agreement: 100%.

5 | CLINICAL SYMPTOMS

Q3: What are the main symptoms of EoE in pediatric patients?

Statement 3:

EoE symptoms vary by age, with young children and infants presenting with symptoms less specific than adolescents (e.g., mimicking gastro-esophageal reflux or feeding difficulties, and poor weight gain).

QoE: High → Agreement: 100%.

Summary of evidence:

EoE causes esophageal inflammation and dysmotility, both of which may contribute to the patient's symptoms. In older children and adolescents, the most common symptoms are solid food dysphagia and esophageal food impaction. However, chest pain unrelated to swallowing can also occur.^{47–49} In younger children and infants, symptoms tend to be more varied and less specific.^{49,50} They can mimic gastro-esophageal reflux symptoms such as vomiting, epigastric abdominal pain, food refusal, eating slowly or requiring water during the meal, coughing while feeding, heartburn or, less frequently, hematemesis. Failure to thrive due to persistent feeding difficulties may be present.

A high degree of clinical suspicion is required, especially in infants with less specific symptoms, and appropriate investigations, including endoscopy with multilevel biopsies, should be performed to make a definitive diagnosis that will allow administration of appropriate treatment.

Q4: How to assess severity of symptoms suggestive of esophageal dysfunction?

Statement 4:

Validated tools are available to assess the severity of symptoms of esophageal dysfunction associated with EoE.

QoE: Moderate → Agreement: 93%.

Summary of evidence:

Patient-reported outcomes are increasingly recognized as important in the management of chronic disease. The Pediatric EoE Symptom Score (PEESS® v2.0) was developed to identify and assess outcomes that are important for patients with EoE.⁵¹ PEESS® v2.0 contains 20 questions grouped into four main domains: dysphagia, GERD, nausea/vomiting, and pain developed for self- and parent proxy- report. The above domains have been validated and demonstrated that they are consistent with clinical symptoms and

histopathological features.⁵² In particular, Martin et al. showed that the parent's report is effective in capturing the child's symptoms, that there is a correlation between symptoms and the eosinophil activity marker EPX staining, that there is a correlation between dysphagia and mast cells infiltration (and their markers), and that PEESS® v2.0 is an objective measure of patient symptomatology, that can be used to assess response to treatment and to better understand the association between biological changes and patient and parent perceptions of well-being. It should be noted however that although PEESS® can be used to assess symptoms severity, it cannot be used to distinguish EoE from non-EoE dysphagia.⁵³

Recommendation 4:

PEESS v2® should be used to assess the severity of pediatric EoE symptoms at diagnosis during disease monitoring, and when evaluating treatment response (see below on clinical monitoring).

SoR: Strong → Agreement: 97%.

6 | DIAGNOSIS

6.1 | Endoscopy and other invasive tests

Q5: Can endoscopy confirm diagnosis of EoE in children?

Statement 5.1:

Upper GI endoscopy with at least 6 biopsies from upper and lower levels of the esophagus (at least two samples from each level) remains the gold standard for diagnosis and follow-up of EoE.

QoE: Low → Agreement: 100%.

Statement 5.2:

The EoE Endoscopic Reference Score (EREFS) is the most valid and reliable available endoscopic score for assessing EoE, but its use in children with EoE needs further evaluation.

QoE: Low → Agreement: 100%.

Statement 5.3:

Patients with suspected EoE who underwent endoscopy during treatment with PPIs, may need to repeat endoscopy after stopping that treatment to rule out the diagnosis of EoE.

QoE: Moderate → Agreement: 100%.

Statement 5.4:**Eosinophilic involvement of other segments of the GI tract does not exclude the diagnosis of EoE.**

QoE: Moderate → Agreement: 97%.

Summary of evidence:

The EoE Endoscopic Reference Score (EREFS) is an easy-to-use, reproducible, and validated score that captures pathologic endoscopic findings associated with EoE. The score assesses the severity of inflammatory features (exudates, edema, furrows), which are more common in young children, and fibrostenotic features (rings and strictures), which are more common in older patients.^{54,55} In addition, crepe paper esophagus is reported a minor sign in some iterations of the EREFS. Children are more likely to have exudates (92.5%), while adults are more likely to have fixed esophageal rings (50% vs. 5%) and stenosis (17.5% vs. 2.5%). In adults with EoE, EREFS correlates with peak eosinophil counts, but its predictive value for the diagnosis or assessment of disease activity is insufficient to preclude histologic evaluation.^{56–63} Therefore, biopsies remain essential for assessing disease activity. Additional pediatric data are needed to confirm the sensitivity and specificity of EREFS for diagnosing and assessing treatment responses in children with EoE.^{54,55,62–64} Scores in older children (>10 years) had a higher predictive value with a higher sensitivity (0.89 vs. 0.63) and a higher negative predictive value (0.87 vs. 0.59), than in younger children (≤10 years).^{54,55} Moreover, it should be noted that up to one-third of children with EoE may have normal macroscopic appearance of their esophagus.^{55,65–68}

The EREFS has also been used to assess EoE activity.^{69–72} An EREFS of ≤2 was associated with well-controlled disease activity and was suggested as a threshold for endoscopic response to therapy. An EREFS of three or four could be considered a partial response and an EREFS of five or more an endoscopic nonresponse.⁷³ However, patients with significant histological disease activity may have low scores, and therefore intra-patient score changes over time may be more meaningful than a single EREFS. Therefore, a combination of clinical, endoscopic and histological features, taking into account age and sex, should be considered to predict the presence of EoE with a high degree of accuracy.⁷⁰

It was recently agreed that EoE may coexist with eosinophilic infiltration of other segments of the GI tract. If the predominant symptoms are suggestive of esophageal dysfunction, then the diagnosis of EoE is applied and is associated with identification of the other affected GI segments (EoE with gastric/duodenal/jejunal/ileal or colonic involvement). If, however, the predominant symptoms are of other GI segments, then the diagnosis of EoE is no longer applicable and should

be replaced by “Eosinophilic gastritis, enteritis or colitis with esophageal involvement.”⁷⁴

Recommendation 5.1:

ESPGHAN EGID WG recommends using endoscopic findings as supportive evidence when evaluating suspected EoE.

SoR: Strong → Agreement: 96%.

Recommendation 5.2:

ESPGHAN EGID WG recommends that esophageal biopsies should be performed whenever a diagnosis of EoE is considered, regardless of the endoscopic appearance of the esophagus.

SoR: Strong → Agreement: 100%.

Recommendation 5.3:

ESPGHAN EGID WG recommends upper GI endoscopy with biopsies from the upper and lower levels of the esophagus (at least six, particularly targeting visible lesions) for the diagnosis and follow-up of childhood EoE.

SoR: Strong → Agreement: 100%.

Practice points:

The EoE Endoscopic Reference Score (EREFS) is currently the most valid and reliable endoscopic metric and can be used in conjunction with symptoms and histology as supportive evidence at diagnosis and when assessing response to treatment in pediatric EoE.

Q6: Are there less invasive alternatives to standard upper GI endoscopy?**Statement 6:**

Alternatives to conventional endoscopy under sedation or general anesthesia have been suggested, but their use is not yet standardized.

QoE: Low → Agreement: 93%.

Summary of evidence:

Alternatives to conventional sedated endoscopy have been suggested. Unsedated transnasal endoscopy (TNE) is safe, less expensive than sedated esophago-gastroduodenoscopy (EGD) and can be performed with topical anesthesia (utilizing audio or visual distractions to decrease patient discomfort). TNE has been studied in the treatment of pediatric EoE, and was found to be safe, provided adequate biopsy samples, was cost-effective, and required less office time than standard endoscopy; 85% of parents but only 52% of pediatric patients preferred it to standard endoscopy with sedation.^{75–77} This requires further validation in larger cohorts.

Both upper endoscopy (EGD) or barium swallow (BS) have been used to identify remodeling sequelae of EoE, each with variable sensitivity. However, inflammatory features are better assessed with EGD.^{66,78–84} The inadequate sensitivity and specificity of EGD for the composite features of EoE limit its potential as a stand-alone diagnostic test. Both BS and EGD can detect fibrostenotic changes not detected by their counterpart and are therefore complementary tests in selected patients.^{36,49,76,78–88} BS may be helpful in determining the length of esophageal strictures and identifying narrow-caliber esophagus that are difficult to assess with endoscopy.

Probe-assisted confocal endomicroscopy, magnifying endoscopy with narrow-band imaging, and endoscopic esophageal ultrasound are promising for evaluating pathologic findings but require further study.^{89,90}

Functional luminal imaging probe (FLIP) measures diameter and distensibility of the esophagus. Endoscopic grading of rings has a significant correlation with distensibility parameters measured with FLIP but not with mild inflammatory features of the EoE.⁹¹ The role of FLIP in clinical practice is not yet clear.

High-resolution manometry can reveal the consequences of esophageal fibrostenotic remodeling on motility in EoE, but its use in patient management has yet to be defined.⁹²

Practice point:

Unsedated Transnasal Endoscopy (TNE) may be considered as a valid alternative to standard endoscopy.

Q7: Is an esophageal pH/impedance study necessary to diagnose pediatric EoE?

Statement 7:

The available evidence on the role of esophageal pH/impedance in the diagnostic workup of EoE in childhood is very limited and further studies are needed to establish the role of this test in patient management.

QoE: Low → Agreement: 100%.

Summary of evidence:

Gastroesophageal reflux may play a role in the pathogenesis of EoE, and abnormal pH-mucosal impedance (pH-MII) tests have been identified in patients with EoE.⁹³ In addition, these tests may help identify patients who are more responsive to PPI treatment.⁹⁴ Despite some correlation between low baseline impedance and mucosal inflammation due to eosinophilic infiltration, the correlation with peak eosinophil counts is low. Impedance tests can, however, be helpful in the differential diagnosis on an individualized basis.^{95,96}

Recommendation 7:

ESPGHAN EGID WG recommends against the use of pH/impedance monitoring in the diagnosis of EoE, however, it may be useful in select cases to identify associated gastroesophageal reflux.

SoR: Strong → Agreement: 97%.

Practice points:

Esophageal pH/impedance may be warranted at the time of diagnosis in children with suspected EoE with symptoms of GERD or co-existing unexplained respiratory symptoms that may be due to concomitant reflux, when endoscopic/histological findings are inconclusive, or when there is a mismatch between symptoms and histologic treatment response.

6.2 | Histology

Q8: How can histology be used for diagnosis and follow-up of EoE in children?

Statement 8.1:

A peak eosinophil count of at least 15 eos/HPF in esophageal biopsies is a highly sensitive and specific cutoff value for the diagnosis of EoE in a clinical context.

QoE: Moderate → Agreement: 93%.

Statement 8.2:

The size of the HPF area depends on the technical characteristics of the microscope and differs between different microscopes.

QoE: Moderate → Agreement: 100%.

Statement 8.3:

The histological EoEHSS is reliable for diagnosis and follow-up, however the clinical necessity of the score needs further evaluation.

QoE: Moderate → Agreement: 100%.

Summary of evidence:

The Eosinophilic Esophagitis Histology Severity Score (EoEHSS) for esophageal biopsies evaluates eight features: Eosinophil density, basal zone hyperplasia, eosinophilic abscesses, eosinophilic surface layering, dilated intercellular spaces (DIS), epithelial surface alterations, dyskeratotic epithelial cells, and lamina propria fibrosis. Severity (grade) and extent (stage) of abnormalities are assessed using a 4-point scale (0 normal; 3 maximal change).⁹⁷ The EoEHSS histologic score provides a method for evaluating histologic changes in the esophagus that goes beyond

eosinophil counts and can provide a more complete pathologic picture of tissue damage. While adding detail which may be helpful in patient follow-up and its clinical utility beyond a standard eosinophil count and description of basal hyperplasia in the pathology report needs to be further assessed for standard clinical use.

Histopathological reports of EoE patients should include either the area of the high-power field used or the eosinophil density per mm.^{2,97–99} Although the distribution of eosinophils in the esophagus can be patchy, the defined cut-off value of 15 eos/hpf (standardized to a field size of 0.27 mm²) taken as the peak concentration in the biopsy is both sensitive and specific for the diagnosis of EoE.¹⁰⁰ The area of 0.27 mm² has been used as the standardized HPF area in the CEGIR consortium studies and can be adopted worldwide to standardize reports by HPF area.

Mast cell density has been reported to correlate with basal zone hyperplasia, dilated intercellular spaces, and furrows, but the clinical relevance is not yet known.

The need to evaluate histology at multiple esophageal levels derives from studies that showed that some patients would be missed if only distal biopsies were taken.^{101,102}

Normalization of eosinophils in the esophageal mucosa is one of the main goals of treatment, along with improvement of symptoms and endoscopic appearance as well as decrease in basal hyperplasia. The definition of histological remission is controversial, as it varies from study to study. The recent COREOS consensus, a very broad consensus of 69 experts, addressed this issue, but in the context of therapeutic and observational studies that differ from clinical practice.¹⁰³ In that consensus, remission was defined as <6 and <15 eos/hpf (25–60 eos/mm²) in RCTs and observational studies, respectively. The experts pointed out that in practice, complete elimination of eosinophils from the esophagus is often not achieved and therefore the less restrictive definition might be a reasonable target. In the summaries of evidence included in our guideline we have inserted whenever appropriate the therapeutic target defined by the authors of the discussed studies.

Recommendation 8.1:

ESPGHAN EGID WG recommends the peak value of 15 eos/HPF as the cut-off value in esophageal biopsy specimens, for the histological diagnosis of EoE in an appropriate clinical context.

SoR: Strong → Agreement: 100%.

Recommendation 8.2:

ESPGHAN EGID WG recommends the use of a standardized eosinophil density reporting tool.

SoR: Strong → Agreement: 100%.

Recommendation 8.3:

ESPGHAN EGID WG recommends converting eos/HPF values to either eos/mm² or to a standardized HPF size (CEGIR HPF) to enable comparison of eosinophil densities examined under different microscopes and for collaborative research or consultation: eos/HPF × 1/(area of microscope HPF in mm²) = eos/mm².

SoR: Strong → Agreement: 100%.

Practice points:

Isolated lower esophageal eosinophilia may pose a higher diagnostic challenge than upper esophageal involvement.

6.3 | Allergy testing

Q9: What is the role of specific IgE and other allergy testing to identify causative food triggers of EoE?

Statement 9.1:

In patients with EoE, specific IgE and skin prick testing (alone or in combination) does not reliably predict triggering antigens in EoE, and the average positive predictive values of these allergy tests are less than 50%. Atopy patch testing has no place in food allergen testing.

QoE: Low → Agreement: 97%.

Statement 9.2:

Controversy exists regarding the role of serum and tissue IgG4 as a predictor of food specific antigenicity in EoE or for its usefulness for disease management.

QoE: Low → Agreement: 86%.

Summary of evidence:

Cumulative data since the first ESPGHAN guideline and previous reports support the concept that specific IgE testing and skin prick testing, as well as atopy patch testing (APT) are of limited value in identifying triggering food antigens responsible for EoE.^{104–111}

Positive skin prick and atopy patch tests, assessing immediate and delayed type responses, respectively, are not reliable in prediction of response to targeted elimination diets in either adult or pediatric patients with EoE.

Most of the evidence was summarized in a meta-analysis published in 2014 which included 1317 patients with EoE (1128 children and 189 adults) receiving different dietary treatments. The strategy of eliminating foods to which a positive skin test was performed (Allergy Testing-Directed Food Elimination) was evaluated in 14 different

studies (of which only 2 included adults) in 626 patients (594 children and 32 adults). Overall efficacy was 45.5% (95% CI: 35.4–55.7), but with a wide variation in response rate ($I^2 = 75.1\%$).¹¹² The two studies conducted in adult patients showed a significantly lower response rate of only 26.6% and 35%. The high efficacy reported by Spergel et al. who identified potential food triggers for EoE in 2002 using a combination of skin prick tests and atopy patch tests,¹¹³ has not been replicated by others. Meta-analysis reported that the combined efficacy of targeted elimination diets did not reach 50% and that remission rates reported in individual studies varied widely.¹¹²

In a more recent, small, prospective pediatric study from 2011 to 2016, EoE remitted in 77% (17/22) of patients who completed a targeted elimination diet based on food-specific IgE (if ≥ 0.1 kU/L, sIgE-ED) to cow's milk, wheat, egg, lentils, peanuts, and hake/shrimp. The authors concluded that the results were comparable to those of the classic six-food empiric elimination diet (EED), with the advantage that fewer foods were eliminated, and the average number of endoscopies was lower.¹¹⁴ However, if these patients had undergone a step-up empiric elimination approach, the number of foods eliminated and the number of endoscopies would have been even lower than with the targeted approach.¹¹⁵

Another recent strategy based on IgE testing has failed to predict foods as triggers for EoE.¹¹⁶ A pilot study in adults investigating a targeted elimination diet (TED) based on blood IgE microarray results (e.g., measuring IgE levels for dietary protein components) showed extremely poor efficacy, with histologic remission achieved in only 7% of patients, leading to premature termination of the study.¹¹⁶ A study in adult patients with EoE investigated the accuracy of combining multiple allergy skin tests and blood tests measuring both immediate and delayed hypersensitivity reactions to detect offending foods. The authors reported that the allergy tests could not predict the foods that were identified by elimination diets and histologic reevaluation in patients who responded to a six-food elimination diet (SFED).¹¹⁷ Later studies also reported low efficacy of TED in children and adult patients.

There are no systematic reviews or RCTs specifically addressing patch testing in pediatric EoE. Only prospective case-control studies have been published. Cumulative data both before and after the publication of the first ESPGHAN guidelines report that APT does not reliably predict food triggers that are later identified by food elimination diets in adult patients with EoE. As a result, atopy patch tests do not currently have a clear role in the evaluation of pediatric patients with EoE. Furthermore, there is no standardized methodology, reagents, or reporting for atopy patch test results.

These results reinforce the concept that EoE is characterized by food hypersensitivity that is not purely

IgE-mediated and, therefore, the use of IgE-based tests should be limited to the treatment of IgE-mediated allergy.^{117–121} In addition, APT, a test used to evaluate delayed sensitization, has some methodology concerns. A recent systematic review did not show superiority in comparison to empirical diet and showed extreme methodological variability in the 16 studies evaluated.¹²² For these reasons, skin allergy testing should not be used as the sole basis for deciding the type of elimination diet to treat EoE.

Although less useful for identifying triggering foods, IgE-based allergy testing before and during an elimination diet may have a role in identifying patients at risk for an immediate hypersensitivity reaction upon reintroduction of eliminated foods. This rare event has been reported sporadically in both children and adults during EoE treatment and remains a concern for both patients and physicians.^{123–125} Risk factors for the development of such reactions have yet to be defined.

An endoscopic esophageal prick test (esophageal mucosal food allergen injections) has been reported, in adults, to induce acute and/or delayed responses in patients with EoE but not controls, but clinical use is still premature and safety concerns exist.¹²⁶

Despite the lack of systematic reviews, some studies suggest that EoE is mediated by IgG4. However, there are few data on targeted food elimination based on food specific IgG4. A relationship between EoE and elevated levels of circulating total IgG4 and food specific IgG4 in serum has been suggested.¹²⁷ Other groups detected IgG4 deposition only in esophageal tissue biopsies.¹²⁸ These results suggest that IgG4 may play a role in the pathogenesis of EoE, possibly in blocking IgE-allergen binding.

Two studies suggest that intra-squamous deposits of IgG4 may differentiate patients with GERD from EoE. In addition, a novel approach using serum CD41 T-cell proliferation and food-specific IgG4 levels in the esophagus was used to establish elimination diets.^{129–131} This resulted in improvement in eosinophil counts, endoscopic severity, and dysphagia symptoms, but only 21% of patients achieved histologic remission.

Recommendation 9:

ESPGHAN EGID WG recommends against using available allergy tests to predict dietary triggers of EoE.

SoR: Strong \rightarrow Agreement: 93%.

Practice point:

IgE-based allergy testing may have utility in identifying patients at risk of developing an acute allergic reaction at the time of food reintroduction following elimination diets.

6.4 | Biomarkers and non-endoscopic techniques

Q10: Are there any non- or minimally invasive biomarkers that are useful for diagnosing or managing treatment in children with EoE?

Statement 10:

Several noninvasive or minimally invasive biomarkers and biomarker panels have shown promise in preliminary studies, but they are not accurate enough for routine use in the diagnosis or clinical management of EoE in children.

QoE: Low → Agreement: 100%.

Summary of evidence:

This issue was not addressed in the 2014 ESPGHAN guideline. Since 2013, several studies have investigated both non- and minimally invasive biomarkers and non-endoscopic techniques for accessing esophageal tissue or biomarkers. If identified, accurate biomarkers could replace the need for multiple endoscopies in the diagnosis and treatment of EoE.

This is particularly true in pediatrics, where endoscopies are often performed under general anesthesia, and there is controversial data on the adverse effects of multiple interventions under general anesthesia/sedation.^{132,133}

Children with active EoE may have higher mean peripheral absolute eosinophil count (AEC) compared with inactive status; however, AEC did not prove to be a sensitive tool for detecting active EoE. Since 2013, more than 45 different biomarkers have been studied for the diagnosis and/or treatment of EoE; most biomarkers have been assessed in isolation, but some have been assessed as panels (Table S1; Supporting Information File). These include plasma proteins and interleukins, cell surface molecules, breath analysis, throat swabs, and urine or stool samples. While many showed statistically significant differences in mean or median values between patients and controls or between untreated and treated patients, most had significant overlap between groups, precluding their use as accurate biomarkers. However, some biomarkers have shown promise, including some biomarker panels that, when used in combination, can provide more accurate results than either marker alone. These include: eosinophil peroxidase/AEC,¹³⁴ AEC for management,^{134–139} eosinophil cationic protein,^{134–140} activated eosinophils,¹⁴¹ IL-10,¹⁴⁰ anti-NC1A¹⁴² (collagen XVII) IgG4,¹⁴³ eosinophil progenitor cells,^{139,144,145} and an eosinophil cell surface marker panel that showed perfect discrimination in a small study in children.¹⁴⁶ A weakness of many studies, highlighted in a systematic review,¹⁴⁷ is the lack of atopic controls. Since most biomarkers are associated with the immune system and

the majority of EoE patients have additional atopic conditions affecting the TH2 pathways, the impact of these associated conditions must be considered. Urinary 3-bromotyrosine is also a promising completely noninvasive technique.¹⁴⁸

While biomarkers are still lacking, non-endoscopic techniques for acquiring either esophageal fluids or tissue are promising. The esophageal string test has shown good accuracy in a prospective pediatric¹⁴⁹ or combined pediatric/adult studies,¹⁵⁰ and the Cytosponge®^{151–154} has been used successfully in adult studies. A recent study of blind esophageal brushing for eosinophil-derived neurotoxin has also been promising.¹⁵⁵ These techniques need to be further validated in general and specifically in children not only for their efficacy but also for their tolerability, as procedures that are considered minimally invasive in adults may cause significant anxiety and discomfort in children.

Recommendation 10:

The ESPGHAN EGID WG recommends against the use of currently available biomarkers as the sole basis for the diagnosis or management of pediatric EoE patients.

SoR: Strong → Agreement: 100%.

7 | TREATMENT

7.1 | Dietary treatment

Q11: Elimination diets: Which is the best approach?

Statement 11.1:

Six food elimination diet (SFED) induces remission in the majority of patients with EoE.

QoE: Moderate → Agreement: 93%.

Statement 11.2:

A step-up approach leads to fewer endoscopies, lower costs, better patient compliance and a decrease in the number of lost school and work-days, as well as better quality of life.

QoE: Low → Agreement: 97%.

Statement 11.3:

The evidence of targeted elimination diet guided by standard allergy testing (including specific IgE and/or skin prick testing) to induce histologic remission is weak and shows high heterogeneity between studies.

QoE: Low → Agreement: 100%.

Summary of evidence:

The EED consists of empiric elimination of common food antigens to induce remission of EoE, followed by stepwise reintroduction of foods with serial endoscopies to identify the specific triggers. Over the past decade, there has been a gradual transition from highly restrictive diets to less restrictive initial diets, which is very promising and increases patient satisfaction.

The SFED eliminates the six most common foods that trigger EoE (cow's milk protein, wheat/gluten, egg, soy, peanuts/tree nuts, fish, and seafood). SFED has achieved clinical and histologic remission in up to 74% of patients with EoE in some studies. A meta-analysis published in 2015 included seven observational studies (four in children and three in adults), conducted in 197 patients (75 children and 122 adults) treated with SFED.¹¹⁰ Histological remission rates of approximately 72% (95% CI: 66%–78%) were reported. Homogeneity between the different studies was extremely high (I^2 statistic = 0), indicating high reproducibility. Locally highly prevalent allergens are often added to the SFED to increase effectiveness (e.g., legumes in Spain, sesame in Israel).

However, SFED poses significant difficulties for patients and providers: compliance due to religious, social, financial, challenges as well as the need for specialist dietetic support, cooking skills and time for cooking sourcing SFED foods. The psychological impact of long term restarted diets on patients and family, decrease the quality of life. A long investigation process, due to the protracted phase of food reintroduction, large number of endoscopies associated with school/work absences, high costs and resource consumption are also relevant issues. A less restrictive four-food elimination diet (FFED) avoiding cow's milk, wheat, eggs, and legumes was recently studied in adult patients with EoE and showed a histologic remission rate of 54%.¹⁵⁶

A more recent study of 78 children and adolescents with EoE from four medical centers¹⁰⁹ reported a 64% histologic remission rate in 50 subjects after an 8-week elimination diet of four foods (cow's milk, eggs, wheat, and soy). After reintroduction of foods, the most common food that triggered histologic relapse were cow's milk (85%), egg (35%), wheat (33%), and soy (19%). A single food triggered an exacerbation in 62% of patients.

In an attempt to start with an even simpler elimination diet than the FFED, a study of 130 patients (25 children) from 14 centers, 97 of whom completed all phases of the study, examined the efficacy of a step-up diet (2-4-6) that began with a two-food elimination diet (TFED) and was extended to an FFED or SFED in nonresponders as needed.¹⁵⁷ The authors reported that 56 patients (43%) achieved histologic remission after TFED. Food triggers in responders to TFED were milk (52%), gluten-containing cereals (16%), and both

(28%). Cow's milk triggered EoE in 18% of adults and in 33% of children. Remission rates after FFED were 60% and 79% after six food-group elimination diet. However, there was a significant dropout of patients between phases of the study as diets became more restrictive. This step-up strategy, also referred to as 2-4-6 FED, reduced the number of endoscopic procedures and the duration of the diagnostic process by 35% compared with SFED. In the above study, the authors investigated the food triggers through individual food group reintroduction. From this, 55 of 60 (91.6%) of responders to TFGED and FFGED had one or two food triggers.¹⁵⁷ Previous studies in children with EoE have also shown that a single food was the trigger of the disease in 74% of patients.¹¹⁷

Because milk proteins are the most frequent triggers of EoE, single elimination of milk has also been assessed. A prospective comparative effectiveness trial was carried out in treatment naive EoE patients (ages 2–18 years) who were treated with either swallowed fluticasone ($n = 24$) or a single food elimination of cow's milk protein ($n = 20$).¹⁵⁸ After 6–8 weeks of treatment, peak esophageal eosinophil counts <15 eosinophils/hpf were observed in 64% of patients treated with cow's milk protein elimination diet and in 80% of patients treated with swallowed fluticasone ($p = 0.4$). However, mean PedsQL EoE showed better quality of life and higher rates of symptomatic improvement in the milk elimination arms.

In TED, diet is managed along the outcome of the SPT and specific IgE, assuming that these tests might help identify the food trigger of EoE. A small retrospective study of 165 children (85% males, mean age 9 years) with EoE reported that 15 of 30 (50%) of patients on a SPT managed diet had combined symptomatic and histologic remission compared with 13 of 15 (87%) of patients on empiric cow's milk elimination ($p = 0.03$), suggesting that an empiric milk elimination diet is an effective option in children.¹⁵⁹ Another recent study of 41 children reported 51% histologic remission and modest improvement in symptoms after a short 8-week milk elimination diet in children.¹⁶⁰ EEDs ($n = 93$) resulted in a slight improvement in weight Z-scores after 1 year of treatment, whereas children treated with topical steroids ($n = 12$) had a slight decrease in weight Z-scores. Height Z-scores remained unchanged in both groups.¹⁶¹

A prospective randomized clinical trial comparing dairy elimination with a four-food diet (milk, egg, wheat, soy) (FFED) in 63 children with EoE,¹⁶² found improvement in symptom scores in both groups, with greater improvement on the more restrictive diet ($p = 0.04$). Histological remission rates (peak eosinophil count < 15 eos/hpf) were also comparable ($p = 1.0$). In contrast, clinically significant improvements in psychosocial ($p = 0.01$) and emotional well-being (anger, $p = 0.03$; anxiety, $p < 0.01$) were observed in

participants who eliminated milk alone. These results suggest that a single food (milk) elimination diet is a reasonable initial treatment option.

The use of excessive elimination diets may have an impact on child's eating habits and even trigger the development of the avoidant/restrictive food intake disorder (ARFID) in those children who maintain the elimination diet after achieving remission of EoE.¹⁶³ It is therefore, important if elimination diet is chosen for treating childhood EoE to consider the step up approach limiting as less foods as possible and to ensure close supervision of the patient by experienced dietitian and child psychologist where available to maintain patient's nutritional status and quality of life.

Recommendation 11.1:

ESPGHAN EGID WG recommends empiric elimination diets as the first-line dietary treatment of EoE in childhood; the choice of eliminated foods should be individualized, based on patients' specific needs.

SoR: Strong → Agreement: 100%.

Recommendation 11.2:

ESPGHAN EGID WG recommends that cow's milk, wheat-containing cereals, and eggs should be the first foods to consider for elimination when implementing step-up empirical elimination diet.

SoR: Weak → Agreement: 97%.

Recommendation 11.3:

ESPGHAN EGID WG recommends against the routine use of TED in the treatment of childhood EoE.

SoR: Strong → Agreement: 97%.

Practice points:

The more restrictive the elimination diet, the greater the burden on the patient and family. Therefore, physicians should involve patients and parents in the decision-making process and educate them about various aspects of the diet to promote compliance as well as optimize growth, development and quality of life.

Cow's milk elimination involves elimination of all milk and dairy containing products. Parents should be educated to avoid cross contamination and to read food labelling for hidden food allergens.

Eliminated foods should be substituted and the diet should be supervised by an experienced dietitian, to avoid nutrient deficiency and ensure compliance and normal growth and development.

If diet becomes a long-term care plan this should be revisited periodically to confirm ability and

willingness to maintain compliance. Sustainability may change depending on access to experienced dietetic support, social circumstances, personal finances and age of the child.

Although wheat seems to be the more relevant that gluten in causing EoE, some families may find it easier to choose gluten-free products for the diet of patients that should eliminate wheat.

Concomitant food limitations because of allergies non-related to EoE, or selective eating disorders may limit use of diets in some cases.

Q12: What is the role of elemental diet in the treatment of EoE?

Statement 12:

Amino acid-based formulas (AAF) are highly effective in children with EoE and induce histological remission in up to 90% of patients, but drawbacks include high cost and poor compliance and palatability, that limit their use to a second-choice treatment.

QoE: Moderate → Agreement: 100%.

Summary of evidence:

The overall efficacy of AAF in inducing histologic remission of EoE was very high in both children and adults (90.4% and 94.4%, respectively).¹¹⁵ The homogeneity of results from the different studies was moderate (I^2 statistic = 52.3%). The effect of AAF is rapid and histological remission of EoE in adults occurs within 2 weeks in some patients.¹⁶⁴

However, AAF has significant disadvantages, such as poor palatability leading to poor compliance in many patients, high cost that is not borne by all patients, prolonged time to reintroduce food requiring many endoscopies, and it is associated with more absenteeism from school/work than other elimination diets. Therefore, AAF is generally reserved for patients who do not respond to SFED and/or medical options and wish to further investigate the causality of various foods, as well as some young children and selected patients fed via gastrostomy tubes.¹⁶⁵

Recommendation 12:

ESPGHAN EGID WG suggests the use of amino-acid formulas as an option in patients with multiple food allergies, failure to thrive, or those with severe disease who do not respond, or are unable, to follow highly restricted diets.

SoR: Weak → Agreement: 100%.

Practice points:

When AAF is used in infants and young children, oral motor skills should be maintained with amino acid-

based semisolid preparations intended for use in the above age groups and switched to the first group of solid foods once remission occurs.

The duration of exclusive AAF before revision endoscopy is at least 4 weeks.

7.2 | Pharmacological treatment

Q13: Are all topical steroids effective for induction and maintenance of remission of pediatric EoE?

Statement 13.1:

Swallowed topical steroids, such as viscous budesonide and swallowed fluticasone have been shown to induce and maintain remission of EoE in both children and adults.

QoE: High → Agreement: 100%.

Statement 13.2:

There is no clear evidence of superiority among the available topical steroids.

QoE: Low → Agreement: 90%.

Summary of evidence:

Swallowed topical corticosteroids are effective in inducing remission in children with EoE.^{166–170} In a systematic review and meta-analysis of five adult studies involving 174 patients, topical fluticasone was used in three studies involving 114 patients and topical budesonide in two studies involving 60 patients.¹⁶⁶ Topical steroids promoted greater histologic remission than placebo, although the clinical improvement in treated patients did not reach significance. Another meta-analysis of 9 RCT involving 438 participants concluded that budesonide had a trend for better histologic improvement. Clinical results were less significant than histologic improvement.¹⁷¹ In the prospective, real world EuropeEER cohort, 173 of 583 pediatric EoE patients received topical oral steroid monotherapy after failure to respond to PPIs. Of these, 71% went into symptomatic remission and 59% into histologic remission with this treatment.⁴⁹

Most studies on topical steroids used different compounded formulations of budesonide (BUD) or fluticasone (FLU), each with several types of formulations and delivery methods, including viscous slurries, swallowed nasal drops, swallowed via metered-dose inhaler puffs, and others. Dellon et al. compared the efficacy of FLU delivered by metered-dose inhaler with BUD as an oral viscous solution in an adult RCT. No difference in response was demonstrated between the two drugs.¹⁷² It is unclear whether these results are applicable to children or whether the results are due to the specific topical steroids, the different doses, or the

route of drug administration.¹⁷³ A network meta-analysis compared all treatment types for EoE from 17 RCTs and concluded that FLU may be the best treatment for children. However, conclusions from indirect comparisons are problematic and require specific studies for confirmation.¹⁷³ Administering the topical steroid treatment for EoE differs to the patient leaflet(s), so clear instructions for administration must be explained to children and caregivers alike, as errors in drug administration are common and may result in decreased efficacy and increased systemic distribution.

The first drug approved by the EMA for treatment of EoE is an effervescent tablet which releases BUD in the oral cavity to be swallowed with saliva. To date the drug has only been studied in adults for both induction of remission (58% at Week 6 and 87% at Week 12), as well as maintenance with a range of 73.5%–75% at Week 48.^{174–176} Longer term follow-up of these patients is ongoing. Recently, the FDA approved a budesonide oral suspension for induction treatment of patients with EoE over 11 years old. Currently, oral topical steroid use in children younger than this age, or where the drug is not commercially available, remains off label, although several clinical trials of new formulations for children are under way.

Recommendation 13.1:

ESPGHAN EGID WG recommends the use of topical steroids as one of the first line treatment options to induce remission of EoE in children.

SoR: Strong → Agreement: 100%.

Recommendation 13.2:

ESPGHAN EGID WG recommends considering the use of topical steroids for maintenance in patients who achieve remission with topical steroids, however the optimal maintenance dose and duration need to be defined.

SoR: Strong → Agreement: 100%.

Practice points:

Careful instruction is needed for the patient and caregiver on proper timing and methods of administration of oral topical steroids, such that they should be taken at least 10 min after eating or drinking and patients should refrain from eating or drinking 30–60 min after swallowing the drug.

Topical steroids via metered-dose inhaler should be administered directly into the mouth and not via a spacer as recommended for asthma (nor via a diskus or turbohaler, where drug delivery requires inhalation). The medication should be administered while patients hold their breath for a few seconds to allow the medication to settle on the mucosa.

Topical steroid slurries, like oral viscous budesonide (OVB), should be administered slowly to allow the drug to settle in the esophagus and not enter the stomach as a single bolus.

When a single daily dose is given, the administration when the child is in bed allows for a longer contact time between the drug and the wall of the esophagus, which may contribute to efficacy.

Q14: Are topical steroids safe even in long-term use in children?

Statement 14:

Use of topical steroids for the treatment of EoE in children is safe.

QoE: Low → Agreement: 97%.

Summary of evidence:

Topical steroids are generally safe and well tolerated. The most frequent adverse effect of topical steroids is oral or esophageal candidiasis, in 2%–15% of patients and is usually asymptomatic. When present, it can easily be treated with oral nystatin.¹⁶⁶ Several studies have reported laboratory evidence of adrenal suppression in EoE children treated with oral topical steroids, with variable results.^{177,178}

Different studies examined different parameters, including morning cortisol and low-dose and high-dose ACTH stimulation tests. A systematic review concluded that published reports are very heterogeneous and that precautions should be taken, especially in patients requiring concomitant steroids by different routes (oral, topical, inhalation, nasal) for different atopic conditions that are often associated with EoE.¹⁷⁷ Younger patients, in whom the dose of topical steroids may be high relative to their body surface area, are another group in whom testing should be considered. Overt adrenal insufficiency is rare, and the duration and optimal treatment for abnormal adrenal stimulation tests remain to be determined. Clinical drug development studies have also reported a low incidence of laboratory-proven adrenal suppression with very rare clinically apparent symptoms or signs.^{178–180} However, some of these studies were adult studies, and well-designed pediatric studies are still being sought. Currently, clinical trials in children are ongoing.

Recommendation 14:

ESPGHAN EGID WG recommends that the total steroid burden is calculated and considered (e.g., systemic, topical, nasal, or inhaled) when treating EoE with topical steroids, as the combination may lead to increased cumulative steroid exposure and possible adrenal insufficiency.

SoR: Weak → Agreement: 100%.

Q15: Is PPI treatment effective for induction of remission in EoE?

Statement 15:

PPIs can induce remission in a proportion of pediatric patients with EoE.

QoE Moderate → Agreement: 100%.

Summary of evidence:

Observational studies have shown that PPIs can induce remission in a proportion of children with EoE.^{12,15,36,181,182} Histologic remission rates varied widely among studies, in part because of differences in definitions of remission. In a prospective study, Gutiérrez-Junquera et al. included 51 children with esophageal eosinophilia.¹⁸³ Histologic response, defined as <15 eos/HPF, was observed in 68.6% of children after 8 weeks of treatment with esomeprazole 1 mg/kg twice daily. Of those, 47% had a complete response, defined as ≤5 and the remainder had a partial response (>5 and <15 eos/HPF). The authors found no differences in history of atopy, allergy testing, pH study results, or endoscopic scores between responders and non-responders to PPI therapy.

A systematic review and meta-analysis of 33 studies, 11 of which were prospective and included data from 619 patients (188 pediatric), found that induction therapy with PPIs resulted in clinical response in 60.8% (95% CI: 48.38%–72.2%) and histologic remission (defined as <15 eos/HPF) in 50.5% (95% CI: 42.2%–58.7%).¹⁸⁴ There were no differences in remission rates between adults and children. There was a trend toward a higher response rate when PPIs were administered twice daily compared with once daily (55.9% vs. 49.7%), and in patients with pathologic pH monitoring (65.4% vs. 49.3%). These factors should be considered when choosing first-line therapy for patients with clinical or endoscopic manifestations of GERD, because such patients may respond very well to PPIs if drug treatment is chosen. In a multicenter observational study conducted in Spain, histologic remission was observed in 51% of 346 children that received high dose PPI. Predictive factors of response were normal findings or absence of fibrostenotic features in baseline endoscopy.¹⁸⁵ Furthermore, PPIs may be necessary as adjunctive treatment if complete remission is not achieved with alternative therapies.

In a recently published study describing data from the EoE connect registry, it was observed that PPI therapy reversed endoscopic features typically associated with fibrosis (rings and strictures) in 83 adult patients who achieved clinical histologic remission, similar to patients who responded to swallowed topical steroids.¹⁸⁶ Recently published retrospective data in adults with EoE suggest that young age, low body mass index, increased peripheral eosinophil count, and

inability to pass an endoscope may predict poor response to PPIs.¹⁸⁷ Several miRNAs have been identified in esophageal biopsies from pediatric EoE patients that may predict response to PPIs and may serve as predictive biomarkers for personalized treatment in the future.¹⁸⁸

The recommended dose of PPIs for children is 1–2 mg/kg omeprazole daily, divided into two doses (or equivalent doses of alternative PPIs) up to 20–40 mg twice daily.⁷ Genetic variations in the CYP2C19 gene affect PPI metabolism and clearance.¹⁸⁹ They may influence both efficacy and the development of potential adverse effects of PPIs. Common variants CYP2C19*17 and STAT6rs324011 have been associated with poor response to PPIs in EoE patients. Some have suggested that response rates could be improved by a genotype-driven approach to dosing PPI.¹⁹⁰

Given the evidence of their efficacy, relatively good safety profile, low cost, and ease of use, PPIs can be considered a first-line treatment for the induction and maintenance of EoE. In cases where topical steroids and elimination diet are used but do not induce complete remission, PPIs may be used as second-line treatment either alone or in combination with other treatment modalities. Because EoE and GERD can co-occur, some patients may benefit from receiving standard doses of PPIs in addition to dietary treatment or treatment with topical steroids to optimally treat both conditions.⁶

Recommendation 15:

ESPGHAN EGID WG recommends the use of proton-pump inhibitors as one of the first line treatment options to induce remission of EoE in children.

SoR Strong → Agreement: 100%.

Q16: Is PPI treatment effective in maintenance of remission in EoE?

Statement 16:

PPIs at lower doses are effective as maintenance therapy in patients who have achieved remission on these drugs.

QoE Moderate → Agreement: 97%.

Summary of evidence:

Until recently, there were very few data on the efficacy of PPIs for maintaining remission in children with EoE. Two very small retrospective case series reported recurrence of symptoms and esophageal eosinophilia over time in all patients.^{181,191} However, in a prospective study of 57 children who responded to an initial 8-week induction with high-dose esomeprazole 1 mg/kg twice daily, 49 (86%) remained symptom-

free and 40 (70.1%) had a sustained histologic response (defined as <15 eos/HPF) after 1 year of maintenance therapy with esomeprazole 1 mg/kg/day.¹⁹² In the majority of patients who responded to therapy (32/40), complete response was maintained. Patients who had demonstrated a complete histologic response during the initiation phase had higher rates of long-term histologic response (81%) during maintenance therapy than patients with only a partial histologic response (>50% decrease in eosinophil count; $p=0.014$). In patients who continued dose titration during the second year, sustained histologic response (92%) was noted at a dose as low as 0.5 mg/kg/day esomeprazole. In the RENESE multicenter observational study, long-term therapy with a step-down strategy effectively maintained histological remission in 68.5% and 85.3% of children at 7 months ($n=108$) and 16 months ($n=34$), respectively. Again, complete initial histological remission (≤ 5 eos/hpf) was associated with a higher possibility of sustained histological remission (OR, 5.08; 95% CI: 1.75–14.68).¹⁸⁵ Similar responses have been reported in some adult studies of PPI maintenance therapy with half or less of the induction doses.^{193,194} Loss of response was significantly higher in patients with a CYP2C19 rapid metabolizer genotype (36% vs. 6%; $p=0.01$). In patients who lost response after discontinuation of therapy, histologic remission was regained after increasing the PPI dose. In addition, children with EoE who initially responded to PPIs but carried the STAT6 variants rs324011, rs167769, or rs12368672 were found to be at increased risk of relapse after 1 year of PPI maintenance therapy.¹⁹⁵

Although PPIs are generally considered safe drugs, reviews of adverse effects in children treated for GERD report frequent events (up to 34%) including headache, diarrhea, nausea, and constipation.¹⁹⁶ Although largely based on adult data, many serious adverse effects may also be relevant to children. Ingestion of PPI potentially alters the gut microbiota, weakens the barrier and facilitates the entry of pathogens across the gastrointestinal barrier leading to an increased risk of certain infections, and may impair the absorption of minerals and vitamins and, to some extent, the digestion of ingested proteins, leading to an increased risk of sensitization to allergens and possibly even the development of allergic diseases and EoE.¹⁹⁷ Early consumption of PPI has been associated with the risk of bone fractures, although causality is not clear.¹⁹⁸ A case-control study of various prenatal, intrapartum, and postnatal factors associated with the later development of pediatric EoE found that among the variables studied the use of acid-suppressive medications had the highest odds ratio for EoE in children (OR: 6.05, 95% CI: 2.55–14.4).³³ In addition, a retrospective cohort study found an association between treatment with acid suppressive medications (PPIs and H2Ras) in the first

6 months of life and the risk of developing food or drug allergies, anaphylaxis, allergic rhinitis, and asthma.¹⁹⁹ Several cases of pediatric patients who developed EoE de novo during long-term use of PPIs have been reported, although causality is difficult to establish.²⁰⁰ The safety of long-term use of PPIs should be discussed with patients as part of the cooperative decision-making process.

Recommendation 16:

ESPGHAN EGID WG recommends the use of proton-pump inhibitors to maintain remission in PPI-responsive children.

SoR Strong → Agreement: 100%.

Q17: What is the ideal treatment for induction?

Statement 17:

PPIs, empiric elimination diets and topical steroids are all options for first-line induction treatments because of their efficacy and safety.

QoE Moderate → Agreement: 100%.

Summary of evidence:

Histologic remission rates between treatment types and even within a given treatment have varied widely in different studies. Studies had different designs, dosing regimens, treatment durations, and definitions of remission, making comparisons difficult. In the previous sections, diet, topical steroids and PPIs were discussed individually, and all three treatment alternatives were found to be associated with good responses. There are no current pediatric studies that directly and prospectively compare the three modalities.

The advantages and disadvantages of each treatment include efficacy and safety of treatment, impact on patient quality of life, and ease of adherence to treatment. The specific disease characteristics, chronicity, severity of symptoms, patient lifestyle, access to medications and supplements, availability of nutritional counseling, safety of anesthesia with respect to concomitant diseases, concomitant atopy and total steroid exposure, cost and other factors should also be considered when choosing a treatment approach. These issues should be discussed with patients and those involved in patient care, and treatment decisions should be made collaboratively.

Thus, the question of the “best” first-line therapy cannot be answered in general terms but must be answered on an individual basis and may change over time depending on patient preference, lifestyle, age, and access to medical care services. Regarding drug response, topical steroids seem to have higher response rates compared to PPIs. However, for patients

considering drug treatment, symptom complexity, cost, and overall steroid burden should be considered.

Recommendation 17:

ESPGHAN EGID WG recommends induction treatment of childhood EoE with either PPI, elimination diet or topical steroids with no evidence of preference.

SoR: Strong → Agreement: 90%.

Practice points:

The choice of therapy must be discussed individually with patients and their families, depending on the disease phenotype, needs and lifestyle of the patient.

In the event of a lack of response, lifestyle modification and/or poor adherence to therapy, alternative first-line treatment should be considered. Combination treatment may be useful in select cases.

Q18: How long should the induction phase last?

Statement 18:

The duration of induction may vary depending on the treatment chosen and disease severity at presentation.

QoE Moderate → Agreement: 93%.

Summary of evidence:

The time interval between intervention and reassessment has ranged from 4 to 14 weeks.^{201–206} Most studies are of poor quality, therefore it is difficult to draw firm conclusions. One study suggested a period of 4 weeks for induction using elemental diet because relatively rapid responses were observed with this treatment,²⁰³ whereas most other studies, and guidelines, recommend 8–12 weeks for the induction phase.^{201,205}

One study, conducted by Philpott et al., specifically examined the timing of induction after elimination diet.²⁰⁴ In patients who did not respond, treatment was discontinued. However, in patients who had partial remission at 6 weeks, extending treatment to a median of 13 weeks resulted in significantly higher remission rates. Similar results were reported in a combined cohort of adults and children treated with PPI. Higher remission rates were seen in those studied after 12 weeks rather than 8 weeks of treatment.⁵⁸

Recommendation 18:

ESPGHAN EGID WG recommends minimum 8–12 weeks of induction for patients on elimination diets, topical steroids or PPIs and not less than 4 weeks on elemental diets before endoscopic reassessment.

SoR: Strong → Agreement: 100%.

Practice point:

The efficacy of therapies should always be evaluated by endoscopy with biopsies.

If only partial response (>50% decrease in eosinophil count) is achieved after early follow-up (4–7 weeks), physicians should consider prolonging the induction and reexamining at 12–16 weeks before changing treatment if the patient's condition permits.

Q19: Should maintenance treatment be recommended to all patients?**Statement 19:**

Maintenance treatment is necessary to keep remission after induction treatment.

QoE Moderate → Agreement: 100%.

Most available data come from studies investigating maintenance therapy with topical steroids.^{207–210} A pediatric study showed that topical steroids produced a significant and sustained response with a reduction in peak esophageal eosinophil counts.²⁰⁷ The mean follow-up time was 20.4 months, and the longest was 68 months (5.7 years) in a group of 54 patients. Few adverse events were reported. Even after prolonged treatment with topical steroids, height and weight Z-scores followed expected growth curves. In adult studies, higher, cumulative steroid doses and longer treatment duration were associated with a higher proportion of clinical and complete remissions. At control visits, more patients on steroids were in clinical remission (31.0%) compared to patients off medication (4.5%) ($p < 0.001$), as well as endoscopic remission (48.8% vs. 17.8%; $p < 0.001$), histologic remission (44.8% vs. 10.1%; $p < 0.001$), and complete combined remission (16.1% vs. 1.3%; $p < 0.001$).

In addition, a recent retrospective study in adults has shown that histologic relapse in EoE is common despite ongoing steroid treatment, regardless of dosage. However, in patients receiving higher doses, relapse occurs later without worsening safety profile.²¹¹ Gutiérrez-Junquera et al. reported histologic remission of 91.6% after PPIs treatment for 2 years in children.¹⁹² Every-other-day administration of topical steroids during maintenance therapy has been found to increase the risk of relapse.²¹²

Sustained remission has been demonstrated in both adults and children after cessation of dietary interventions for EoE, but such patients appear to be rare, and the duration of remission in these patients is not clear.^{213–215} Prospective assessments are still lacking.

If a decision is made to discontinue therapy as part of the shared decision-making process, reexamination clinically and endoscopically recommended to detect disease exacerbation and fibrosis progression.

Symptoms that develop slowly over time are often overlooked or ignored by patients and therefore may be missed by clinicians who do not assess patients using validated techniques. A combined/alternative treatment approach deserves evaluation in a larger prospective study.²¹⁶

Recommendation 19:

ESPGHAN EGID WG recommends maintenance therapy to all patients after achieving histological remission.

SoR: Strong → Agreement: 100%.

Practice points:

A dose reduction of the drug may be considered in patients in remission,

In patients on medication, high doses can be considered to maintain EoE, but the benefits over lower doses appear to be small.

In patients undergoing an elimination diet, reintroduction of foods should be gradual to determine those triggers that require further elimination, and thus pursue the least restrictive regimen.

Q20: How long should maintenance treatment be recommended?**Statement 20.1:**

Most patients require long-term treatment to maintain clinical and histological remission.

QoE: High → Agreement: 100%.

Statement 20.2:

Reduction or maintenance of treatment may be guided by disease phenotype and severity, and the specific needs of patients.

QoE: Low → Agreement: 97%.

Summary of evidence:

There are no prospective data on the best duration of maintenance therapy in pediatric EoE. Few studies report the results of long-term follow-up between 6 and 17 months.^{192,207–209,216–218} A study by Reed et al. found a substantial loss to follow-up in patients on a TFED.²¹⁶ Therefore, recommendations are made based on indirect evidence and expert opinion. Most patients who discontinued treatment do not remain in histological remission; however, the rate of sustained clinical remission is higher. Rates of disease progression in these patients are unclear. In a large cohort of adults with EoE, sustained untreated combined remission was seen in only 1.3% of patients who discontinued treatment.

The advent of validated noninvasive tests may be helpful to guide the need for continuous treatment.

Recommendation 20.1:

ESPGHAN EGID WG recommends a maintenance period of at least 1 year.

SoR: Strong → Agreement: 90%.

Recommendation 20.2:

ESPGHAN EGID WG suggests that decisions to maintain, reduce, or withdraw treatment should be determined by the severity of the disease and the specific needs of the patient.

SoR: Weak → Agreement: 97%.

Practice points:

After reducing or stopping treatment, close monitoring, both clinical and endoscopic/histological should be performed to prevent disease recurrence and progression.

Safety assessments should be conducted during maintenance, addressing the specific potential problems (steroids: adrenal insufficiency, candidiasis, Diet: growth delay or malnutritional, PPIs: bone health, etc.).

Figure 1 shows a proposed algorithm for follow-up of patients with EoE.

Q21: How should patients be assessed during the maintenance phase? How often?

Statement 21:

There is no evidence on the frequency of follow ups in an asymptomatic patient with EoE.

QoE: Low → Agreement: 97%.

Summary of evidence:

Clinical assessment using validated questionnaires are useful to assess the maintenance of clinical remission and should be performed regularly.^{219,220}

In case of clinical relapse, endoscopic and histological re-evaluation is needed. In complete clinical remission of the disease, endoscopic and histological follow-up evaluation needs to be individualized based on the disease phenotype and disease severity at diagnosis. In general, despite the lack of evidence, the expert opinion of the authors is that endoscopic and histological re-evaluation should be considered 1–3 years after obtaining a sustained remission on stable medical or dietary treatment, given the possible incongruence between symptoms and tissue healing, as well as the potential risk for fibrotic evolution. Due to the chronicity of EoE, similar evaluations should be performed periodically throughout follow-up.

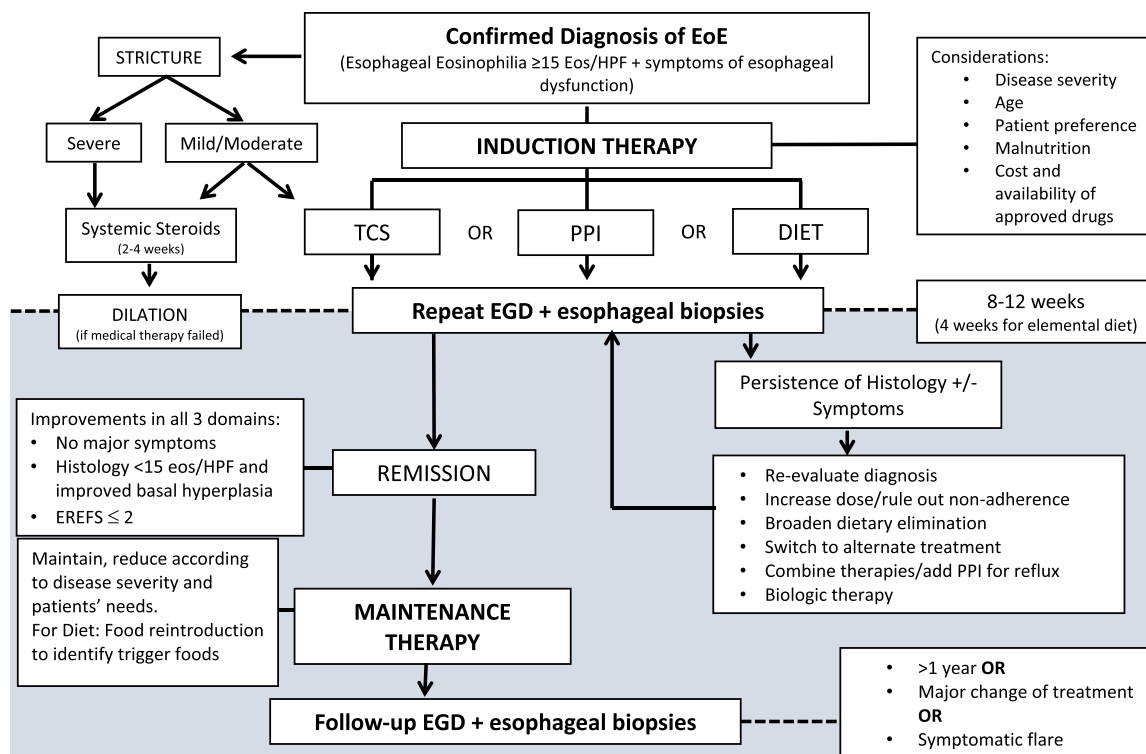


FIGURE 1 Proposed algorithm for management and monitoring of eosinophilic esophagitis (EoE).

Recommendation 21.1:

ESPGHAN EGID WG recommends periodic clinical assessment, and individualized endoscopic and histological evaluations during maintenance phase.

SoR: Strong → Agreement: 97%.

Recommendation 21.2:

ESPGHAN EGID WG recommends endoscopic and histological evaluation in case of clinical relapse during maintenance.

SoR: Strong → Agreement: 100%.

Recommendation 21.3:

ESPGHAN EGID WG suggests endoscopic and histological re-evaluation after 1-3 years during the maintenance phase in cases of stable clinical remission.

SoR: Weak → Agreement: 100%.

7.3 | Clinical predictors of treatment response

Q22: What are the predictors of treatment response and risk factors for tissue remodeling in patients with EoE?

Statement 22.1:

Duration of noncontrolled EoE disease is an important risk factor for developing fibrostenotic disease, but there are currently no accurate clinical predictors of response to different EoE treatments at the time of diagnosis.

QoE: Moderate → Agreement: 97%.

Statement 22.2:

Early diagnosis and effective EoE treatment are important to prevent esophageal remodeling and the risk of stricture formation.

QoE: High → Agreement: 100%.

Summary of evidence:

A recent retrospective analysis included 721 patients with EoE.²²¹ Histological, endoscopic, and clinical features were identified and stratified by age and duration of undiagnosed disease. The inflammatory phenotype was more common early in the disease course, and patients with a longer duration of untreated disease were more likely to have the fibrotic phenotype, including strictures. Consistent with these findings is another study reporting that the risk of developing a

fibrotic endoscopic phenotype doubled with each 10-year increase in age.²²² In an analysis of data from 256 EoE patients, it was found that early EoE therapy likely interrupts or prevents esophageal tissue remodeling.²²³ Although data on the natural history of EoE are still sparse, the studies already available show an association between the duration of undiagnosed disease and the occurrence of long-term complications, including stricture formation. Therefore, it is of great importance to diagnose and treat EoE early. Recent studies report different disease phenotypes and suggest that some patients have an inflammatory phenotype that progresses differently from the fibrostenotic phenotype. A recent characterization of EoE endotypes has also shown that endotype 1 (EoEe1), which usually has milder endoscopic findings compared with the other two end types, is more likely to respond to PPIs.^{224,225} Further investigation of early phenotypes and progression may have implications for future treatment recommendations for pediatric EoE.

Potential predictors of successful steroid therapy have been investigated. Konikoff et al. conducted a randomized, double-blind, placebo-controlled study on ingestion of fluticasone in pediatric patients with active EoE.²²⁶ Thirty-six patients were randomly assigned to receive either 880 µg or placebo twice daily for 3 months. Topical corticosteroids had a more pronounced effect in nonallergic, younger, smaller, and lighter individuals. In addition, two other studies confirmed that patients with the allergic variant of EoE may be more resistant to topical therapy with fluticasone.^{227,228} Immunohistochemical analysis revealed that higher tryptase and eotaxin-3 levels were also associated with a better response to steroids.²²⁹ In addition, the authors concluded that patients with a fibrostenotic phenotype of the disease at baseline were less likely to respond to topical steroids. Young age, negative allergy tests, and an inflammatory EoE phenotype are potential predictors of successful steroid therapy in children with EoE.

EoE and PPI responsive EoE are now considered the same disease, and PPIs are one of the three recommended initial treatments.⁶ Patients with PPI-responsive EoE have similar clinical, histological, and endoscopic features as PPI-nonresponsive EoE.²³⁰ Preliminary evidence is now available for good predictors of successful PPI therapy. A recent study reported that younger age, lower BMI, and increased peripheral eosinophil count predicted the absence of response to PPIs in adults.¹⁸⁷ As noted above, the presence of fibrostenotic phenotype was associated with less probability of response to PPI in pediatric patients.¹⁸⁵

Recommendation 22:

ESPGHAN EGID WG recommends awareness of disease manifestations and individualized EoE

treatment to prevent esophageal tissue remodeling and potential stricture formation.

SoR: Strong → Agreement: 100%.

7.4 | Treatment of refractory EoE

Q23: Are there other treatment options for refractory EoE?

Statement 23.1:

Anti-IL-13 and anti-IL-4 receptor antibodies have shown benefit for treatment of adults and teenagers with EoE.

QoE: Moderate → Agreement: 100%.

Statement 23.2:

There is limited evidence on treatment with anti-IL-5 α and anti-IL-5 antibodies in children with EoE.

QoE: Low → Agreement: 93%.

Statement 23.3:

Neither the CRTH2 antagonist OC000459 nor the mast cell stabilizer cromolyn sodium are effective in inducing clinical and histological remission in patients with EoE.

QoE: Moderate → Agreement: 100%.

Statement 23.4:

Montelukast (a leukotriene receptor antagonist) is not effective in maintaining clinical and histological remission in EoE.

QoE: Low → Agreement: 100%.

Statement 23.5:

There is no evidence of efficacy of thiopurines in children with EoE.

QoE: Low → Agreement: 90%.

Statement 23.6:

Omaliuzumab is not effective in the treatment of pediatric EoE.

QoE: Moderate → Agreement: 100%.

Summary of evidence:

Chemoattractant receptor-homologous molecule on Th2 cells (CRTH2) is a prostaglandin D2 receptor expressed in Th2 cells, eosinophils, and basophils that mediates chemotaxis. OC000459 is a selective CRTH2 antagonist that was evaluated in a randomized, double-blind, placebo-controlled study of 26 adults with active

steroid-refractory or dependent EoE. After 8 weeks of treatment, a decrease in symptom score and a reduction in esophageal eosinophil infiltration were observed, but histological remission was not achieved.²³¹

Since the first ESPGHAN guideline in 2014, several additional small studies have demonstrated poor responses to mast cell stabilizers.^{232,233} Montelukast was not superior to placebo in maintaining clinical remission.²³⁴ Histological response was not evaluated in either of these studies.

In 2007, a series of three adults treated with azathioprine and 6-mercaptopurine was reported. It showed long-term clinical and histological remission when treated with azathioprine. In these patients with severe and systemic steroid-dependent EoE (one of whom had eosinophilic gastroenteritis), administration of azathioprine or 6-mercaptopurine resulted in and maintained long-term steroid-free clinical and histological remission.²³⁵ In pediatric EoE, only a single case report has been published in abstract form. A 6-year-old boy with EoE who was unresponsive to topical steroids (budesonide, fluticasone, and ciclesonide) showed long-term clinical remission and a significant decrease in eosinophil count (to 15 eos/hpf) when treated with azathioprine.²³⁶

Over the past several years biologics targeting different molecules involved in the type-2 atopic cascade have been studied in patients with EoE.

Dupilumab is a fully human anti-IL-4 receptor- α antibody that inhibits signaling from IL-4 and IL-13 and has shown benefit in moderate to severe atopic dermatitis, asthma, and chronic sinusitis with nasal polyposis. Dupilumab was tested in 47 adults with EoE in a randomized, double-blind study over 12 weeks. Significant reductions in symptom scores and esophageal eosinophil counts were observed in the treatment group, with 82% of treated patients achieving histological remission (defined as less than 15 eos/hpf).²³⁷ Dupilumab also significantly improved most components of the validated histological score (EoE-HSS), the endoscopic EREF score, and esophageal distensibility as measured by the Functional Lumen Imaging Probe (FLIP). In addition, dupilumab normalized the expression of many EoE disease signature genes, including those associated with type 2 inflammation, hyperplasia, remodeling, and eosinophils.²³⁸

In a recent Phase 3 randomized, double-blind clinical trial in adults and adolescents over 12 years of age, two arms were included: dupilumab 300 mg weekly versus placebo and dupilumab 300 mg each 2 weeks versus placebo for 24 weeks. Results were similar in terms of histological remission (defined as <6 eos/hpf, 60% and 59%, respectively), but only the weekly dose was associated with significant clinical response versus placebo.²³⁹

A recent study reported that in 29 of 45 pediatric patients with EoE who received dupilumab for treatment of atopic disease, the need for other medications decreased and clinical and histological remission occurred.²⁴⁰

In 2022, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) expanded the approval of dupilumab to include a new indication for the treatment of EoE in patients 12 years of age and older who weigh at least 40 kg.

Based on positive results from a phase 3 study in children aged 1–11 years old (EoE KIDS trial) the FDA recently approved treatment with dupilumab for this age group as well (M Chehade et al., UEGW, 2022; M Chehade, ACG, 2023).

IL-13 is also an important Th2 cytokine involved in the pathogenesis of EoE by stimulating eosinophil chemotaxis through the production of eotaxin and promoting epithelial barrier dysfunction. QAX576 (decitreumab), an antibody directed against IL-13, was studied in a randomized double-blind trial in 15 adults and showed a 60% decrease in eosinophil numbers and normalization of esophageal gene expression that lasted for 6 months but had no effect on symptoms.²⁴¹

RPC4046 (cendakimab) is a novel IL-13 targeted antibody that prevents binding of IL-13 to both IL-13R α 1 and IL-13R α 2 receptors. Cendakimab was assessed in 99 adults with EoE in a phase 2 trial who were randomly assigned to receive two different doses (180 or 360 mg) of cendakimab or placebo for 16 weeks. Cendakimab produced a significant decrease in eosinophil counts (mean change in eosinophil density was 94.8 eos/hp with 180 mg and 99.9 eos/hpf with 360 mg vs. 4.4 eos/hpf in placebo), with 50% of treated patients achieving histological remission. A significant reduction in validated endoscopic and histological scores and overall clinical assessment of disease severity was seen in the higher dose, as well as a nonsignificant reduction in dysphagia score. Improvement in endoscopic and histological features was also observed in steroid-refractory patients treated with cendakimab.²⁴² In addition, cendakimab significantly reduced epithelial–mesenchymal transition markers in adults with active EoE, and the effect was greater at higher doses, suggesting a possible reduction in the risk of fibrostenotic complications.²⁴³ Phase 3 trials are ongoing in adolescents and adults. Patients treated with cendakimab sustained or improved their clinical, endoscopic and clinical measures in a 1-year open label extension study in 66 adults.⁵⁶ Subgroup analysis suggested efficacy in both steroid-refractory and non-steroid-refractory patients.

Omalizumab, an anti-IgE antibody, did not show to be effective in EoE. Omalizumab was assessed in a small observational study of 15 children and adults treated for 12 weeks, with clinical improvement

observed, but only 33% of them achieved histological remission (<15 eos/hpf).²⁴⁴ In a randomized double-blind trial, 30 adults were treated with the anti-IgE antibody omalizumab ($n=16$) or placebo ($n=14$) for 16 weeks.²⁴⁵ There was no significant reduction in esophageal eosinophil count and no decrease in symptoms in treated subjects compared with placebo control.

The Th2 helper cytokine IL-5 is involved in the pathogenesis of EoE via maturation and activation of eosinophils. Two anti-IL-5 antibodies (available for the treatment of eosinophilic asthma) have been studied: reslizumab and mepolizumab. Reslizumab was studied in a large randomized double-blind trial in 226 children comparing three different doses of reslizumab with placebo. There was improvement in symptoms in all groups, with no difference between active treatment and placebo, and a significant reduction in esophageal eosinophil infiltration with reslizumab. However, most patients did not achieve the strict definition of histological remission (<5 eos/hpf).²⁴⁶ The relatively short duration of the trials may have influenced the results. In a retrospective observational study, clinical and histological improvements were observed in 12 children treated with reslizumab (median 3 years and maximum 9 years), and 92% were in histological remission with no serious adverse events. Patients were instructed to avoid all foods that could cause exacerbation of symptoms during reslizumab treatment, so dietary restrictions may have confounded the results.²⁴⁷

In a randomized double-blind trial, the anti-IL-5 antibody mepolizumab was compared with placebo in 11 adults. Treatment with mepolizumab was not associated with improvement in symptoms, and although eosinophil counts were significantly reduced, no patients achieved histologic remission.²⁴⁸ Mepolizumab was also studied in 59 children with EoE unresponsive or intolerant to standard therapy in a randomized trial with three different doses but no placebo arm. Similar to the results in adults, no significant change in symptoms was observed, and although there was a reduction in eosinophil density, only 8.8% of patients achieved histological remission.²⁴⁹

Benralizumab, an anti-IL-5 α antibody, was effective in producing complete tissue depletion of eosinophils.²⁵⁰ However, a double-blind placebo-controlled trial of benralizumab in adolescent and adult patients with EoE failed to demonstrate clinical improvement in the treatment arm compared to placebo. The trial was terminated prematurely. The failure of drugs, specifically depleting eosinophils to improve symptoms indicates that non-eosinophil mediated inflammation plays a significant role in the pathogenesis of EoE. This discrepancy between eosinophil density and ongoing inflammation and dysmotility needs further attention and new methods of action to control both inflammation and symptoms.

There is anecdotal experience with the use of the anti- $\alpha 4\beta 7$ -integrin antibody vedolizumab in EoE with conflicting results. In two case reports of adults with Crohn's disease and concurrent EoE, vedolizumab was associated with histological remission without specific EoE treatment.^{251,252} Vedolizumab was administered to five adults with eosinophilic gastroenteritis (three with esophageal involvement). There was overall clinical and histological improvement in two of them, but an increase in esophageal eosinophilia was observed in one case.²⁵³

Recommendation 23.1:

ESPGHAN EGID WG recommends that dupilumab can be used in selected cases of children over 1 year old weighing >15 kg with EoE refractory to conventional treatment and in those with concomitant atopic burden with approved indications for biologics.

SoR: Strong \rightarrow Agreement: 100%.

Recommendation 23.2:

ESPGHAN EGID WG suggests against the routine use of other biologics to treat childhood EoE, but they may be considered in clinical trials or specialized centers until such drugs obtain regulatory agency approvals.

SoR: Weak \rightarrow Agreement: 97%.

Recommendation 23.3:

ESPGHAN EGID WG suggests against the use of CRT2 antagonist OC00459 for treatment of pediatric EoE.

SoR: Weak \rightarrow Agreement: 100%.

Recommendation 23.4:

ESPGHAN EGID WG recommends against the use of cromolyn sodium, or leukotriene receptor antagonists for treatment of pediatric EoE.

SoR: Weak \rightarrow Agreement: 100%.

Recommendation 23.5:

ESPGHAN EGID WG suggests against the routine use of thiopurines for treatment of children with EoE refractory to first line treatment.

SoR: Weak \rightarrow Agreement: 100%.

Recommendation 23.6:

ESPGHAN EGID WG suggests against the use of omalizumab for the treatment of pediatric EoE.

SoR: Weak \rightarrow Agreement: 97%.

7.5 | Esophageal strictures—How to treat and follow-up?

Q24: What is the best method for diagnosing esophageal strictures in pediatric patients with EoE?

Statement 24.1:

Endoscopic assessment and barium swallow are complementary for the evaluation of suspected strictures or narrow-caliber esophagus in patients with EoE.

QoE: High \rightarrow Agreement: 100%.

Statement 24.2:

Endoscopy has the advantage of being able to assess inflammatory aspects of EoE, while barium studies can assess the length, severity and positioning of a narrow caliber esophagus.

QoE: Moderate \rightarrow Agreement: 100%.

Summary of evidence:

Pediatric and adult/pediatric studies reported a wide variation in the frequency of strictures and narrow-caliber esophagus (0%–41%).^{37,55,254–256} Definitions of strictures, diagnostic methods, and patient characteristics differed among studies. The EREFS (described in Section D, under Q5) attempts to assess the endoscopic presence of strictures and can be used for longitudinal follow-up.⁶³

Barium swallows can be useful to determine the length of esophageal strictures and to evaluate the severity of narrow caliber esophagus, which are often difficult to assess endoscopically. In addition, barium swallows are useful to determine esophageal anatomy in cases where severe strictures prevent passage of even a narrow endoscope. New modalities such as endoscopic ultrasound (EUS), high-resolution manometry (HRM) with esophageal intrabolar pressure (IBP), and FLIP are promising techniques that may help distinguish fibrostenotic from inflammatory strictures and personalize patient treatment in the future.^{80,89,92} However, these studies are rarely performed in children outside of clinical trials or highly specialized centers and, although promising, are not yet recommended for routine patient care.

Recommendation 24.1:

ESPGHAN EGID WG recommends a barium swallow before dilation if the anatomy or caliber of the esophagus cannot be clearly defined by upper GI endoscopy.

SoR: Strong \rightarrow Agreement: 97%.

Recommendation 24.2:

Patient characteristics such as age, symptoms and chronicity of symptoms should be considered when devising a diagnostic plan.

SoR: Weak → Agreement: 97%.

Practice points:

Upper GI endoscopy and barium swallow series can be used to identify remodeling sequelae of EoE.

Inflammatory features are often missed by barium swallow and can be better assessed by endoscopy.

Q25: Is esophageal dilation necessary and safe for of strictures in pediatric EoE?

Statement 25.1:

Inflammatory esophageal strictures may regress with standard medical/dietary treatment.

QoE: Moderate → Agreement: 97%.

Statement 25.2:

Esophageal dilation is safe and can rapidly improve symptoms of dysphagia, without affecting the ongoing inflammatory process.

QoE: High → Agreement: 97%.

Statement 25.3:

Treatment with short term systemic steroids can significantly reduce the need for mechanical esophageal dilation in moderate to severe strictures associated with pediatric EoE.

QoE: Very low → Agreement: 93%.

Summary of evidence:

Most studies have shown that mild inflammatory EoE-associated strictures in children resolve with standard drug [PPIs and/or topical steroids (TCS)] or dietary treatment. A study in adults has shown that dilation for mild strictures does not provide additional benefit in terms of symptoms compared with standard treatment without dilation.²⁵⁷ Thus, in patients with symptomatic EoE without severe fibrostenotic EoE strictures, endoscopic dilation of the esophagus does not appear to be a necessary initial treatment. Although no comparable data are available for pediatrics, the short course of disease in most children compared with adults seems to suggest that inflammatory rather than fibrostenotic strictures are more common, and hence the high response rate of severe pediatric strictures to short courses of systemic steroid treatment.²⁵⁸ However, drug treatment alone may not be the best choice for the management of severe dysphagia associated

with severe strictures in pediatric EoE, although it may reduce the development of strictures.^{83,259–262}

A retrospective study of 20 children with moderate-to-severe EoE and strictures that prevented passage of a standard or pediatric endoscope showed that a short course of systemic steroids (2–4 weeks, followed by rapid tapering to standard treatment) resulted in symptomatic improvement in all patients and complete endoscopic resolution of the stenosis in 95%. There was no significant increase in BMI between presentation and follow-up, and only three of the patients required esophageal dilation during the duration of follow-up.²⁵⁸ This contrasts with esophageal dilation as the primary treatment modality for EoE-associated strictures, in which the majority of patients will require at least one additional dilation.²⁶⁰

Esophageal dilation is also indicated in children with dysphagia despite histological improvement with standard treatment, as mild fibrostenotic changes with resulting altered motility may not allow adequate peristalsis and lead to subsequent dysphagia or bolus impaction. Dilation of the esophagus may improve symptoms but does not affect the underlying inflammatory process or histological remission.^{259,260} Dilation of EoE strictures should be performed in conjunction with standard induction and maintenance therapy (as described elsewhere in this guideline).^{258–260} Results of a small study in adults suggest that drug treatment may be less effective if the length of the stricture is more than 1 cm.²⁶³

Recommendation 25.1:

ESPGHAN EGID WG recommends esophageal dilation in highly selected cases with severe esophageal narrowing that persists despite other forms of treatment or in cases where a rapid symptomatic improvement is required.

SoR: Strong → Agreement: 88%.

Recommendation 25.2:

ESPGHAN EGID WG suggests that a short course of systemic steroids be considered as an alternative to dilation in the presence of moderate to severe esophageal strictures with severe symptoms.

SoR: Weak → Agreement: 93%.

Practice points:

Standard first line treatments can be considered for the treatment of mild EoE associated strictures in children.

Q26: What method should be used for esophageal dilation in children with EoE?

Statement 26:

Both hydrostatic balloon dilation and Savary-Gilliard bougies are effective and safe in children with EoE, with very low complication rates.

QoE: Low → Agreement: 100%.

Summary of evidence:

Esophageal strictures can be dilated with either a hydrostatic balloon or Savary-Gilliard bougies. Both dilation techniques appear to be effective and safe and have a very low complication rate in children.²⁶⁴ Data comparing these techniques in children are sparse.^{83,265} Low complication rates have been described (i.e., perforation 0 to <0.3%, chest pain after the procedure <5%, bleeding <1%, and hospitalization <1%).^{81,266–268} No correlation was found between peak eosinophil count and risk of complications.^{83,261} Hydrostatic balloon dilation allows visual inspection of esophageal stenosis before, during, and after the procedure, but has its limitations in multiple and long strictures unless performed under fluoroscopy, whereas Savary-Gilliard bougies allow dilation of multiple or long strictures more easily. Both dilation techniques should start with small diameter dilation and progress slowly at each session until the target diameter or resolution of symptoms is achieved, that is, “start small and go slow.”²⁶⁶ In general, it is recommended to perform no more than 3 dilations in 1-mm increments at each session.

Recommendation 26:

ESPGHAN EGID WG suggests the use of either hydrostatic balloons or Savary-Gilliard bougies for esophageal dilation as both are safe and effective. The choice of technique should be based on the experience of physician.

SoR: Weak → Agreement: 88%.

Practice point:

For descriptive purposes, EoE strictures can be divided into three degrees of severity: Mild - allows passage of standard gastroscope (9 mm) but with resistance, Moderate—allows passage of pediatric gastroscope (6 mm) but not standard gastroscope (9 mm), Severe—does not allow passage of pediatric gastroscope (6 mm).

8 | QUALITY OF LIFE—HOW TO ASSESS?

Q27: How is health related quality of life defined and best assessed in children with EoE and parent proxy?

Statement 27.1:

Health related quality of life in children with EoE and in their parent proxies can be assessed accurately with validated questionnaires.

QoE: Moderate → Agreement: 88%.

Statement 27.2:

Health related quality of life assessed with validated questionnaires, correlates inversely with clinical and histological disease activity, as well as with the use of an elimination diet.

QoE: Moderate → Agreement: 93%.

Summary of evidence:

Assessment of quality of life (QoL) was not addressed in the 2014 guideline. One of the major unresolved issues related to the diagnosis and treatment of EoE has been the definition of the optimal end point of treatment (e.g., symptom relief and histologic histological normality).²⁶⁹ While adult patients have reported symptom improvement and quality of life as important short- and long-term treatment goals, less has been published about patient preferences, motivators, and barriers to treatment in children.^{269–271} A joint pediatric and adult guideline on EoE states that EoE significantly affects patients' health-related quality of life (HRQoL) and impairs their social and psychological functioning (LE Moderate, 100% consensus).⁷ Using an 8-question knowledge test and a 9-question Shared Decision Making survey, the greatest barrier of treatment with topical steroids was the possible side effects (63.4%), whereas for the elimination diet were the inconvenience of adhering to the restrictive diet (27.6%), multiple endoscopies (26.8%), poor quality of life and socialization (23.7%), and inadequate nutrition (28.4%).²⁷⁰ Other factors affecting quality of life of patients with EoE included the number of physicians involved (in some settings there is engagement of pediatricians, pediatric gastroenterologists and allergists that may lead to some contradictions) and frequency of treatments, as well as the financial burden of treatment in a total number of 181 parents of children with EoE. The authors reported that 60.2% of children also received complementary medicine and 23.2% received complementary products.²⁷²

Furthermore, parents of children with EoE who had to follow an elimination diet were less likely to go out to eat, were concerned about the reaction of others, and needed more time to feed their child than the control group.²⁷³ A specific EoE module of the PedsQL™ for measuring HRQoL was introduced as the PedsQL™ EoE module with questionnaires specifically for children aged 5–7 years, 8–12 years, 13–18 years, and their parent representatives.²⁷⁴ Since then, it has been

used to assess HRQoL in children with EoE in 550 children and 800 Parent–Teacher Associations.^{274,275} PedsQL™ EoE module scores were worse in patients with active histological disease than in those in remission (children's self-report: 63.3 vs. 69.9; $p < 0.05$; parent proxy report: 65.1 vs. 72.3; $p < 0.01$). In addition, positive PedsQL™ EoE module scores (indicating good quality of life) of children and parents correlated negatively with PEES v2.0 symptom scores of EoE disease activity and with proximal peak eosinophil counts and architectural changes on the EoE Histology Scoring System ($p < 0.05$).²¹⁹

A study in the USA in four centers involving 108 children and adolescents with EoE, during 12 months of treatment for EoE, found that symptom scores, PedsQL total, physical and psychological and family impact scores improved but self-reported PedsQL did not. The average number of symptoms reduced from 3.5 to 3.0 with most common residual symptoms comprising abdominal pain, nausea, early satiety, and nocturnal symptoms. Children younger than 7 years had more symptoms and severity and the authors concluded that the chronicity of EoE determined the burden of the children's HRQoL.²⁷⁶

Family's functioning using the PedsQL™ FIM test was better in older children with EoE ($r = 0.35$; $p = 0.0004$)²⁷⁷ and the same was true for parent HRQoL ($r = 0.28$; $p = 0.006$), but worse in younger children with EoE. Furthermore, family impact scores were better if children with EoE were treated with swallowed steroids ($n = 75$), than with elimination diets ($n = 61$) or combined treatment ($n = 63$).²⁷⁷ Similarly, children who were placed on elimination diets had worse QoL scores using the PedsQL™ EoE module, compared to those who were not (patient self-report:

61.6 vs. 74.3; $p < 0.01$, parent proxy report: 65.5 vs. 74.7; $p < 0.01$).²¹⁹

Recommendation 27:

ESPGHAN EGID WG recommends the use of validated HRQoL questionnaires in the care of patients with EoE as one of the composite outcome measures evaluating treatment response, following translation and validation in different languages.

SoR: Strong → Agreement: 93%.

9 | TRANSITION OF CARE

Q28: How should transition of care be addressed in pediatric patients with EoE?

Statement 28:

A multidisciplinary team of pediatric and adult gastroenterologist, dietitian and a transition coordinator is optimal for a successful transition to adult care, as well as a joint review of the medical records and disease course, followed by a joint visit with patient, parents and team present.

QoE: Moderate → Agreement: 93%.

Summary of evidence:

Pediatric patients with EoE who reach adulthood require continuous therapy and chronic disease management. In addition to drug and dietary treatment, there is also a need for recurrent endoscopic assessments with potential need for interventions such as dilations.^{278,279} EoE has a significant impact on

TABLE 2 Main differences from previous guidelines.

Topic	2014 Guideline	Update
Proton-pump inhibitor use	PPIs are used to define EoE patients by demonstrating nonresponse to PPI	PPIs are no longer used as a diagnostic tool rather as a treatment option (Statement 1.2)
Systemic steroids	Not specifically mentioned for use	A short course of systemic steroids may be used as treatment option for severe pediatric EoE associated strictures (Statement 25.3)
Biomarkers and noninvasive techniques	Not discussed	Addressed in current guideline (Statement 10)
Quality of Life	Not discussed	Addressed in current guideline (Statements 27.1 and 27.2)
Endoscopy Scores	Subjective observations discussed	EREFS score discussed
Histology scores	Eosinophil cutoff discussed and subjective assessment of ancillary findings.	EoEHSS discussed; need for report format that is comparable between centers.
Biologics for EoE	No medical agency approved biologics	First biologic approved by FDA and others in clinical studies. (Statement 23.1)

Abbreviations: EoE, eosinophilic esophagitis; EoEHSS, eosinophilic esophagitis histology scoring system; EREFS, endoscopic reference score; FDA, food and drug administration; PPIs, proton-pump inhibitor.

TABLE 3 Suggested doses of drugs used for induction and maintenance of childhood eosinophilic esophagitis (EoE).

	Age group	Induction dose non-stricturing and mild symptoms	Induction dose stricturing or severe symptoms	Initial maintenance dose (usually half of the induction dose for 3–6 months) ^a
Budesonide ^b	Infant 1–3 years	0.5 mg × 1/d–0.5 mg × 2/d	0.5 mg × 2/d	0.25 mg × 1/d–0.5 mg × 2/d
	Child 4–10 years	1 mg × 1/d	1 mg × 2/d	0.5 mg × 1/d–1 mg × 1/d
	Adolescent 11–18 years	1 mg × 2/d	1 mg × 2/d–2 mg × 2/day	0.5 mg × 1/d–1 mg × 1/d
Fluticasone propionate ^{b,c}	Infant 1–3 years	88 µg × 1/d–250 µg × 1/d	88 µg × 2/d–250 µg × 2/d	44 µg × 1/d–125 µg × 1/d (in some cases 125 µg × 2/d)
	Child 4–10 years	250 µg × 1/d–250 µg × 2/d	500 µg × 1/d–500 µg × 2/d	250 µg × 1/d–500 µg × 1/d
	Adolescent 11–18 years	500 µg × 1/d–500 µg × 2/d	500 µg × 2/d–500 µg × 3/d	500 µg × 1/d
Proton-pump inhibitors (given as omeprazole dose—adjust to equivalent dosing of any PPI)	Infant 1–3 years	1 mg/kg × 2/d00	1 mg/kg–2 mg/kg × 2/d0000 ^d	1 mg/kg × 1/d
	Child 4–10 years	1 mg/kg × 2/d (max 60 mg/d)	1 mg/kg–2 mg/kg × 2/d (max 60 mg/d) ^d	0.5 mg–1 mg/kg/d (max 30 mg)
	Adolescent 11–18 years	1 mg/kg × 2/d (max 80 mg/d)	1 mg/kg–2 mg/kg × 2/d (max 80 mg/d) ^d	1 mg/kg × 1/d (A.M. dosing) (max 40 mg/d)
Dupilumab	> 1 year and 15–30 kg	200 mg/2 wk	200 mg/2 wk	200 mg/2 wk
	30–40 kg	300 mg/2 wk	300 mg/2 wk	300 mg/2 wk
	> 40 kg	300 mg/wk	300 mg/wk	300 mg/wk

Note: Dosing for individual patients must be evaluated by the prescribing physician. Readers should be aware that these drugs have been used off-label because FDA/EMA approvals for some of the drugs have only recently been provided. Individual dosing may be needed for each patient and the proposed values must be regarded as guides, but confirmation is needed by the clinician in charge of the patient. These recommendations are based on the clinical experience of the authors in lieu of high-grade randomized studies.

^aAfter 3–6 months another dose titration may be considered on an individual basis (often another decrease of dose by 25–50%).

^bFor once daily dosing, night time dosing is recommended to extend contact time of drug with esophageal wall. The drug should be taken after tooth brushing, and optimally no food or drink should be given for an hour. If twice daily dosing, give morning dose after breakfast.

^cFluticasone multi-dose inhalers are supplied at different doses in different countries, therefore dosing may be slightly different depending on availability.

^dPPI's seem to be inferior to topical steroids at inducing remission in the presence of strictures, and therefore are not recommended. If signs of concomitant reflux esophagitis are present, may consider low dose PPI together with a topical steroid initially.

patients' health-related quality of life and affects their social and psychological functioning. Because EoE is a chronic disease, its increasing incidence and prevalence require chronic care and thus a transition of healthcare delivery.

Healthcare Transition is the “purposeful, planned transition of adolescents and young adults with chronic physical and medical conditions from a child-centered to an adult-centered healthcare system.”^{280,281} Lack of patient knowledge about disease and treatment leads to poor treatment adherence and loss to follow-up. The presence of significant disparities between gastroenterologists treating adult and pediatric patients with EoE may further impact diagnostic rates, appropriate treatment, monitoring, and long-term outcomes and negatively affect the transition from pediatric to adult care.^{282,283}

Questionnaires such as the STARTx questionnaire²⁷⁹ can be used to assess the knowledge and readiness for a successful transition. Details and timing of the transition should be individualized. The literature consistently emphasizes the importance of having a dedicated transition coordinator present in the pediatric and adult clinic to establish a transition care program. This person ensures that the patient engages in developmentally appropriate self-management and self-help tasks to prepare for interaction with adult providers.

Recommendation 28:

The ESPGHAN EGID WG recommends that a multidisciplinary team engaging pediatric and adult specialists (physician, dietitian, nurse, and psychologist) work closely together, with the patient and their family in an individualized process to transfer the care of appropriately prepared patients by the end of adolescence.

SoR: Strong → Agreement: 97%.

10 | CONCLUSIONS

EoE can have a profound impact on the quality of life and mental health of affected children and their families. These include eating behaviors, social difficulties, anxiety, sleep problems, depression, and school problems.^{270,272} Rapid advances in knowledge about risk factors for EoE, endoscopy as main diagnostic method, the three pillars of first line treatment and new therapies on the horizon for pediatric EoE warrant reevaluation of previous statements and recommendations. The EGID working group of ESPGHAN conducted a comprehensive review of the current literature to update our previous guideline.⁵ Table 2 summarizes the major issues that warranted updating statements and recommendations. Table 3 provides suggested doses for each of the discussed medications, both for induction and maintenance of remission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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