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ESOPHAGUS

Monitoring Patients With Eosinophilic Esophagitis in Routine Clinical Practice - International Expert Recommendations

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BACKGROUND & AIMS: **There are no studies or recommendations on optimal monitoring strategies for patients with eosinophilic esophagitis (EoE). Our objective was to develop guidance on how to monitor patients with EoE in routine clinical practice, on the basis of available clinical evidence and expert opinion.**

METHODS: **A multidisciplinary, international group of EoE experts identified the following important 3 questions during several consensus meetings: why, by what means, and when to monitor patients with EoE. A steering committee was named, and 3 teams were formed to review literature and to formulate statements for each topic. In a Delphi survey, a level of agreement of ≥75% was defined as threshold value for acceptance. In a final conference, results were presented, critical points and comments on the statements were discussed, and statements were rephrased/rewritten if necessary.**

RESULTS: **Eighteen EoE experts (14 adult and pediatric gastroenterologists, 2 pathologists and 2 allergists) with a median of 21.7 years in clinical practice, mostly academic or university-based, completed the Delphi survey, which included 11 statements and a proposed algorithm for monitoring patients with EoE. Each statement attained ≥75% agreement. Participants discussed and debated mostly about the statement concerning surveillance intervals for EoE patients with stable disease.**

*Authors share co-first authorship.

Abbreviations used in this paper: EOE, eosinophilic esophagitis; eos/hpf, eosinophils per high-powered field; eos/mm2, eosinophils per square millimeter; EREFS, Endoscopic Reference Score; EUREOS, European Consortium for Eosinophilic Diseases of the GI Tract; fCC, final consensus (video) conference; oDS, online Delphi survey; PEC, peak eosinophil count; TIGERs, The International Gastrointestinal Eosinophilic Researchers.

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CONCLUSIONS: **It was concluded that effective maintenance treatment probably reduces the development of EoE complications, and regular, structured, and, under certain conditions, individualized clinical follow-up is recommended to assess disease activity while opening a window to monitoring side effects, adjusting therapy, and encouraging adherence to treatment. Follow-up should comprise symptom assessment and periodic or repeated endoscopy with histological assessment in specific EoE settings.**

Keywords: Delphi; Disease Monitoring; Eosinophilic Esophagitis; Surveillance.

Eosinophilic esophagitis (EoE) is a chronic, allergic disease of the esophagus affecting both children and adults, defined by clinical symptoms of esophageal dysfunction and histologically by a dense eosinophilic infiltration of the esophageal epithelium with a count of $\geq$15 eosinophils per high-powered field (eos/hpf). Other causes of esophageal eosinophilia must be excluded.[1,2] Histopathological findings indicate that EoE is active if the peak eosinophil count (PEC) is $\geq$15 eos/hpf, whereas histological remission is defined as PEC $\leq$15 eos/hpf.[3] EoE is a life-long disease which currently cannot be cured; however, effective medical[4-7] and/or dietary therapies[8] can control active inflammation in patients with EoE. These therapeutic interventions have been suggested to reduce and/or prevent disease progression to a mixed inflammatory/fibrostenotic phenotype, including complications such as food bolus impaction,[9] strictures, and the need for endoscopic interventions.[10] In patients with EoE, long-term therapy and management is required for the vast majority of patients, in particular, given the only moderate correlation between symptoms and histological inflammation.[11] Apart from clinical, diagnostic, and therapeutic guidelines, no evidence-based recommendations on the clinical monitoring of patients with EoE are at present available. We identified an unmet need to address open questions with regard to monitoring patients with EoE. The lack of data from observational or interventional studies on this topic renders it especially difficult to provide any recommendations on surveillance strategies in patients with EoE in routine clinical practice. Therefore, the aim of this international and multidisciplinary initiative was to reach an international consensus on strategies for monitoring patients with EoE.

Methods

We performed an iterative and structured process with feedback according to standard Delphi methods.[12] The International Gastrointestinal Eosinophilic Researchers (TIGERS) and European Consortium for Eosinophilic Diseases of the GI Tract (EUREOS) consortia agreed to collaborate on this topic, and an international, multidisciplinary team spanning specialties of pediatric and adult gastroenterologists, pathologists, and allergists with expertise in EoE care was assembled. "Expert" participants were defined as having >10 years of subspecialty care of patients with EoE, >5 relevant research publications, and membership in EUREOS or TIGERS (one participant [SO] has 6 years experience of EoE subspecialty care but is a member of EUREOS' steering committee and has published 12 scientific articles on EoE). Three EUREOS members (UvA, AB, and LB) acted as steering committee and reviewed the literature on 3 questions: (1) why, (2) by what methods, and (3) when to monitor patients with EoE. Results were shared, presented, and discussed in a video conference on March 29, 2021, with all panel members; chairs for each questions group were appointed, and collaborators were assigned on the basis of their expertise. Each group elaborated 3 to 4 statements on its specific follow-up question. Statements were presented and discussed in a second video conference on May 18, 2021. According to expert discussion and feedback, statements were redefined, and an online Delphi survey (oDS) was conducted using the SurveyMonkey platform from May 20 to August 10, 2021, including 11 statements and a proposed algorithm for the surveillance of patients with EoE. Participants were asked to rate any given approval of, and potential suggestions on, each statement. The percentage of agreement (agree/disagree) was calculated, and a threshold of $\geq$75% agreement was approved for acceptance.[12] After the oDS, a final consensus (video) conference (fCC) was conducted on October 18, 2021, to present and discuss critical points and comments on the statements in the oDS. Active participation was sought from every participant, and participants' comments were reviewed, discussed, rephrased, and, if found appropriate, adopted. Although each statement in the oDS surpassed the 75% threshold, during the fCC discussion, there was significant debate on statement 10. The steering committee rephrased this statement and forwarded it by email in July 2022 to all participants asking for their vote (agree or disagree). Level of evidence was evaluated according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) guidelines[13] (very low, low, moderate, high). Account was taken of risk of bias, imprecision, inconsistency, indirectness, and dose-response gradient and all residual confounders.[13]

Results

Eighteen EoE experts with a mean practice experience of 21.7 years (range, 6–35 years) took part in this initiative: 11 adult gastroenterologists, 3 pediatric

gastroenterologists, 2 pathologists, and 2 allergists. Practice settings were mostly (16/18) academic or university-based. Most participants (17/18) stated that they saw 10 to 50 (13/18) or >50 (4/18) patients with EoE per month.

All of the participants completed the oDS (Survey Monkey). The fCC was attended by 15 of 18 participants. The email vote in July 2022 was completed by all participants.

Initial and modified/rephrased statements and level of evidence to the questions on why, by what means, and when to monitor patients with EoE are listed in Table 1.

What You Need to Know

Background

Eosinophilic esophagitis (EoE) is a chronic disease of the esophagus. Optimal monitoring strategies for patients with EoE in routine clinical practice do not exist.

Findings

EoE experts formulated 11 statements and a proposed algorithm on how to monitor patients with EoE.

Implications for patient care

A regular, structured, and under special circumstances individualized clinical follow-up is recommended to assess disease activity, side effects of medical treatment, and possible complications of EoE.

Comments on the Statements

Monitoring EoE patients – WHY?

1. EoE is a chronic condition that currently cannot be cured. Cessation of treatment leads to disease recurrence. EoE therefore requires long-term management.[14] Effective treatment ameliorates symptoms and increases quality of life.[4,15,16]

2. Numerous studies show that untreated active EoE leads to unwanted effects in the longer term, such as esophageal remodeling and progressive fibrosis and stricture.[17,18] Longstanding untreated EoE leads to a greater need for endoscopic interventions, such as stricture dilations and endoscopic removal of food impactions.[19] Further, the natural course of untreated EoE also leads to increasing esophageal dysmotility.[20] Recent data suggest that not all patients will have fibrostenotic disease, and endotypes may exist, supporting an individualized approach to care.[21]

3. Although natural-course studies are not yet available, children who are continuous or intermittent responders do not seem to develop clinical complications such as strictures.[22] Also, for adults, studies suggest effective treatment reduces food impactions and need for dilations compared with untreated or inadequately treated subjects.[23]

4. Treatments may become ineffective and/or be stopped by patients on their own initiative. Regular clinical follow-up allows detection of this and adjustment of management (dosing and/or formulation). Scheduled follow-up may also improve adherence to therapy. It has been shown that gaps in care lead to worse outcomes.[24] New or more appropriate therapies may become available in the future, which can be discussed at a follow-up visit.

5. Symptoms do not correlate well with esophageal inflammation and should not be used as the sole measure of disease activity. Even with validated structured symptom assessments, the correlation with histological activity is only moderate.[11] Explanations for this might be the presence of strictures, other concurrent conditions such as gastroesophageal reflux disease and motility disorders, functional symptoms, and side-effects of treatments.

Monitoring EoE patients – WHAT?

6. For diagnosis of EoE, consensus recommendations include a threshold of 15 eos/hpf of esophageal biopsies or as eos/mm^2, viewed at 400× magnification.[1–3,25] EoE is considered to be active on a histological basis if the PEC is >15 eos/hpf and/or 60 eos/mm^2. Histological remission in EoE is considered present if the PEC decreases to <15 eos/hpf and/or 60 eos/mm^2.[26]

7. The Endoscopic Reference Score (EREFS) is the most commonly applied classification system, describing changes in endoscopic appearance. It is a simple, standardized reporting system for clinical use.[27,28] EREFS findings are highly responsive to treatment and can therefore be used as an outcome measure; furthermore, it has been shown to correspond to changes in histological activity in both children and adults with EoE.[29-31] An EREFS threshold <2 is consistent with clinical and histological response defined as <15 eos/hpf and 30% symptom decrease using the Dysphagia Symptom Questionnaire.[32,33]

8. Noninvasive tissue sampling of the esophagus or sample surrogate tissue may decrease the need for invasive endoscopic procedures, including anesthesia, and the risk of endoscopic procedures in the future, especially for children with EoE. The esophageal string test is a sensitive method for detecting esophageal eosinophilic inflammation,[34] and Cytosponge is a minimally invasive method for assessing mucosal eosinophil density.[35] Further research is necessary to support the use of these 2 minimally invasive methods in clinical practice routine. Blood markers, oral swabs, breath condensates, and stool and urine

Table 1. Statements on the Questions Why, by What Means, and When to Monitor Patients With EoE

	Statement	oDs (May–August 2021)	Final consensus conference October 2021[a]	Grade of certainty[b]
Monitoring patients with EoE – why?				
1.	EoE is a chronic condition that currently cannot be cured, but disease remission can be achieved in most patients with medications and/or by elimination diets.	18/18 (100%)	14/14 (100%)	High
2.	Current data suggest that chronic ongoing inflammation in EoE leads to remodeling in the long term and increases the risk for future complications such as esophageal food impactions and the need for dilations.	17/18 (94%)	14/14 (100%)	Moderate
3.	Effective maintenance treatment probably reduces the development of EoE complications.	18/18 (100%)	14/14 (100%)	Low
4.	Original: Follow-up contacts will not only allow the physician to adjust treatment, and to monitor treatment side effects, but may also improve treatment adherence.	17/18 (94%)	–	Low
	Revised: Regular clinical follow-up permits assessment of disease activity while monitoring side effects, adjusting therapy, and encouraging treatment adherence.	–	14/14 (100%)	Low
5.	Original: Exclusive on-demand follow-up is not recommended because symptoms do not always correlate with histological activity.	18/18 (100%)	–	Moderate
	Revised: Exclusive symptom-based (=on demand) follow-up is not recommended because symptoms only moderately correlate with endoscopic and histologic disease activity.	–	15/15 (100%)	Moderate
Monitoring patients with EoE – what?				
6.	To monitor disease activity in adult and children with EoE, histologic activity should be assessed using peak eosinophil count eos/hpf and/or eos/mm^2.	17/18 (94%)	15/15 (100%)	Low
7.	Endoscopic activity should be assessed using the endoscopic reference score (EREFS).	16/18 (88%)	15/15 (100%)	Low
8.	Original: Noninvasive biomarkers are currently not recommended to monitor EoE disease activity in clinical routine.	16/18 (88%)	–	Moderate
	Revised: Noninvasive biomarkers are currently not recommended to monitor EoE disease activity in routine clinical practice.	–	14/15 (100%)[c]	Moderate
Monitoring patients with EoE – when?				
9.	Follow-up assessment including endoscopy with biopsies should be performed 8 to 12 weeks after the initiation of any induction treatment for active EoE or any major treatment change (eg, switch in treatment modality; withdrawal of maintenance therapy).	16/18 (88%)	15/15 (100%)	Low
10.	Original: In patients with stable disease with (or without) any EoE-directed therapy a follow-up interval including endoscopy of 12 to 24 months is recommended but should be individualized under certain circumstances.	16/18 (88%)	No consensus	–
	Revised: In patients with stable disease with (or without) any EoE-directed therapy, we suggest regular clinical follow-up every 12 to 24 months. Periodic repeat endoscopy can be considered on an individual basis, such as in patients with worsening symptoms or an established/suspected stricture that may require intervention, when modification of treatment approach is being considered, and others in whom clarification of esophageal histology is desired.	–	18/18 (100%)[d]	Low

Table 1. Continued

	Statement	oDs (May–August 2021)	Final consensus conference October 2021[a]	Grade of certainty[b]
11.	Original: In patients with known stricturing phenotype and the need of prior endoscopic dilation, follow-up interval with endoscopy should be individualized.	16/18 (88%)	No consensus	–
	Revised: In patients with a history of stricturing phenotype and the need of prior endoscopic dilation, follow-up interval with endoscopy should be individualized.	–	18/18 (100%) §	Low

Note: Data are presented as sample/total (percentage).
EOE, Eosinophilic esophagitis; eos/hpf, eosinophils per high-powered field; eos/mm^2, eosinophils per square millimeter; oDS, online Delphi survey.
[a]This started with 14 participants, and after 20 minutes, a further participant joined the meeting, so that 15 participants had joined by the end of the 1.5-hour meeting.
[b]Level of evidence was evaluated according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE):[13] very low, low, moderate, or high.
[c]One participant withdrew from voting, declaring a conflict of interest (see text).
[d]A new vote on the modified statements 10 and 11 was held by email in July 2022, in which all 18 participants voted (see text).

samples are not recommended for use in clinical practice.[36] (GF declared a conflict of interest and did not vote on statement 8)

Monitoring EoE patients – WHEN?

9. Although there is strong consensus on diagnostic outcome measures to determine efficacy or inadequate response of any initiated therapeutic intervention, the ideal interval after any major change in therapy has not been clearly determined. The lack of consensus for timing assessment of treatment effect is reflected by varying intervals in controlled therapeutic interventional trials. The clinician's decision should take into account the clinical severity of the disease,[37] estimated risk of imminent subsequent food impaction, and presence of stenosis, as well as mode of action and reported outcome of the chosen medical, dietary, or mechanical treatment. An interval of 6,[2,5] 8, 10, 16,[38-40] or up to 24 weeks[41] may be appropriate.

10. Long-term data available for patients under therapy or after treatment withdrawal are limited. There is general consensus that structured follow-up is mandatory. This includes patients with verified remission under proton pump inhibitor or swallowed topical corticosteroid therapy and dietary intervention, as loss of response to therapy remains a concern in long-term responders. Moreover, progression from an inflammatory towards a fibrostenotic phenotype may occur, specifically in patients with insufficient response.[1,2,18,42] Follow-up may specifically be indicated within a lower range of the above-mentioned 12- to 24-month interval in patients undergoing withdrawal from therapy for any reason on account of recurrent disease, which may occur without clinical symptoms.[23,43] A recently published EoE clinical severity index may become helpful in the future for individualizing the approach and timing of monitoring.[37]

11. In patients with a relevant reduction in initial esophageal diameter, several dilations may be required. Fortunately, successful restoration of an esophageal diameter of $\geq$15 mm is achievable in the majority of patients following a strategy of intensified initial follow-up examinations with dilation even in patients with severe strictures. Initial esophageal diameter and histological remission were found to be associated with treatment success in patients with severe strictures.[44]

Discussion

In routine clinical practice of both general practitioners and gastroenterologists, questions from patients with EoE about follow-up strategies are common. They represent a major unmet need for care providers. Although there is wide agreement about diagnostic criteria and treatment modalities – following published guidelines, systematic reviews, and consensus recommendations[1,2,43] – there is a paucity of recommendations on follow-up. Despite existing effective therapeutic regimens, clinicians still lack guidance regarding follow-up strategies for the short- and long-term management of patients with EoE. Furthermore, potential discrepancy between clinical symptoms and histological activity, alongside a paucity of data on disease progression after diagnosis and under anti-inflammatory treatment, both make it difficult to justify the indication for an upper endoscopy to patients with EoE, specifically in the absence of dysphagia with or without treatment.

In this transatlantic, multidisciplinary, iterative, structured, and scientifically based process, experts considered statements on the most important questions: why, by what means and when to monitor patients with EoE. In the Delphi process, every statement reached $\geq$75% agreement. There was strong consensus that an

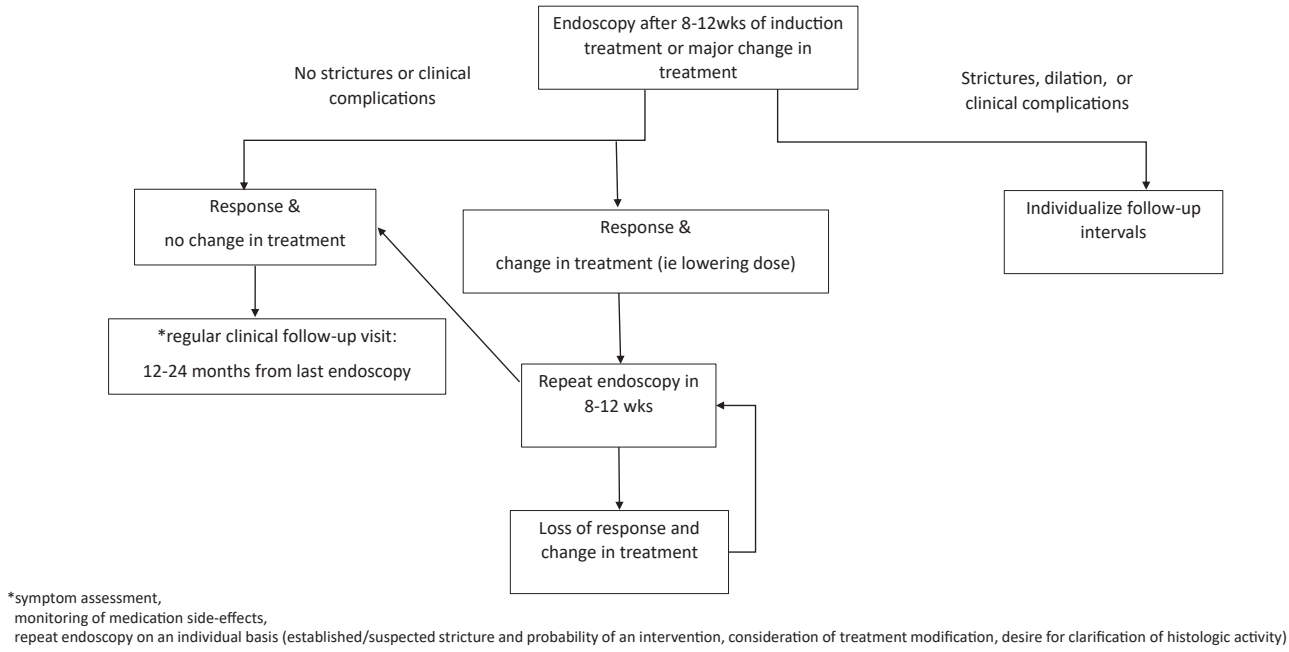

Figure 1. Suggested algorithm for structured follow-up examination of patients with EoE.

appropriate interval for confirmation of a clinical-histological remission, either after induction treatment or after any change in medical/dietary intervention, is 8 to 12 weeks, given the speed of action of treatment with diets and topical corticosteroids. This interval can be extended for slower-acting therapies (eg,monoclonal antibodies).

In the fCC, results of the Delphi round were presented: experts discussed statement 10 concerning the time intervals for performing esophagogastroduodenoscopy in patients with EoE with stable disease, because scientific data on this specific clinical setting are rare and obtained mostly from retrospective studies. Finally, agreement was reached that patients with EoE with a confirmed clinical-histological remission should receive a clinical follow-up visit 12 to 24 months after the last endoscopy. Routine clinical consultation can promote and enhance patients' adherence to medical treatment, potentially reveal therapeutic side effects, and indicate possible secondary loss of treatment response. Follow-up surveillance endoscopy in patients with EoE with stable disease, with or without anti-inflammatory therapy, can be performed 12 to 24 months after the last endoscopy (Figure 1). A retrospective cohort study showed that a >2-year gap in routine clinical care is associated with increased disease activity and progression to fibrostenosis, especially in patients who were not followed-up regularly.[24] That result supports our recommendation for structured follow-up intervals within a range of 12 to 24 months, including assessment of symptoms and, if clinically indicated, consideration of an upper gastrointestinal endoscopy for clarification of histological activity.

This guidance may support clinicians in their daily practice in the decision-making processes for the management of their patients with EoE in the short and long term and may prevent future complications due to missed or neglected follow-up strategies.

In summary, our expert-based Delphi approach leads us to conclude that effective maintenance treatment probably reduces the development of EoE complications, and regular clinical follow-up is recommended as it permits assessment of disease activity while opening a window to monitoring side effects, adjusting therapy, and encouraging treatment adherence. Follow-up should comprise careful symptom assessment but should also include endoscopy in cases of clinical relapse, suspected stricture, when treatment modification is considered or indicated, and if assessment of histological activity is desired.

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