UPDATE

Synopsis of European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Guidelines (2024) on the Diagnosis and Treatment of Eosinophilic Esophagitis

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ABSTRACT

The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) 2024 guidelines on eosinophilic esophagitis in children provide a systematic approach to the diagnosis and management of this rising disease entity in children. We present a concise update of the guideline to simplify management protocols, thus improving patient outcome.

Keywords: *Children, Dupilumab, Proton pump inhibitor, Six-food elimination diet, Topical steroids*

Eosinophilic esophagitis (EoE) was first described in 1978 but is being increasingly recognized as a distinct clinicopathological entity over the past three decades [1]. It is a chronic, antigen-mediated inflammatory disease, characterized by symptoms of esophageal dysfunction resulting from severe eosinophil-predominant inflammation (≤15 eosinophils/high power field) after exclusion of secondary causes of esophageal eosinophilia [2].

Epidemiology

Over the past three decades, EoE has evolved from a rare disease entity to a frequent cause of upper gastrointestinal (GI) tract dysfunction. It is now the second most common cause of reflux and the most common cause of food bolus impaction in children and adolescents in the developed countries [3,4]. A meta-analysis reported an annual overall pooled incidence of 3.7/100,000 (95% confidence interval, CI 1.7, 6.5); the incidence in adults (7/100,000; 95% CI 1, 18.3) was much higher than that in children (5/100,000; 95% CI 1.5, 10.9) [4]. Numerous studies from developing countries have reported an increase in the EoE epidemiology in children, a trend seen in other allergic/atopic diseases such as inflammatory bowel disease, atopic dermatitis, allergic rhinitis etc [3,5]. Most recently, a cross-sectional study from North India reported a prevalence of 3.5% in children undergoing elective upper gastrointestinal endoscopy [5]. The recent ESPGHAN 2024 guidelines have re-emphasized the fact that pediatricians and pediatric gastroenterologists need to be aware of the rising prevalence of EoE and the clinical scenarios where to suspect EoE and initiate further evaluation [3].

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Diagnostic Criteria

EoE can have a varied spectrum of symptoms that include reflux-like symptoms, refusal to feed and vomiting in younger children, and food bolus impaction, dysphagia (due to strictures from long-standing esophagitis) in older children. The diagnosis of EoE has undergone several updates in the last two decades with the birth of new concepts and evidence. Gastro-esophageal reflux disease (GERD) and EoE were considered two distinct entities. Hence, in 2014 guidelines, ruling out GERD by documenting non-response to an 8-week trial of proton pump inhibitor (PPI) was mandatory before making a diagnosis of EoE [6]. However, latest evidence suggests that EoE and GERD are a part of the same disease spectrum [2,3]. In 2018, an international consensus revised the EoE diagnostic criteria and removed PPI trial from the diagnostic criteria [2]. ESPGHAN 2024 guidelines adopted the latest internationally accepted definition [3]. Considering the limitation of applying allergy-based testing (atopy patch test, specific antibody testing) in children, current guidelines also recommended against using available allergy testing to routinely diagnose and treat EoE. **Table I** summarizes the differences between 2014 and 2024 guidelines. The EoE Endoscopic Reference Score (EREFS) is an easy to use, validated score that has been highlighted in the latest guidelines to capture endoscopic findings associated with EoE such as mucosal edema, exudate, rings, furrows and strictures [3].

Management

The management of EoE aims to control symptoms and esophageal inflammation and prevent further complications [3]. In children with EoE, current treatment options can be categorized into three 'D's – **D**iet (elimination or elemental), **D**rugs (high-dose proton pump inhibitors [PPI], topical steroids, biologics) and **D**ilatation for strictures. Choosing the best

Table I Main Differences Between 2024 and 2014 Guidelines by European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

	2014 ESPGHAN Guidelines	*2024 ESPGHAN Guidelines*
Trail of PPI as part of diagnostic criteria	Nonresponse to PPIs was used to define EoE	PPIs no longer used as a diagnostic tool; rather recommended as a treatment option.
Eosinophilic involvement of other segments of the gastrointestinal (GI) tract does not exclude the diagnosis of EoE.	Not addressed	EoE may coexist with eosinophilic infiltration of other segments of the GI tract.
Clinical symptom assessment tools	Not discussed	Pediatric Eosinophilic Esophagitis Symptom Score (PEESS) advocated for assessing treatment response and monitoring
Endoscopic evaluation	Subjective observations of endoscopy discussed	Objective assessment using Endoscopic Reference Score (EREFS) suggested for further evaluation
Histology scores	Peak eosinophil cutoff/hpf discussed and subjective assessment of ancillary findings.	Eosinophilic Esophagitis Histologic Scoring System (EoEHSS) is suggested to assess the disease activity using peak eosinophil count.
Systemic steroids	Not specifically mentioned for use	Short course of systemic steroids may be used as treatment option for severe pediatric EoE associated strictures
Biologics	No biologics advocated	First biologic approved by FDA and for children > 1 year of age
Biomarkers and noninvasive techniques	Not discussed	Discussed in current guideline
Quality of Life	Not discussed	Addressed in current guideline

EoE Eosinophilic esophagitis, FDA Food and Drug Administration, hpf High power field. PPI Proton pump inhibitor

treatment depends on disease phenotype and endotype (severity, presence of strictures, nutritional status). **Fig. 1** describes an algorithmic approach for the management of EoE.

A step up approach for elimination diet (2>4>6 food elimination diet), has been advocated to reduce the number of endoscopies, lower costs, better compliance and better quality of life. Recently, the upfront use of single-food elimination diet (cow's milk elimination) has demonstrated encouraging results, but further studies are needed to assess the efficacy of this approach [3].

According to the 2024 guidelines, PPIs are considered the first-line therapeutic options on the same level as steroids and elimination diet [3]. Topical steroid is another group of drugs with proven clinical, endoscopic and histological benefit. Topical steroid slurries can be easily prepared, which have better drug delivery and have made the treatment of EoE much easier [8]. Oral budesonide slurry can be prepared by mixing with sucralose (1 g packet per 1 mg of budesonide). The dose of budesonide as an oral viscous slurry is 1 mg daily for children below 10 years of age and 2 mg daily for older children and adults [3,7]. Interestingly in the latest guidelines, short-term systemic steroids have been recommended to reduce the need for mechanical esophageal dilation in moderate to severe strictures associated with pediatric EoE [3].

Better understanding of the underlying patho-physiology of EoE has led to the identification of new therapeutic targets. The antibodies against IL-5, IgE, chemoattractant receptor homologous molecule on Th2 cells and tumor-necrosis factor-α have not been found effective [3]. The new kid on the block, dupilumab, which is an IL-4 antagonist, has shown promising results in children with refractory EoE [8]. In May 2022, dupilumab was approved by the FDA as the first and only drug specific for treating EoE for children aged 12 and above [10]. Most recently, Food and Drug Administration (FDA) has approved dupilumab for children > 1year or weighing more than 15 kilograms [3,8,9].

Maintenance

EoE, being a chronic, relapsing disease, maintenance therapy is recommended to prevent relapse [3]. However, there is still no consensus regarding the optimal drug, dose and duration. Low-dose PPI, topical steroids and dupilumab have been used in children with EoE [3]. Montelukast has not been found to be effective as a maintenance therapy [3].

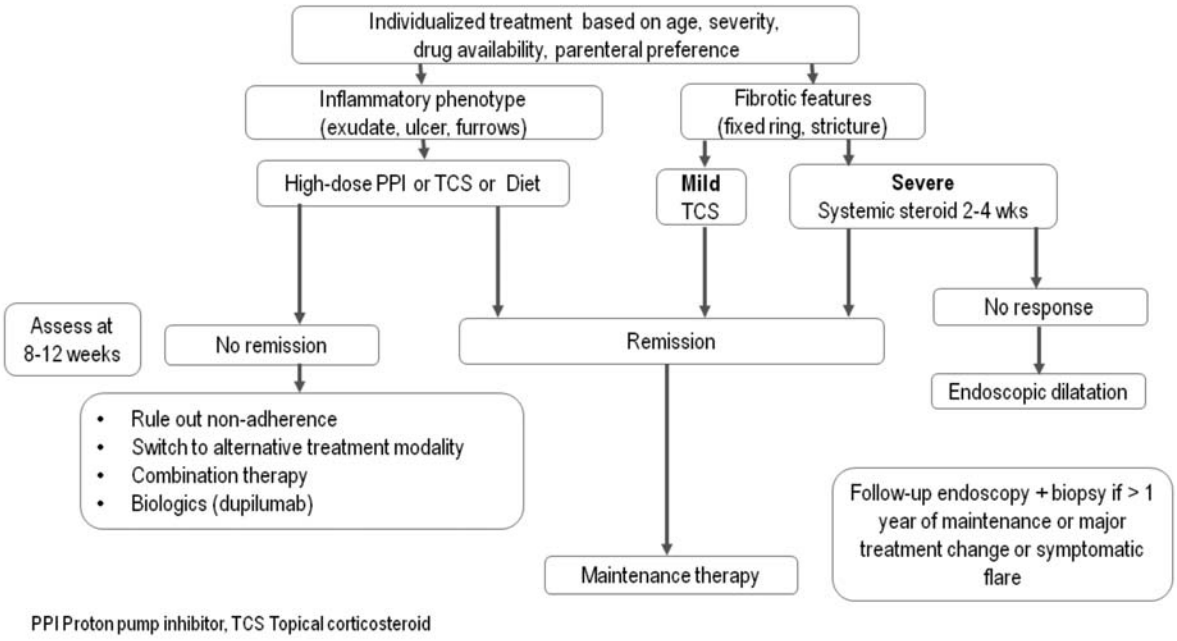

Fig. 1 Algorithmic approach to the management to children with eosinophilic esophagitis.

Monitoring

ESPGHAN 2024 guidelines have advocated endoscopy and biopsy 1-3 yearly in patients with stable clinical remission, or in case of symptomatic flare, or major treatment changes. The Pediatric Eosinophilic Esophagitis Symptom Score (PEESS), a validated tool has been endorsed for evaluating treatment response and disease monitoring [3].

Key Challenges

Clinicians and patients may face different challenges during the treatment. Although elimination diets offer a good, non-pharmacologic therapeutic option, its restrictive nature can lead to non-adherence, isolation from peers, the extra cost of exceptional food alternatives, cross-contamination while preparing meals, or possibly nutritional deficiencies. Furthermore, repeated endoscopies during the reintroduction of food groups can lead to extra financial and psychological burden on patients and their families. Targeted biologic therapy, especially dupilumab have shown promising results; however, long-term efficacy and safety data is still not available. EoE and its long-term complications often lead to poor quality of life [3]. Therefore, it is crucial to incorporate psychosocial support into patient care and engagement in support groups.

Future Directions

There are still several unmet needs regarding the diagnosis and treatment of EoE. Apart from dupilumab, several other drugs (CRTH2 antagonist, lirentelimab) are being explored as a potential treatment option for EoE. The KRYPTOS trial (Phase 2/3) showed that lirentelimab (Siglec-8 blockers) achieved a statistically significant eosinophil reduction in esophageal biopsy. These new therapeutic options highlight the need for further comprehensive trials [10].

Minimally invasive disease-monitoring methods and biomarkers are being evaluated to aid the long-term monitoring. Cytosponge is a sponge-containing capsule that collects esophageal tissue as it is pulled back after being swallowed, offering an easy method to assess EoE inflammatory activity [3]. Another monitoring tool currently being assessed is the Esophageal String Test, which assesses eosinophil-derived granule proteins from secretions in the esophagus that stick to the string as it is removed [3]. Additionally, a new way to perform serial endoscopies is through a transnasal endoscopy, that can be done without sedation while maintaining a visual assessment of the esophagus and histopathologic testing [3]. Unsedated transnasal endoscopy has recently been tested in a clinical trial with good efficacy, safety and cost-effectiveness for acquisition of biopsy samples [3].

However, these non or minimally invasive methods need further validation studies for definitive recommendation. Several biomarkers such as eosinophil peroxidase, eosinophil cationic protein, IL 10, anti NC1A142 (collagen XVII) IgG4, eosinophil progenitor cells, are being studied in children with EoE [3]. However, there are still investigational and not to be used for the diagnosis or management of pediatric EoE.

Role of Pediatricians

Pediatricians should be aware of this disease entity as the

Box I Secondary Causes of Esophageal Eosinophilia

Gastro-esophageal reflux disease (GERD)
Esophageal crohn's disease
Infections (Fungal, viral)
Hypereosinophilic syndrome
Connective tissue disorders
Drug hypersensitivity reactions
Pill esophagitis
Graft versus host disease (GVHD)
Hyper IgE syndrome
Autoimmune disorders
Vasculitis
Achalasia

prevalence of EoE is rising rapidly in the developing world. EoE should be suspected in children presenting with refractory-GERD, non-specific gastrointestinal symptoms in the presence of concomitant atopic disorders or peripheral eosinophilia or food bolus impaction in older children. However, secondary causes of esophageal eosinophilia should be carefully excluded before making a definitive diagnosis of EoE (**Box 1)**. Pediatricians need to be aware of the rapidly evolving diagnostic and therapeutic modalities for EoE patients.

CONCLUSION

EoE is a rising entity and poses significant diagnostic and therapeutic challenges. Ongoing research has led to a greater understanding of the underlying etiopathogenesis and new therapeutic approaches. Dupilumab has shown promise as a treatment option with potential disease-modifying ability. It will be critical to evaluate the least invasive diagnostic modality for the assessment of disease activity, and the best treatment strategies, with an emphasis on the development of new, easily administered and inexpensive treatment options. Collaboration among clinicians and researchers will be of utmost importance to meet the unmet needs of management of EoE.

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