UNIVERSITÀ
DI PAVIA
PhD IN BIOMEDICAL SCIENCES
DEPARTMENT OF BRAIN AND BEHAVIORAL SCIENCES
UNIT OF NEUROPHYSIOLOGY

Implementing Precision Medicine in Pediatric Eosinophilic Gastrointestinal Disorders

PhD Tutor: Prof. Gian Luigi Marseglia

PhD dissertation of Martina Votto
Matr. n. 496223

Academic year 2022/2023

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To my uncle Michele, a doctor, a mentor, and a father.

Living without you is hard, but your example and spirit guide me and my medical activity every day.

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Introduction

State of the art on pediatric EGIDs

Eosinophilic gastrointestinal diseases (EGIDs) are emerging disorders characterized by chronic/remittent eosinophilic inflammation affecting the gastrointestinal (GI) tract from the esophagus to the anus without secondary causes of intestinal eosinophilia [1]. Based on the site of the inflammation, EGIDs have been recently classified into eosinophilic esophagitis (EoE) and non-EoE EGIDs [2]. Based on the site of inflammation, non-EoE EGIDs are distinguished into eosinophilic gastritis (EoG), enteritis (EoN), and colitis (EoC) [2]. EoE is currently considered the prototype of EGIDs and is a chronic, antigen-mediated disease that explicitly involves the esophagus [1]. The first case of EoE was reported in 1978 and was misinterpreted as an esophageal motility disorder [3]. Subsequently, esophageal eosinophilia was considered a feature of gastroesophageal reflux disease (GERD) [4]. EoE was recognized as a distinct clinical entity by Attwood and Straumann only in the early 1990s [5, 6].

In the last decade, several efforts have been made to understand the pathophysiology and natural history of these proteiform diseases. However, non-EoE EGIDs are still less understood disorders, and no standardized guidelines on diagnosis and management are currently available.

Epidemiology

The epidemiology of non-EoE EGIDs is limited to a few observational studies. In the general population, prevalence is estimated at 3–8/100,000 cases, although in patients with gastrointestinal symptoms, it was about 2% [7] (**Chapter 1**).

EoE has evolved from a rare condition to a commonly encountered disease in pediatric clinical practice and it is a significant cause of upper gastrointestinal morbidity [8]. The global prevalence of EoE is 0.5–1 cases/1,000 persons [8]. During the last years, several studies reported a dramatic increase in EoE epidemiology, especially in children in Western Countries [9-14]. This increase in EoE epidemiology was, at least partially, an actual increase and not only an artificial effect due to raised awareness. This phenomenon occurred parallelly with the dramatic rise in the global prevalence of allergic diseases observed during the past few decades and might partly be explained by the hygiene hypothesis [15, 16]. Despite some genetic factors associated with an increased risk of developing EoE, environmental factors are probably the most relevant pathogenetic players [8]. In children living in Westernized Countries, one of the most impressive changes in environmental factors exposure observed in the last decades is related to dietary habits with increased consumption of modified and enriched foods [17,18] **(Chapter 2)**.

Pathogenesis

The pathogenesis of EGIDs is still largely undefined. EGIDs are multifactorial diseases involving genetic and environmental factors [17]. In EoE, these factors are responsible for altering the esophageal barrier through intricate interactions, with loss of cell-to-cell adhesion mechanisms and consequent increased permeability, allowing abnormal exposure to allergens and other luminal components [19, 20]. Alteration of the esophageal barrier leads to the epithelial release of alarmins, like thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33. These mediators drive the differentiation of T helper 2 (Th2) effector cells, with the consequent production of several Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) and massive recruitment of eosinophils [21]. Simultaneously, luminal antigens, encountering antigen-presenting cells, activate specific antigen Th2 differentiation, with additional releasing of inflammatory cytokines, eosinophils recruitment,

and plasma cell activation with specific IgE production [21]. However, IgEs, pivotal in several atopic diseases, do not have a primary role in EoE pathogenesis [17].

The effect of genetics seems to unfold in conjunction with environmental factors, including early-life exposures [18]. Early life is a critical period during which the immune system and gut microbiota mature and become susceptible to early environmental exposures [17]. Formula feeding, neonatal intensive care admission, prematurity, maternal fever, antibiotic and acid suppressant use in infancy, and cesarean delivery were potential early risk factors of EGIDs [17] (**Chapter 2**).

While eosinophilic gastritis and enteritis show the same pathogenetic mechanisms of EoE, the pathogenesis of eosinophilic colitis is different from that of other non-EoE EGIDs and is mainly related to apoptosis gene expression, reduced epithelial cell proliferation, and minimal evidence of Th2 inflammation [22].

Diagnosis

EoE is characterized clinically by symptoms of esophageal dysfunction and histologically by ≥15 eosinophils per high power field (eos/HPF) [23]. Other causes of esophageal eosinophilia should always be ruled out, particularly GERD, celiac disease, Crohn's disease, achalasia, HIES, and drug hypersensitivity. Pediatricians should diagnose EoE based on a combination of symptoms and histological and endoscopic findings, as no single feature is sufficient to establish a definitive diagnosis. Therefore, essential diagnostic instruments are 1) medical history, 2) endoscopic features, and 3) histological examination.

Diagnosis of non-EoE EGIDs is challenging and often requires more endoscopies with potential misdiagnosis and diagnostic delays. The diagnostic cut-offs of tissue eosinophils vary according to the specific site of the GI tract [1]. Endoscopy is the gold standard for the diagnosis and follow-up of EGIDs [23]. Therefore, there is a critical need for noninvasive tools and biomarkers to

replace such invasive monitoring. Despite several efforts to identify potential noninvasive biomarkers, none have been incorporated into guideline recommendations [24] (**Chapter 4**).

Clinical Features and Heterogeneity of EGIDs

EoE symptoms vary with age [1, 25]. Toddlers and young children generally experience food refusal, feeding difficulties, recurrent vomiting and/or regurgitation, and failure to thrive. School-aged children often reported abdominal/epigastric pain and refractory GERD, whereas adolescents and adults usually present dysphagia and food impaction [25]. Children can also develop compensative feeding habits (drinking during meals, eating slowly, chewing carefully, cutting food into small pieces, lubricating foods with sauces or liquids) or avoiding some foods (meat, crusty bread, and pills) [26].

Notably, clinical, endoscopic, and histological features reflect the evolution of EoE inflammation through time. Different clinical patterns or phenotypes have been identified [27]. The "inflammatory" pattern is generally observed in children and is defined by the endoscopic evidence of edema, erythema, linear furrowing, and the prevalent eosinophilic infiltration at the biopsy [27-29]. Instead, the "fibro-stenotic" phenotype affects adults who typically experience dysphagia and food impaction episodes [26-29]. This phenotype is endoscopically characterized by fixed esophageal rings and/or strictures resulting from tissue remodeling and esophageal fibrosis [26-29]. The clinical and histological heterogeneity might reflect and partially explain the heterogeneous response to currently available therapies [27]. While diet and medical treatments may reduce tissue fibrosis in childhood, this remodeling process may persist despite the resolution of inflammation in adulthood [30].

Several studies have shown that patients with EoE have concomitant allergic comorbidities, such as allergic rhinitis, asthma, atopic dermatitis, and IgE-mediated food allergy [31]. On the other hand, several non-atopic diseases are further associated with EoE, such as inflammatory bowel

disease, connective tissue disorders, autism and attention deficit hyperactivity disorders, esophageal atresia, celiac disease, as well as monogenic disorders [32, 33-36] (**Chapter 3**).

Recently, Biedermann et al. identified a new clinically defined syndrome in adults with EoE called the food-induced immediate response of the esophagus (FIRE) [37]. FIRE syndrome encompasses esophageal symptoms occurring rapidly after contact with the esophageal surface with a specific food. This syndrome is mainly triggered by fruits, vegetables, and drinks, just like the pollen food allergy syndrome (PFAS). The pathogenesis of this novel syndrome is still unclear; a local immunologic factor causing an immediate mucosa response has been postulated [38]. We described the first case of pediatric FIRE syndrome (**Chapter 3**).

Symptoms of non-EoE EGIDs depend on the site (stomach, intestine, or colon) and the depth (mucosal, muscular, or serosal layer) of the eosinophilic inflammation. They are generally represented by abdominal pain, nausea, vomiting, and diarrhea [1]. Patients with non-EoE EGIDs may rarely develop GI complications, such as intestinal obstruction or eosinophilic ascites. However, they may commonly experience malnutrition or weight loss [1].

In sum, EGIDs are clinically heterogeneous diseases with symptoms depending on the age at onset, the site of inflammation, response to treatments, and related comorbidities (allergic and not allergic), thus defining a *spectrum* of different diseases (**Chapter 3**).

Therapy of pediatric EoE

EoE treatment aims to control symptoms and esophageal inflammation and prevent complications. The therapeutic options are divided into three categories: Drugs (medical therapy), Diet (elimination of culprit foods), and Dilation (mechanical therapy) [1, 25] **(Chapter 5)**. The only currently approved treatment options for EoE are budesonide effervescent tablets for adults in most European Countries and dupilumab, which the FDA and EMA approved for patients ≥ 12 years

[39]. Therefore, treatments routinely used in pediatric clinical practice, like proton pump inhibitors (PPIs) or topical corticosteroids, are not approved for EoE, so they are prescribed off-label.

Pharmacological therapy

Swallowed topical corticosteroids

Topical corticosteroids are effective in inducing EoE remission. Meta-analyses of topical corticosteroids in the form of swallowed fluticasone or viscous budesonide demonstrate the superiority of these medications to placebo for esophageal eosinophilia, endoscopic findings, and GI symptoms [40]. A further meta-analysis confirmed the efficacy of swallowed budesonide compared to placebo [41]. A recent randomized trial to compare fluticasone and viscous budesonide for EoE treatments showed that viscous budesonide provided a significantly higher level of esophageal exposure to the therapeutic agent with lower eosinophil counts [42]. Moreover, some evidence shows oral budesonide can reverse esophageal fibrosis [43]. Despite regular therapy, the increase in esophageal eosinophil counts is also described [44, 45].

There are many unresolved questions about the chronic use of topical steroids. There is no consensus regarding dosage, formulation, frequency, and how to obtain remission using minimal steroid dosage. Long-term side effects are a significant concern, and no studies have been conducted regarding bone health in patients for longer than one year [46]. The most common side-effect of topical steroids is oral and esophageal candidiasis [47]. Topical corticosteroids are typically administered once or twice daily, and dosing depends on age and disease severity. Patients should spray fluticasone without a spacer in the back of their mouth and swallow the dose. No food or drink is allowed 30 minutes after administering the medication [46].

Proton pump inhibitors

The response rates to PPI therapy in the EoE population can vary widely from 30% to 70% [23]. In a meta-analysis of 32 studies on PPI treatment in EoE, 50.5% of patients achieved histologic

remission [48]. The dosage effective in EoE treatment is 1-2 mg/kg in children and 40 mg of omeprazole (or equivalent dosages for other PPIs) once or twice daily. The mechanism of action of PPIs in EoE is still unclear. PPIs are well-established inhibitors of gastric parietal H+/K+-ATPase, and this effect may reduce acidic injury to the esophagus and cause epithelial healing. Also, PPIs show anti-cytokine properties, directly inhibiting epithelial STAT6, a key transcription factor for the secretion of pro-inflammatory chemokines and cytokines [49, 50]. No clinical features or biomarkers discern a patient who will respond to PPI monotherapy from resistance. Differences in the pathophysiology between PPI-responsive and PPI-resistant EoE remain determined and might be related to different genetic polymorphisms or molecular transcripts.

Biological therapies

The increasing knowledge of EoE pathogenesis has allowed several therapeutic targets to be identified and tested. The humanized antibodies against IL-5, such as mepolizumab and reslizumab, were tested in three controlled trials in children and adults with active EoE, demonstrating reduced tissue eosinophilia and a favorable safety profile. Unfortunately, clinical improvement was minimal [51-53]. A phase III trial using benralizumab, a monoclonal antibody against the IL-5 receptor, is active [53, 54].

Two RCTs with the anti-IL-13 agent and one with the anti-IL-4 receptor antagonist dupilumab showed promising results [55, 56]. In a phase II study, a monoclonal antibody against IL-13 improved endoscopic and histological disease activity in the short and long term146, 147. Dupilumab is currently the most advanced biologic therapy in EoE treatment. Dupilumab is a human monoclonal antibody targeting the α-chain subunit of the IL-4 receptor, which is shared between IL-4 and IL-13 [57]. The phase III study of dupilumab demonstrated significant beneficial treatment effects on clinical symptoms, eosinophil counts, and esophageal distension [53].

Therefore, the FDA, then EMA, recently approved dupilumab for treating adolescents (> 12 years) and adults with active EoE. Trials in children younger than 12 years are recruiting, but preliminary results showed promising effects.

Diet therapies

Diet therapy

In 1995, Kelly et al. successfully demonstrated the efficacy of the exclusive aminoacidic-based formula diet in children with EoE [58]. The elemental diet (ED) consists in removing all foods. Thus, patients are exclusively fed an aminoacidic-based formula for at least six weeks [23, 59, 60]. The ED is the most effective treatment, and several studies reported high complete remission rates in children with active EoE [61]. EoE patients treated with the ED experienced a significant reduction in their symptoms and achieved complete histologic remission in 90 and 94% of pediatric and adult cases, respectively.

Moreover, the highest efficacy rates are primarily observed in patients with a non-stenotic phenotype [62-66]. In toddlers or young children with active EoE complicated by failure to thrive, the ED has generally been considered a valid and valuable therapeutic option with the highest patient compliance [67]. Although the ED can induce rapid disease remission in only two weeks, several disadvantages limit its adherence [68]. The poor palatability, highly restrictive nature, costs, and psychosocial isolation are the main reasons for treatment discontinuation and low compliance [63, 67, 69]. For these reasons, ED is often not considered a first-line approach because of its limitations [67]. Therefore, it is a therapeutic option in severe EoE cases, or it is often proposed as rescue therapy or a temporary solution in adults and adolescents with refractory EoE [62, 67] (**Chapter 5**).

Empirical food elimination diet (FED)

FED is the most widely used diet treatment for EoE. The first proposed FED was founded on avoiding the six (6-FED) most common food triggers of EoE in the Western diet: milk, wheat/gluten, egg, soy/legumes, peanut/tree nuts, and seafood/fish [70]. The efficacy (histologic remission) of 6-FED is about 74% in children [71]. In children, the most common food trigger is cow's milk (up to 85% of cases), followed by wheat/gluten (up to 60% of cases), egg, and soy/legumes, with geographic variations [61]. Consequently, nuts and fish/seafood rarely trigger EoE. Most children who histologically recover with 6-FED are allergic to only 1–3 foods [29]. Although 6-FED is less restrictive than the elemental diet, avoiding all six food groups can still be challenging. Several drawbacks limit the adherence to 6-FED due to the high level of dietary restriction and the need for frequent upper GI endoscopies to identify the culprit food(s) [67]. For these reasons, 6-FED is generally not considered the ideal therapeutic approach in children. Subsequent studies proposed and assessed less restrictive FEDs that avoided the most common EoE food triggers. The 4-FED (milk, wheat, egg, and soy/legumes-free diet) induced histologic remission in 54% of children [72, 73]. In studies evaluating the efficacy of 4-FED, milk and wheat were the most common triggers of EoE [67]. Children avoiding these two foods (2-FED) achieved complete remission in 40% of cases. The elimination of cow's milk (1-FED) demonstrated disease-remission rates of 44–51% in pediatric patients [62]. In a recent systematic review with meta-analysis, the overall efficacy of a milk-free diet was about 70% [71].

Recently, Molina-Infante et al. proposed a step-up approach that consists of the initial elimination of one (1-FED) or two (2-FED) more common allergenic foods (milk and wheat) [74]. If complete remission is not achieved, the diet is further restricted to 4 and eventually to 6 foods [74]. The step-up approach is generally preferred in children because it leads to faster and earlier identification of food triggers, avoids unnecessary diet restrictions, and reduces the number of endoscopies (**Chapter 5**).

Therapy of pediatric non-EoE EGIDs

No validated guidelines are available on the clinical management of patients with non-EoE EGIDs. Although reported in case reports and small uncontrolled case series, different therapeutic options are described. The first-line treatments are food-elimination diets and oral corticosteroids [1].

Diet therapies

Dietary therapy is considered a first-line treatment for EGIDs [75]. Recently, Lucendo et al. reported that the ED induced clinical remission in about 75% of children with eosinophilic gastroenteritis and colitis, but the low compliance limited its usefulness, especially in adolescents and adults [76]. Chehade et al. demonstrated that ED is more effective than FED in children with severe eosinophilic gastroenteritis complicated by protein-losing enteropathy [77]. However, there are no extensive studies on the long-term efficacy and safety of ED, and evidence is limited to a few case reports and small case series. FED is the most commonly and efficaciously used dietary option, with about 82% of the clinical response rate [75]. Eliminated trigger foods are cow's milk, wheat, egg, soy/legumes, fish, and nuts.

Corticosteroids

Corticosteroids are the mainstay of therapy if dietary treatment fails or is impractical and in case of severe or complicated eosinophilic gastroenteritis and colitis [75, 78]. Most case series have reported clinical remission in 50 to 90% of patients with EGIDs treated with corticosteroids [1, 79]. Oral prednisone at 20-40 mg/day or higher doses (0.5–1 mg/kg/day) is generally recommended for two weeks [75, 80]. Once clinical remission is achieved, the prednisone dose is tapered over the next 6-8 weeks until it is stopped [81]. Maintenance treatment with a low prednisone dose (5–10 mg/day or the minimum required dosage to guarantee the clinical response) might be necessary for patients with disease relapse during or after drug tapering [75, 81]. The undesirable long-term side effects limit the use of systemic corticosteroids. An alternative to prednisone is budesonide, a synthetic steroid with high topical glucocorticoid activity that

minimizes systemic side effects [82]. Although budesonide is described in a few case reports, it might be considered an effective and safe option. The recommended dose of budesonide is 9 mg/day; then, it can be tapered to 6 mg/day and 3 mg/day for maintenance therapy [80, 82].

Monitoring of EGIDs

EGIDs are chronic/remittent diseases that require lifelong therapy. Neither guidelines nor consensus recommendations on the long-term management of EoE and non-EoE EGIDs have been published so far. A diagnostic work-up includes the assessment of symptoms and growth, endoscopic alterations, and histological abnormalities. The diagnostic work-up should be performed around 3-4 months after initiating a novel treatment or after each relevant therapeutical change [83]. Under stable conditions and solid adherence to treatment, a diagnostic work-up once per year is adequate for most patients.

Patients following a dietary regimen should be widely informed of the need for repeated follow-up endoscopies. Food reintroduction in patients on a 6-FED requires at least six endoscopies and several months to identify the culprit food(s). In children exclusively fed with the aminoacidic-based formula, the food-reintroduction process is even longer and loaded by several endoscopies. Once the culprit food(s) is identified, the long-term diet therapy is based exclusively on avoiding the food(s) responsible for esophageal inflammation [84].

Recent evidence suggests that children treated with topic steroids can undergo a progressive dose reduction after a successful induction therapy until the lowest effective dose. This approach was effective in about 50% of children treated with viscous budesonide and was safe [85].

Several factors may negatively influence the nutritional status of patients with EGIDs [86]. Children with EoE generally present GI symptoms, like vomiting or food refusal, that may limit adequate dietary intake [86]. Patients with previous food impaction episodes may risk developing anxiety and eating disorders, compromising adequate nutrient intake [69, 87].

Another critical point is that EGIDs are often delayed or misdiagnosed, especially in the first two decades of life [88, 89].

The coexistence of multiple food allergies might be a further reason for failure to thrive and undernutrition. On the other hand, long-term restrictive FEDs may compromise adequate micronutrient intake, although they do not appear to worsen child growth or body mass index (BMI) [86, 90]. Nutritionists have a crucial role in pediatric EoE. A nutritionist should meticulously evaluate the diet of patients to determine the degree of exposure to high-risk groups of foods and the potential nutritional and psychological effects of their elimination [91, 92]. Before beginning diet therapy and during the follow-up period, pediatricians should periodically assess the nutritional status of children and rule out potential dietary deficiencies. Then, clinical (symptoms, comorbidities, feeding habits/disorders) and anthropometric data should be collected and carefully evaluated to address the best therapeutic choice **(Chapter 3)**.

Another critical point concerns the patient's education. Pediatricians should carefully inform patients and their families regarding what they can eat and provide the appropriate resources for additional information [67]. Patients should also be advised on the risk of potential allergen contamination. According to specific local legislation, clinicians should educate patients and families to read and correctly interpret the labels of food products [67]. The precautionary allergen labeling ("may contain") is not mandatory in some Countries [67]. However, the risk of allergen cross-contamination and trace exposure for foods reporting this warning is variable and still not established in EoE patients [67].

The chronic nature of EoE, comorbidities, long-term restrictive therapies, and strict endoscopic follow-up are the main stressful factors for patients and their families [69]. It is evident that EoE significantly impacts the QoL of patients [69]. Therefore, psychological support should be provided when behavioral, mood diseases or eating disorders are suspected [69].

Unmet needs

EGIDs are relatively recent diseases; hence, their management is burdened by several complex unmet needs (Table 1) [93]. Standardized and universal guidelines for optimal long-term management, including histologic, endoscopic, and clinical monitoring, are still unavailable. Moreover, there is an urgent need for noninvasive biomarkers of disease activity to reduce invasive endoscopic monitoring **(Chapter 4)**.

Another critical point is the diagnostic delay. It was widely demonstrated that the definitive EGID diagnosis occurs with a variable diagnostic delay of 2-6 years, resulting in a higher risk of esophageal fibrosis, failure to thrive, significant psychological burden, or intestinal complications. Improving clinical, endoscopic, and histologic recognition may also help the diagnostic process and the differential diagnosis of these conditions **(Chapter 4)**.

EGIDs are heterogeneous diseases with a variable response to treatments. Therefore, there is a need for targeted therapies to restore intestinal function by regulating the immune response to luminal triggers. In this context, the efforts should be addressed to identify subgroups of patients according to their molecular, genetic, histologic, endoscopic, and clinical features. Multicenter studies should be encouraged to collect the highest number of children with EGIDs.

EGID patients may present other coexistent allergic and non-allergic diseases, including nutritional deficiencies and psychological issues. Managing children with a multidisciplinary team (pediatric allergists, gastroenterologists, endoscopists, nutritionists, psychologists) can help address comorbidities and ensure global childcare and health.

Table 1 Unmet needs, possible solutions, and scientific efforts during the Ph.D. activity.

Unmet needs	Possible solutions	Research activity during the Ph.D.
EGID pathogenesis and natural history	Extensive characterization (genetic, molecular, and clinical) of patients. Long-term multicenter observational studies.	Identification of phenotypes and endotypes of EGID. Promotion of the first national observational on pediatric EGIDs (GOLDEN study).
Diagnostic delay	Improving scientific awareness. Definition of non-esophageal EGID guidelines.	Assessment of the effect of diagnostic delay in EGID children.
Comorbidities	Promote the multidisciplinary approach.	Institution of the Center for Pediatric Eosinophilic Gastrointestinal Disorders (CPED), where pediatric allergists, gastroenterologists, nutritionists, and endoscopists follow children with EGIDs.
EGID long-term management	Definition of new international guidelines on long-term management of EoE and non-esophageal EGIDs.	Elaboration of EAACI guidelines (ongoing). Participation in European registry (CONNECT study).
Noninvasive biomarkers	Molecular characterization of EGIDs.	Assessment of serum galectin-10 as a new noninvasive biomarker of EoE.
Targeted therapies	Extensive characterization (clinical and molecular) of EGID patients. Multicenter studies.	Identification of phenotypes and endotypes of EGID. Promotion of the first national observational on pediatric EGIDs (GOLDEN study).

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Study aims

The primary aim of the Ph.D. research was to ***implement Precision Medicine*** in pediatric EGIDs management, evaluating the epidemiological, clinical, endoscopic, and histologic features of children and adolescents with these emerging conditions followed at the Pediatric Center for Eosinophilic Gastrointestinal Disorders (CPED) in Pavia, Italy.

EGIDs are heterogeneous conditions with variable clinical presentation, comorbidities, natural history, and treatment response. No studies have been published to date stratifying EGID children into clinical phenotypes. Therefore, we secondly aimed to ***characterize EGID heterogeneity*** by performing cluster analysis.

Predicting the response to medical therapy and disease courses is a critical challenge for clinicians and experts in EGIDs. The upper GI endoscopy remains the gold standard of EGID diagnosis and follow-up. Therefore, identifying noninvasive biomarkers is a critical and urgent need, especially in the pediatric age. We finally aimed to ***identify potential biomarkers*** of disease, helping clinicians to improve the diagnosis and management of pediatric EGIDs.

Collaterally, we also aimed to:

1) improve the awareness of EGIDs,
    - realizing the first systematic review with meta-analysis on non-EoE EGID epidemiology;
    - investigating the pathogenesis of EoE, analyzing the role of early life exposures and ultraprocessed foods;
    - extensively evaluate the clinical aspect of pediatric EGIDs, revising currently available literature on (allergic and non-allergic) comorbidities, psychological issues, and nutritional features;

2) analyze the potential and conflicting role of allergen immunotherapy in EGID development, actively participating to Italian and European Task Forces;
3) assessed two critical aspects of EGID management, the diagnostic delay and child growth, identifying a clinically relevant link between them.

To achieve these goals, we also collaborated with National and International Scientific Societies (Italian Society of Pediatric Allergy and Immunology [SIAIP], European Academy of Allergy and Clinical Immunology [EAACI], European Society of Eosinophilic Oesophagitis [EUREOS]) research Centers to improve clinical knowledge of EGIDs, participating in a European registry (CONNECT Study) and promoting a national multicenter study on pediatric EGIDs (GOLDEN Study).

Chapter 1

EPIDEMIOLOGY OF EGIDs

Original Article

Epidemiology of Nonesophageal Eosinophilic Gastrointestinal Diseases in Symptomatic Patients: A Systematic Review and Meta-Analysis

Amelia Licari, MD[a,*], Martina Votto, MD[a,*], Luigia Scudeller, MD[b], Annalisa De Silvestri, MSc[b], Chiara Rebuffi, MD[c], Antonella Cianferoni, MD, PhD[d], and Gian Luigi Marseglia, MD[a] *Pavia, Italy; and Philadelphia, Pa*

What is already known about this topic? Nonesophageal eosinophilic gastrointestinal diseases (non-EoE EGIDs) are rare, but they are emerging gastrointestinal diseases that might affect adults and children. The exact epidemiology is still unclear.

What does this article add to our knowledge? We found a higher prevalence of non-EoE EGIDs than what is estimated in existing populations-based studies.

How does this study impact current management guidelines? Management guidelines of non-EGIDs in adults and children are still lacking.

BACKGROUND: Primary eosinophilic gastrointestinal diseases (EGIDs) are increasingly described disorders that include eosinophilic esophagitis (EoE), eosinophilic gastritis, gastroenteritis, and colitis. The exact epidemiology of nonesophageal EGIDs (non-EoE EGIDs) is still unclear.
OBJECTIVE: To evaluate the epidemiology of non-EoE EGIDs in adults and children referred to outpatient clinics for gastrointestinal symptoms.
METHODS: We conducted a systematic review and meta-analysis using a protocol registered and published with the international prospective register of systematic reviews (PROSPERO CRD42018111437). We searched PubMed, EMBASE, Web of Science, Scopus, and CINAHL for cohort or cross-sectional studies published since 1990, evaluating the incidence and prevalence of non-EoE EGIDs. We assessed study quality and risk of bias using items derived from the Strengthening the Reporting of Observational Studies in Epidemiology statement.
RESULTS: A total of 576 articles were identified. Ten studies with 13,377 participants were included in the analysis, with the results showing high heterogeneity. No significant publication bias was found. The overall prevalence of non-EoE EGIDs in patients with gastrointestinal symptoms was 1.9% (95% confidence interval: 0.575-3.894; $I^2 = 92.72\%$; $P < .001$). Because none of the examined studies were prospectively designed, incidence rates could not be determined.
CONCLUSIONS: More prospective, large-scale, multicenter studies are needed to evaluate reported data and to further investigate the epidemiology of non-EoE EGIDs and their possible risk factors and comorbidities. © **2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:1994-2003)**

Key words: *Primary eosinophilic gastrointestinal diseases; Epidemiology; Prevalence; Incidence; Gastrointestinal symptoms*

Primary eosinophilic gastrointestinal diseases (EGIDs) represent a heterogeneous group of rare but increasingly described disorders, characterized by a prevalent eosinophilic inflammation in specific gastrointestinal (GI) tracts.[1-3] The exact pathogenesis is still unknown; however, T helper 2 immune response may play a central role in dysfunctional eosinophilic inflammation against allergens or with autoimmune etiopathology.[4,5] EGIDs include eosinophilic esophagitis (EoE), gastritis (EoG), gastroenteritis (EoGE), and colitis (EoC). Nonesophageal eosinophilic gastrointestinal diseases (non-EoE EGIDs) are defined by the abnormal eosinophilic infiltration in the GI tract not limited to the esophagus and in the absence of secondary causes of GI eosinophilia (food hypersensitivity, drug reactions, parasite infections, malignancies, and inflammatory bowel diseases [IBDs]).[1-4,6,7] Since their first description in 1937,[8] few case reports, case

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Abbreviations used

CEGIR- Consortium of Eosinophilic Gastrointestinal Researchers
CI- Confidence interval
EGID- Eosinophilic gastrointestinal disease
EoC- Eosinophilic colitis
EoE- Eosinophilic esophagitis
EoG- Eosinophilic gastritis
EoGE- Eosinophilic gastroenteritis
GI- Gastrointestinal
HPF- High power field
IBD- Inflammatory bowel disease
Non-EoE EGID- Nonesophageal eosinophilic gastrointestinal disease
STROBE- STrengthening the Reporting of OBservational studies in Epidemiology

series, and retrospective studies have been reported on non-EoE EGIDs,[9-15] with rare studies often limited to specific geographical areas in the discussion of incidence and prevalence of the disease.[16] Therefore, the exact epidemiology of non-EoE EGIDs remains still unknown. There are no systematic reviews or meta-analyses on the global epidemiology of EGIDs at any age.

We performed a systematic review and meta-analysis to estimate the incidence and prevalence rates of non-EoE EGIDs in adults and children referred to outpatient clinics for GI symptoms.

METHODS

The protocol of our systematic review and meta-analysis was registered and published with the international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=111437; register number CRD42018111437) before starting the study. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to report our results.[17]

Outcomes

Primary outcomes (Table I) for the systematic review were the incidence and prevalence of non-EoE EGIDs in adult and pediatric patients referred to outpatient clinics for GI symptoms. The main analysis focused on overall prevalence, whereas secondary analyses included prevalence estimates based on demographic data, symptoms, allergic comorbidities, and diagnostic criteria.

Search strategy

A highly sensitive and extensive search strategy was designed to retrieve all articles combining the terms of EoG, EoGE, and EoC, and epidemiology from the major electronic bibliographic databases (PubMed, EMBASE, Web of Science, Scopus, and CINAHL). Conference proceedings were acquired from abstract books and the annual Digestive Diseases Week, American College of Gastroenterology Meetings, United European Gastroenterology Week, and from the European Society for Pediatric Gastroenterology Hepatology and Nutrition Congresses. We included all articles and conference proceedings published in all languages from 1990 to 2018. The search strategy used generic terms to avoid excluding possible eligible articles (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Search results were compiled using the citation management software Refworks. According to the quality standards for reporting meta-analysis of observational studies,[18] 2 researchers independently screened the reference lists of eligible articles. Full texts of records deemed eligible were retrieved and independently assessed for inclusion by the same investigators. Any discrepancies were resolved by discussion and consensus. The authors of publications reporting unclear data, subjected to multiple interpretations, were contacted by e-mail for clarification or to request supplemental information. Figure 1 illustrates the search strategy process.

TABLE I. Inclusion criteria

Criteria	Specifics
Population	Adult/pediatric patients referred to outpatient clinics for gastrointestinal symptoms
Study design	Cross-sectional and cohort studies
Outcome	Prevalence or incidence of eosinophilic gastroenteritis and eosinophilic colitis
	Description of diagnostic criteria in studies
	Description of therapy in studies (dietary treatment, corticosteroids, other drugs)
	Explore variation of prevalence estimates according to:
	• Age (adult vs pediatrics)
	• Gender (males vs females)
	• Country (developing vs developed countries; US vs European countries)
	• Symptoms (GI symptoms: abdominal pain, nausea, vomiting and diarrhea, gastrointestinal bleeding, anemia, protein-losing enteropathy, malabsorption; pediatric symptoms: failure to thrive, amenorrhea, delayed puberty; complications: ascites, pancreatitis, bowel obstruction, bowel perforation, intestinal ulcer, cystitis, hepatitis)
	• Allergic diseases (asthma, allergic rhinitis or atopic dermatitis, and food or drug allergy)
	• Age at symptom onset
	• Age at diagnosis
	• Localization of eosinophilic inflammation (stomach, duodenum, jejunum, ileum, large intestine; mucosal or muscular or serosa involvement)
	• Diagnostic criteria (endoscopy, number of eosinophils/HPF, peripheral eosinophilia, allergy tests [skin prick test, total IgE level, allergen specific IgE], capsule endoscopy, magnetic resonance, computed axial tomography)
	• Years (1990-2000-2010-2018)

GI, Gastrointestinal; *HPF*, high power field.

Study selection (inclusion/exclusion criteria)

We included cohort and cross-sectional studies about the epidemiology of primary non-EoE EGIDs, reporting prevalence/incidence with a 95% confidence interval (95% CI). Our analysis excluded clinical guidelines, case reports, consensus documents, clinical trials, and reviews that did not provide epidemiological data and studies about the secondary causes of intestinal hypereosinophilia. We also excluded electronic surveys and epidemiological studies based on health plan claims databases to obtain a more reliable estimate of the epidemiology of non-EoE EGIDs in patients referred to clinics for GI symptoms. The inclusion criteria are described in Table I.

Risk of bias assessment

Eligible articles were assessed for risk of bias, according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[19] Moreover, for cohort and cross-

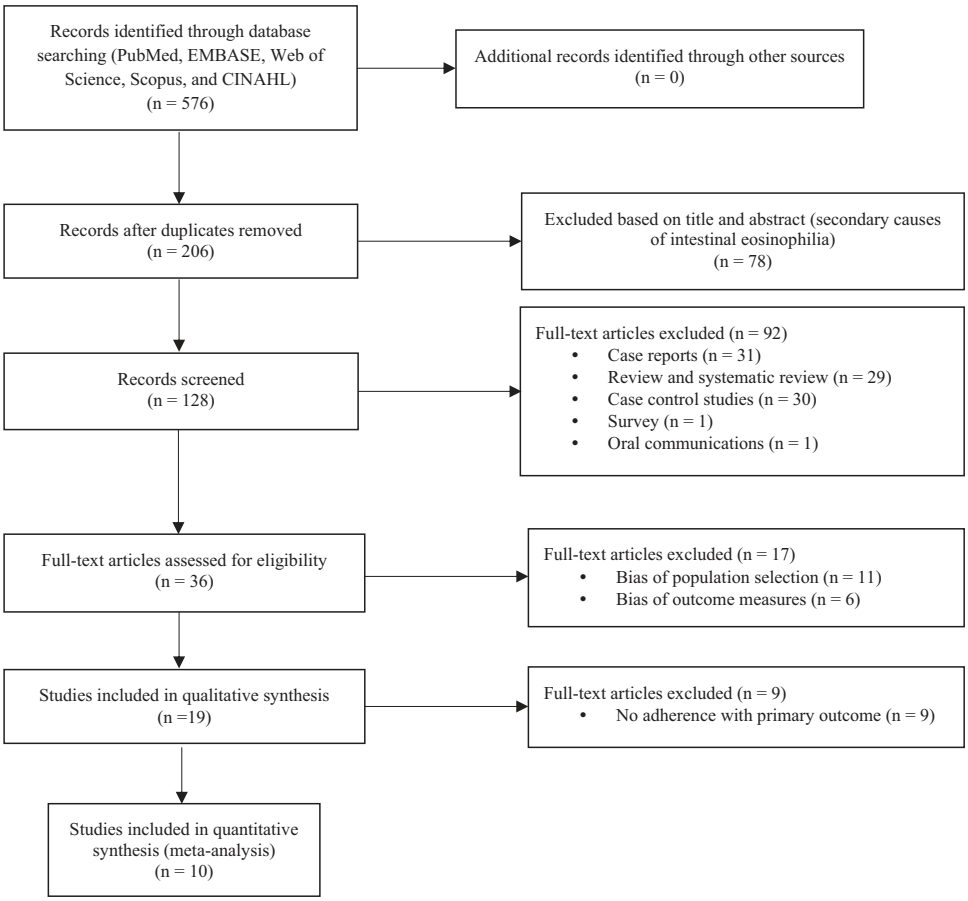

FIGURE 1. Study flowchart from identification to inclusion of final articles.

sectional studies, risk of bias was assessed through a question tool developed specifically for this review and derived from the STROBE statement: (1) Were more than 90% of patients followed up until the end of the study? (2) Were all patients free of the outcome of interest at baseline included? (3) Were the diagnoses/exclusions free from outcome misclassification? The last 2 items were used to assess the included cross-sectional studies (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Two investigators independently assigned an overall risk of bias to each eligible study, and if they disagreed, a third reviewer was consulted. All studies with 1 or more risks of bias were excluded.

Data extraction

Two reviewers independently extracted information from each eligible study using a standardized data extraction sheet and then proceeded to cross-check the results. We extracted the following information: first author name; year of publication; type of study (cross-sectional or cohort study); country and language; type of patients (children or adults); age and gender of participants; sample size; prevalence and/or incidence with 95% CI; localization of eosinophilic inflammation; number of eosinophils per high power field (Eo/HPF); peripheral eosinophilia; allergy and imaging tests; therapies; symptoms (abdominal pain, nausea, vomiting and diarrhea, GI bleeding, anemia, protein-losing enteropathy, malabsorption, failure to thrive, amenorrhea, delayed puberty); clinical complications (ascites, pancreatitis, bowel obstruction, bowel perforation, intestinal ulcer, cystitis, hepatitis); and atopic comorbidities (asthma, allergic rhinitis, atopic dermatitis, food and drug allergy). If not directly reported, the prevalence rate was calculated. Risk of bias assessment for all included studies was also evaluated. Disagreements between reviewers regarding data extraction were resolved through discussion and consensus.

TABLE II. Quality assessment of included studies

	Risk of bias for cross-sectional studies	
Author, year	**1***	**2†**
Tilma et al, 2018[21]	Yes	Yes
Hui and Hui, 2018[22]	Yes	Yes
Bonagura et al, 2017[23]	Yes	Yes
Alhmoud et al, 2016[24]	Yes	Yes
Al Quorain et al, 2000[25]	Yes	Yes
Channaiah et al, 2017[26]	Yes	Yes
Guo and Abassa, 2016[27]	Yes	Yes
Kusakari et al, 2012[28]	Yes	Yes
Panackel et al, 2010[29]	Yes	Yes
Kerdsirichairat et al, 2010[30]	Yes	Yes

Non-EoE EGID, Nonesophageal eosinophilic gastrointestinal disease.
*1: Were all patients free of the outcome of interest at the time of the study included?
†2: Were diagnosis/exclusion of non-EoE EGIDs free from outcome misclassification?

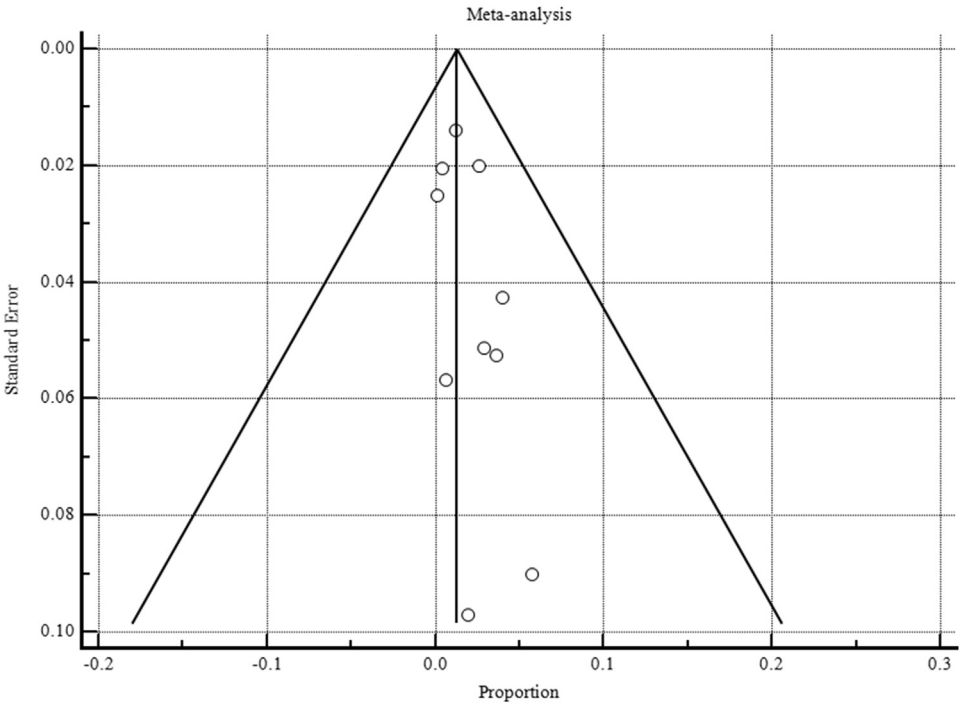

FIGURE 2. Funnel plot for publication bias.

Data synthesis and statistical analysis

We estimated prevalence or incidence and their corresponding 95% CI, as calculated as an exact binomial proportion (from affected and the total of enrolled patients). Prevalence was estimated by pooling results of cross-sectional studies or cohort studies at baseline.

Incidence was estimated by pooling results of cohort studies that were free of non-EoE EGIDs at baseline. Estimations of prevalence and incidence were calculated with the aid of a fixed- or random-effects meta-analysis weighted for inverse variance following DerSimonian and Laird's method. Heterogeneity between studies was evaluated with a χ^2 test and quantified with the I^2 statistic. I^2 is a measure of the level of heterogeneity, expressed in 3 categories on the basis of low, moderate, and high I^2 values (25%, 50%, and 75%, respectively).[20] Publication bias was evaluated by means of a funnel plot. For the secondary outcomes, planned subgroup analyses were based on the geographic origin of studies (developed vs developing countries) and age (adults vs children). We used the statistical software package MedCalc (Statistical Software 19.1, Ostend, Belgium).

RESULTS

A total of 576 articles were found. After removing 370 duplicates, 206 were reviewed on title and abstract, and of this group, 78 articles were excluded because they focused on secondary causes of non-EoE EGIDs. One hundred and twenty-eight full texts were screened, and 92 were excluded on the basis of the specific article type (reviews, systematic reviews, case-control studies, case reports, oral communication, survey). Thirty-six articles were assessed for eligibility (cross-sectional and cohort studies). Only 10 articles met the inclusion criteria and were included in the final meta-analysis (Figure 1).

Quality assessment

The 10 included cross-sectional studies showed low risks of bias (Table II). Publication bias was not detected (Figure 2), but common methodological flaws included the method of data collection and the definition of the study period.

Study characteristics

None of the articles included for the analysis were published before 2000. Two studies were conducted in the United States,[24,30] 2 in Europe (1 in Denmark[21] and 1 in Italy[23]), 5 in Asia (2 in India,[26,29] 1 in China,[27] in Malaysia,[22] and in Japan[28]), and 1 study was conducted in Saudi Arabia.[25] A total of 13,377 patients (adults and children) were enrolled, and all of them were affected by primary non-EoE EGIDs diagnosed by endoscopy and histology. Three studies reported the diagnostic cutoff value of tissue eosinophils for HPF.[21,22,24] While 2 studies were based only on pediatric patients[21,28] and 5 on adult patients with non-EoE EGIDs,[22,23,26,27,30] 3 studies were characterized by mixed population.[24,25,29] The distribution of the population by sex was reported only in 4 articles, and male sex ranges from 38% to 100% of affected patients. Male sex is prevalent in children with non-EoE EGIDs (64% vs 36%).[21] Study characteristics are summarized in Table III.

Prevalence and incidence of non-EoE EGIDs and analysis of subgroups

In the 10 retrieved studies, the overall prevalence of non-EoE EGIDs among patients referred to clinics for GI symptoms was 1.9% (95% CI: 1.035-2.992; $I^2 = 92.70\%$; $P < .0001$) (Figure 3). Data on the prevalence of non-EoE EGIDs in adults were obtained from 5 studies. In adults with GI symptoms, the

TABLE III. Characteristics of included studies

Author, year	Study design	Study period	Country	Language	Reference population	Age of patients	Sex (%)		Prevalence of non-EoE EGIDs (%) (95% CI)
							Male	Female	
Tilma et al, 2018[21]	Cross-sectional	2011-2016	Denmark	English	381	Children	64	36	2.90 (1.450-5.107)
Hui and Hui, 2018[22]	Cross-sectional*	2009-2015	Malaysia	English	2.469	Adult	62.5	37.5	2.592 (2.002-3.298)
Bonagura et al, 2017[23]	Cross-sectional	2003-2013	Italy	English	105	Adult	n.a.	n.a.	1.905 (0.232-6.712)
Alhmoud et al, 2016[24]	Cross-sectional	2004-2014	United States	English	361	Adult and children	38	62	3.601 (1.931-6.079)
Al Quorain et al, 2000[25]	Cross-sectional	1983-1996	Saudi Arabia	English	1.590	Adult and children	100	0	0.126 (0.0152-0.454)
Channaiah et al, 2017[26]	Cross-sectional	n.a.	India	English	309	Adult	n.a.	n.a.	0.647 (0.0785-2.318)
Guo and Abassa, 2016[27]	Cross-sectional*	n.a.	China	English	122	Adult	n.a.	n.a.	5.738 (2.338-11.465)
Kusakari et al, 2012[28]	Cross-sectional	2001-2011	Japan	English	552	Children	n.a.	n.a.	3.986 (2.514-5.972)
Panackel et al, 2010[29]	Cross-sectional	2009-2010	India	English	5.100	Adult and children	n.a.	n.a.	1.196 (0.916-1.534)
Kerdsirichairat et al, 2010[30]	Cross-sectional	2003-2010	United States	English	2.388	Adult	n.a.	n.a.	0.419 (0.201-0.769)

CI, Confidence interval; *n.a.*, not available; *non-EoE EGID*, nonesophageal eosinophilic gastrointestinal disease.
*People with non-EoE EGIDs were enrolled as a cohort-study; measures of prevalence were evaluated as a cross-sectional study.

prevalence of non-EGIDs was 1.9% (95% CI: 0.575-3.894; $I^2 = 92.72\%$; $P < .0001$ for heterogeneity) (Table IV). The limited number of available studies did not allow us to analyze the prevalence of non-EoE EGIDs in children. Pooling results by patient country indicate that the prevalence of non-EoE EGIDs was 2.4% (95% CI: 0.723-5.515; $I^2 = 92.7\%$; $P < .001$ for heterogeneity) in developed countries and 1.5% (95% CI: 0.703-2.886; $I^2 = 94.16\%$; $P < .0001$ for heterogeneity) in developing countries (Table V).

Because none of the included articles were prospectively designed, we were unable to assess the incidence rate.

Description of clinical features, endoscopic findings, and therapies in included studies

The limited number of available studies and the lack of details in reports did not allow us to analyze the prevalence of non-EoE EGIDs according to the planned subgroups (gender, age at diagnosis and symptoms onset, clinical symptoms, therapies, allergic comorbidities, localization of eosinophilic inflammation, and diagnostic tests).

Symptoms reported in the 10 studies included in our analysis are summarized in Table VI. Abdominal pain is the main GI symptom in children with non-EoE EGIDs (94%),[21] whereas diarrhea is the most prevalent symptom (100%) in adults.[26] Only 1 study conducted by Alhmoud et al[24] in pediatric patients and 1 in adult patients reported this information. In their retrospective cohort study of 13 non-EoE EGID cases, they noted the following clinical presentations: nausea (31%), vomiting (31%), GI bleeding (8%), anemia (15%), weight loss (15%), and failure to thrive (15%) reported in adults and children.

Constipation is described in 3% of patients with non-EoE EGIDs.[22] Ascites and bowel obstruction are also reported as clinical complications.[24] Atopic comorbidities (Table VII) range from 25% to 54% of patients with non-EoE EGIDs.[21,22,24] Asthma, allergic rhinitis, and eczema are reported in 54% of patients and food allergy in 38% of patients with non-EoE EGIDs.[24]

Regarding the diagnostic management, 4 studies reported endoscopic findings.[21,22,24,29] A normal mucosa is the prevalent endoscopic finding reported in the included studies (35% to 100%), as described in Table E3 (available in this article's Online Repository at www.jaci-inpractice.org). None of the included studies reported other diagnostic tests, such as specific serum IgE levels, skin prick test, imaging, or blood tests.

Therapies are described in only 3 studies[21,22,24] (Table VIII). Steroid therapy was reported with 100% efficacy in children with non-EoE EGIDs.[21] Effective response to first-line therapy (steroids, diet, montelukast, and ketotifen) was reported in 89% to 100% of all patients with non-EoE EGIDs.[21,22,24]

DISCUSSION

Our study represents the first systematic review and meta-analysis of prevalence for non-EoE EGIDs in patients referred to outpatient clinics for GI symptoms. The included studies were conducted in Europe, North America, and Asia. Epidemiological data from Central and South America, Australia, and Africa are still lacking.

We found a higher overall prevalence of non-EoE EGIDs (1.9%) in symptomatic patients than that estimated from population-based studies that were mainly realized in the United

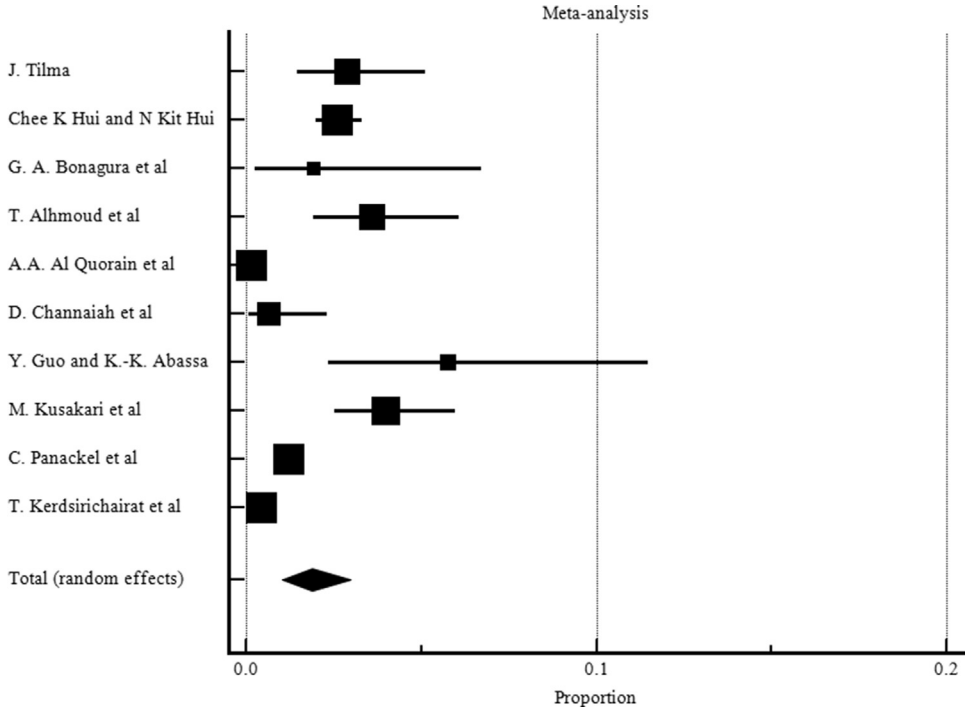

FIGURE 3. The overall prevalence estimates of non-EoE EGIDs. Summary estimates are expressed as a percentage of patients with non-EoE EGIDs. *Non-EoE EGID*, Nonesophageal eosinophilic gastrointestinal disease.

States using survey or health plan claims databases. Spergel et al[31] reported an overall prevalence of 28/100,000 people for non-EoE EGIDs by administering an electronic survey to allergists and gastroenterologists. In addition, in a retrospective analysis of a large population-based database of more than 35 million US people, Mansoor et al[32] reported a prevalence rate for EoGE and EoC of 5.1/100,000 and 2.1/100,000 people, respectively. Finally, using diagnostic (The International Classification of Diseases, Ninth Revision) codes through a health plan claims database, Gupta et al[33] and Alhmoud and Qeadan[34] reported an overall prevalence of 6/100,000 and 1.7/100,000 patients, respectively, whereas Jensen et al[16] estimated the prevalence of EoGE and EoC as 8.4/100,00 and 3.3/100,000, respectively. An older study estimated that the prevalence of EoGE in the United States was 2.5/100,000 people, using an electronic survey.[35] The differences in the prevalence between these large studies can be attributed to the discrepancy in the study design (retrospective studies on the prevalence of non-EoE EGIDs in US people), methods of data collection (electronic surveys and databases), data analyses, and sample size. In addition, as described in a retrospective study of Consortium of Eosinophilic Gastrointestinal Researchers (CEGIR), non-EoE EGIDs have increased in frequency over the past decade.[36] Despite the heterogeneity of the studies, our findings add to the literature by more accurately depicting the prevalence rates in real-life situations of patients with GI symptoms accessing health care, rather than what is seen in the general population.

TABLE IV. Prevalence of non-EoE EGIDs in adults referred to outpatient clinics for gastrointestinal symptoms

Study	Sample size	Proportion (%)	95% CI*
Hui and Hui[22]	2469	2.592	2.002-3.298
Bonagura et al[23]	105	1.905	0.232-6.712
Channaiah et al[26]	309	0.647	0.0785-2.318
Guo and Abassa[27]	122	5.738	2.338-11.465
Kerdsirichairat et al[30]	2388	0.419	0.201-0.769
Total (fixed effects)	5393	1.373	1.080-1.721
Total (random effects)	5393	1.872	0.575-3.894

CI, Confidence interval; *non-EoE EGID*, nonesophageal eosinophilic gastrointestinal disease.
*CI was calculated as an exact binomial proportion.

They offer insight to alert clinicians to suspect and diagnose early these emerging disorders.

Our analysis revealed that the prevalence of non-EoE EGIDs varies widely among studies and by locale. The prevalence of non-EoE EGIDs reported in developing countries is lower (1.5%) than what is described in developed countries (2.4%). In a single large Asian retrospective cross-sectional study, Yoon et al[37] reported an overall prevalence for non-EoE EGIDS of 0.6/100,000, lower than what has been described in earlier US studies. Environmental (diet, lifestyle, intestinal microbiome, allergen exposition) and genetic factors might explain the different prevalence of non-EoE EGIDs in Caucasians than in African Americans and Asians.[31,32]

TABLE V. Prevalence of non-EoE EGIDs in developing and developed countries

Developing countries				Developed countries			
Study	Sample size	Proportion (%)	95% CI	Study	Sample size	Proportion (%)	95% CI
Hui and Hui[22]	2469	2.592	2.002-3.298	Tilma et al[21]	381	2.887	1.450-5.107
Al Quorain et al[25]	1590	0.126	0.0152-0.454	Bonagura et al[23]	105	1.905	0.232-6.712
Channaiah et al[26]	309	0.647	0.0785-2.318	Alhmoud et al[24]	361	3.601	1.931-6.079
Guo and Abassa[27]	122	5.738	2.338-11.465	Kusakari et al[28]	552	3.986	2.514-5.972
Panackel et al[29]	5100	1.196	0.916-1.534	Kerdsirichairat et al[30]	2388	0.419	0.201-0.769
Total (fixed effects)	9590	1.269	1.055-1.514	Total (fixed effects)	3787	1.245	0.917-1.651
Total (random effects)	9590	1.462	0.513-2.886	Total (random effects)	3787	2.446	0.723-5.151

CI, Confidence interval; *non-EoE EGID*, nonesophageal eosinophilic gastrointestinal disease.

Our results indicated that the prevalence of non-EoE EGIDs in adults is 1.9%. Mansoor et al[32] reported the prevalence of EoGE in children as slightly higher than in adults (5.3/100,000 and 5.1/100,000, respectively), whereas the prevalence of EoC was higher in adults than in children (1.6/100,000 and 2.3/100,000, respectively). However, a high prevalence (10.7/100,000 people) of non-EoE EGIDs in the United States has been described in people less than 20 years of age.[16] Finally, the age at onset of EGIDs varies widely, and large epidemiological studies in children are needed.

Unfortunately, none of the selected studies were prospectively designed to evaluate the incidence rate.

Surprisingly, our results showed that the prevalence of non-EoE EGIDs among symptomatic patients is higher than the prevalence rates estimated for IBD in all ages. The highest reported prevalence rates of IBD were in Western countries (especially in Europe and North America) and corresponded to 505/100,000 people for ulcerative colitis and 322/100,000 for Crohn's disease.[38] This highlights the clinical relevance of these emerging conditions.

The low number of selected studies with complete epidemiological data did not allow us to analyze the stratified prevalence or meta-regression, according to all planned secondary analyses.

We could therefore only describe data on symptoms, allergic comorbidities, endoscopic features, and therapies in the included studies. The main reported symptoms were unspecific.[1-4,6,36] The prevalence of allergic comorbidities (asthma, allergic rhinitis, eczema, and food allergy) was similar to those reported by Mansoor et al[32] and Pesek et al,[36] and confirms the strong association between EGIDs and atopic diseases.

A normal mucosa is the prevalent endoscopic finding reported, particularly in patients with EoGE and EoC, who might present nonspecific endoscopic patterns.[1,6,39]

First-line therapy (diet, oral steroids, montelukast, and ketotifen) was considered effective in most included studies. Diet and steroids were the first-line therapies in patients with EoE-EGIDs.[1,4,6,39] Food-elimination diet and elemental diet improved clinical symptoms and reduced mucosal eosinophils in more than 75% of children with non-EoE EGIDs.[40,41] Retrospective studies have reported clinical remission in 50% to 90% of patients with EGIDs treated with oral corticosteroids (prednisone and budesonide).[1,39,42-44] In the CEGIR study, the therapeutic approach varied widely across centers and disease localization (EoG, EoGE, and EoC); however, the response to therapies was achieved in most enrolled patients.[36] The efficacy of montelukast and ketotifen in EGIDs remains controversial and is limited to a few case series.[39]

We found extensive heterogeneity among the included studies and the few subgroups that we could assess, without significant publication bias. Heterogeneity is probably due to several factors: first, the sample size varied from 105 to 5100 patients. Second, only 2 studies included just pediatric patients,[21,28] whereas the others included adult only and mixed population.[22-27,29,30] Finally, different diagnostic histological criteria might have been used. In fact, management guidelines for non-EoE EGIDs in all ages are still lacking, and different cutoffs of intestinal eosinophils for the histological diagnosis are reported in literature.[1,4,45] Unfortunately, the cutoff of intestinal eosinophils per HPF is specified in only 3 included studies (in all 3, >20 Eo/HPF).[21,22,24]

CONCLUSIONS

This is the first systematic review and meta-analysis focusing on the epidemiology of nonesophageal GI diseases in adults and children referred to outpatient clinics for GI symptoms. Our research showed that non-EoE EGIDs seem to be highly prevalent disorders, with rising prevalence rates in recent years.[36] Non-EoE EGIDs affect approximately 1.9% of patients referred to the hospitals for GI symptoms, so physicians may recognize these disorders and consider their prevalent chronic nature,[46] and the impact on patients' quality of life.[47] Finally, our results may lead researchers to develop shared management guidelines in adults and children. More prospective, large-scale, multicenter studies are needed to evaluate reported data and to further investigate the epidemiology of non-EoE EGIDs and their possible risk factors and comorbidities.

Acknowledgments

M. Votto and A. Licari contributed equally to study conception, data extraction, risk of bias rating, and manuscript writing. L. Scudeller and A. De Silvestri contributed to study conception and design, analysis and interpretation of data, and statistical analyses. C. Rebuffi conducted the article retrieval. A. Cianferoni and G. L. Marseglia revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript, including the authorship list. The guarantor of the article was A. Licari.

TABLE VI. Summary of clinical symptoms reported in included articles

Author, year	Abdominal pain	Nausea	Vomiting	Dysphagia	Diarrhea	Gastrointestinal bleeding	Constipation	Anemia	Protein-losing enteropathy	Malabsorption	Weight loss	Failure to thrive	Delayed puberty and amenorrhea	Ascites	Bowel obstruction	Other clinical complication*
Tilma et al, 2018[21]	94%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hui and Hui, 2018[22]	36%	n.a.	n.a.	n.a.	47%	0	3%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Bonagura et al, 2017[23]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Alhmoud et al, 2016[24]	62%	31%	31%	n.a.	31%	8%	n.a.	15%	n.a.	n.a.	15%	15%	n.a.	23%	8%	n.a.
Al Quorain et al, 2000[25]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Channaiah et al, 2017[26]	n.a.	n.a.	n.a.	n.a.	100%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Guo and Abassa, 2016[27]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Kusakari et al, 2012[28]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Panackel et al, 2010[29]	63%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Kerdsirichairat et al, 2010[30]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

n.a., Not available.
*Other clinical complications: bowel perforation, pancreatitis, intussusception, intestinal ulcer, eosinophilic cystitis, and hepatitis.

TABLE VII. Summary of comorbidities described in included articles

Author, year	Atopy	Asthma	Sinusitis	Allergic rhinitis	Eczema	Urticaria	Food allergy	Drug allergy
Tilma et al, 2018[21]	25%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0%
Hui and Hui, 2018[22]	33%	17%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Bonagura et al, 2017[23]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Alhmoud et al, 2016[24]	54%	54%	n.a.	54%	54%	n.a.	38%	n.a.
Al Quorain et al, 2000[25]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Channaiah et al, 2017[26]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Guo and Abassa, 2016[27]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Kusakari et al, 2012[28]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Panackel et al, 2010[29]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Kerdsirichairat et al, 2010[30]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

n.a., Not available.

TABLE VIII. Therapeutic management and its efficacy in included articles

	First-line therapy			Response to first-line therapy		Second-line therapy			Response to second-line therapy	
Author, year	Steroids	Diet	Other therapies	Yes	No	Steroids	Diet	Other therapies	Yes	No
Tilma et al, 2018[21]	100%	n.a.	n.a.	100%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hui and Hui, 2018[22]	n.a.	n.a.	100%*	89%	11%	100%	n.a.	n.a.	100%	n.a.
Bonagura et al, 2017[23]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Alhmoud et al, 2016[24]	46%	23%	11%†	90%	10%	100%	n.a.	n.a.	100%	n.a.
Al Quorain et al, 2000[25]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Channaiah et al, 2017[26]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Guo and Abassa, 2016[27]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Kusakari et al, 2012[28]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Panackel et al, 2010[29]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Kerdsirichairat et al, 2010[30]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

n.a., Not available.
*Montelukast and ketotifen.
†Montelukast.

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ONLINE REPOSITORY

TABLE E1. Search strategy

Search strategy
PubMed: ("Eosinophilic gastrointestinal disorders" OR "Eosinophilic gastrointestinal disorder" OR "Eosinophilic gastroenteritis" OR "Eosinophilic colitis") AND ("prevalence"[mesh] OR "incidence"[mesh] OR prevalence OR incidence). Filters: Publication date from 1990/01/01 to 2018/05/28.
Web of Science Core Collection: TS = ("Eosinophilic gastrointestinal disorder*" OR "Eosinophilic gastroenteritis" OR "Eosinophilic colitis") AND (prevalence OR incidence). Filters: Publication date from 1990/01/01 to 2018/05/28.
Scopus: TIABKW ("Eosinophilic gastrointestinal disorder*" OR "Eosinophilic gastroenteritis" OR "Eosinophilic colitis") AND (prevalence OR incidence). Filters: Publication date from 1990/01/01 to 2018/05/28; publication type: article, review, conference paper, editorial, note, letter, short survey.
CINAHL: ("Eosinophilic gastrointestinal disorder*" OR "Eosinophilic gastroenteritis" OR "Eosinophilic colitis") AND ("prevalence"MH OR "incidence"MH OR prevalence OR incidence). Filters: Publication date from 1990/01/01 to 2018/05/28; academic journals.
Embase: ('eosinophilic gastroenteritis'/exp OR 'eosinophilic colitis'/exp OR 'eosinophilic gastrointestinal disorder*' OR 'eosinophilic gastroenteritis' OR 'eosinophilic colitis') AND ('prevalence'/exp OR 'incidence'/exp OR prevalence OR incidence). Filters: [1990-2018]/py.

TABLE E2. Risk of bias assessment of included studies

Cohort studies	Cross-sectional studies
Selection bias of the cohort: were all patients free of the outcome of interest at baseline included?	Selection bias: were all patients free of the outcome of interest at the time of the study included?
Losses to follow-up: were all patients (or a relevant proportion >90%) followed up until the end of the study?	Outcome ascertainment: were diagnosis/exclusion of non-EoE EGIDs free from outcome misclassification?
Outcome ascertainment: were diagnosis/exclusion of non-EoE EGIDs free from outcome misclassification?	

non-EoE EGID, Nonesophageal eosinophilic gastrointestinal disease.

TABLE E3. Endoscopic findings

	Macroscopic findings	
Author, year	**Normal**	**Abnormal**
Tilma et al, 2018[E1]	100%	0%
Hui and Hui, 2018[E2]	92%	8%
Bonagura et al, 2017[E3]	n.a.	n.a.
Alhmoud et al, 2016[E4]	54%	46%
Al Quorain et al, 2000[E5]	n.a.	n.a.
Channaiah et al, 2017[E6]	n.a.	n.a.
Guo and Abassa, 2016[E7]	n.a.	n.a.
Kusakari et al, 2012[E8]	n.a.	n.a.
Panackel et al, 2010[E9]	35%	65%
Kerdsirichairat et al, 2010[E10]	n.a.	n.a.

n.a., Not available.

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E3. Bonagura GA, Ribaldone DG, Fagoonee S, Sapone N, Caviglia GP, Saracco GM, et al. Microscopic colitis in patients with mild duodenal damage: a new clinical and pathological entity ("lymphocytic enterocolitis")? World J Gastrointest Pathophysiol 2016;7:307-13.

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E6. Channaiah D, Mohammad KS, Kini R, Kumar KP. Yield of colonoscopy with biopsy in the evaluation of chronic diarrhea. Indian J Gastroenterol 2017;36:A76.

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E10. Kerdsirichairat T, Chavalitdhamrong D, Kijsirichareanchai K, Sul J, Jutabha R. Significant incidental gastric findings on esophageal and small bowel capsule endoscopy studies. Am J Gastroenterol 2010;105:S529-30.

Chapter 2

PATHOGENESIS OF EGIDs

frontiers in Pediatrics

MINI REVIEW
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Early Life Risk Factors in Pediatric EoE: Could We Prevent This Modern Disease?

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Eosinophilic esophagitis (EoE) is a chronic antigen-mediated inflammatory disease that affects the esophagus. In the last 20 years, a large number of epidemiological studies showed a significant increase in the incidence and prevalence of EoE, especially in developed countries. This phenomenon might correlate to the overall increase in pediatric allergic diseases or might be a result of improved medical awareness and knowledge through modern diagnostic instruments. Since 1993, when EoE was first recognized as a distinct clinical entity, several signs of progress in the pathophysiology of EoE were achieved. However, a few studies reported data on early risk factors for pediatric EoE and how these factors may interfere with genes. Currently, the most defined risk factors for EoE are male sex, Caucasian race, and atopic comorbidities. Other putative risk factors may include alterations in epithelial barrier function and fibrous remodeling, esophageal dysbiosis, variation in the nature and timing of oral antigen exposure, and early prescription of proton pump inhibitors and antibiotics. Notably, the timing and nature of food antigen exposure may be fundamental in inducing or reversing immune tolerance, but no studies are reported. This review summarized the current evidence on the risk factors that might contribute to the increasing development of EoE, focusing on the possible preventive role of early interventions.

Keywords: eosinophilic esophagitis, allergy, risk factors, early life exposures, food allergens, microbiome, prevention

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INTRODUCTION

EoE is a chronic, antigen-mediated, inflammatory disease of the esophagus characterized by symptoms due to esophageal inflammation, dysmotility, and fibrosis (1, 2). EoE occurs in children and adults, and symptoms are often non-specific and depending on the age of onset (1, 2). While in toddlers and children EoE presents with inflammatory symptoms mimicking gastroesophageal reflux disease (GERD), in adolescents and adults EoE frequently appears with food impaction, dysphagia, odynophagia, or esophageal strictures, as a consequence of the ongoing fibrosis process (1, 2). EoE is a multifactorial disorder resulting from the combination of genetic predisposition, epithelial barrier dysfunction, environmental risk factors (**Table 1**), and allergen sensitization, leading to a T helper type 2 (Th2) atopic inflammation of the esophagus (2).

Since 1993, when EoE was first recognized as a distinct clinical entity, several signs of progress in the pathophysiology of EoE were achieved; however, few studies reported data on early risk factors and how these factors might interfere with the genes in the disease onset and evolution. EoE is strictly associated with atopic disorders (asthma, atopic dermatitis, IgE mediated food allergy, allergic rhinitis), suggesting that EoE and allergic diseases share the same environmental risk factors and early life exposures.

We reviewed the recent evidence about the well-known risk factors of EoE, also reporting the less-investigated early exposures, to open future ideas of investigation in the limited field of prevention. Finally, we speculate about the possible strategies for EoE prevention.

WHY IS EoE A MODERN DISEASE OF WESTERN COUNTRIES?

Recently, it was estimated that EoE affects 1/2,000 patients in the United States, with higher prevalence rate in adults (43.4/100,000; 95% CI, 22.5–71.2) than in children (29.5/100,000; 95% CI, 17.5–44.7), prevailing in Caucasian patients and male sex (**Table 1**) (1, 3, 19). In the last 20 years, a large number of epidemiological studies showed a significant increase of incidence and prevalence of EoE especially in children in Western Countries, varying widely across North America and Europe (19–21). This interesting phenomenon might be related to (1) an overall increased incidence of allergic and non-allergic diseases, (2) the chronic disease-course of EoE, and (3) the improved medical awareness and knowledge through modern diagnostic instruments (18). Although EoE is associated with some genetic polymorphisms (22, 23), this rapid increase in EoE frequency might indicate a prevalent role of environmental risk factors in disease development.

Hygienic Hypothesis, Dysbiosis, and Esophageal Infection

The hygienic hypothesis postulated for the first time in 1989 by Strachan (24), and recently reviewed (25), has explained the global rise of allergic and autoimmune diseases. Animal and human studies demonstrated that the increased frequency of allergic diseases in developed countries is a consequence of the modern hygienic conditions and fewer bacterial, viral, and parasitic infections during infancy and childhood (26). Although fundamental to reduce infectious diseases, an excessively hygienic environment in early life might induce adverse effects on the host microbiome, altering certain strains of necessary commensal bacteria (dysbiosis). Furthermore, microbial dysbiosis might arise from the modern lifestyle that is characterized by limited physical activity, low intake of fibers, a diet high in saturated fats, and more frequent use of antibiotics. An impaired microbiota might also result from early life events such as cesarean section, premature birth, early antibiotic exposure, and formula feeding (**Table 2**) (27). Patients with EoE showed differences in the esophageal microbiome and an increase of bacterial load compared to patients with GERD and healthy controls (28, 29, 62). Harris et al. have demonstrated that the esophageal microbiome in children with untreated and active EoE is characterized by the predominance of *Haemophilus* strain, compared to patients with disease-remission and healthy controls (29). Also, Benitez et al. characterized the bacterial composition of the oral and esophageal microenvironments from children with EoE and healthy controls, showing that specific bacterial strains (mainly Firmicutes) were more abundant in the esophagus compared to the oral cavity in EoE patients (62). These data suggest that eosinophilic inflammation might specifically alter the esophageal microbiota, and the oral microbiota could not be used as a surrogate for monitoring the disease activity.

Evidence on the role of the microbiome in EoE pathogenesis is still limited to a few studies. However, two possible hypotheses could explain the relationship between the gut microbiome and EoE: (1) early life risk factors might specifically influence the correct development of the esophageal microbiome, predisposing to EoE, (2) eosinophilic inflammation could lead to esophageal dysmotility and decrease the esophageal compliance; thus EoE itself might induce esophageal microbiome alteration (28). Both hypotheses might coexist in a vicious circle, and the first one opens the unexplored field of the early prevention of EoE. Currently, only a single study in a murine model showed the beneficial effect of the probiotic *Lactococcus lactis* NCC 2287 on the esophageal inflammation (63). Although raising evidence explained the pivotal role of the well-balanced gut microbiome in the correct development of the immune system (25), the precise mechanisms whereby hygienic environment and dysbiosis interact with each other and result in allergic and autoimmune disease is still understood (64). Moreover, further studies are needed to clarify the role of dysbiosis in EoE pathogenesis and to identify possible preventive strategies.

Infectious diseases might act as promotive or protective factors for atopic diseases, including the EoE. Studies reported the development of EoE after herpes simplex virus (HSV) infection in immunocompetent adults and children. These data suggest that HSV esophagitis might predispose to EoE, impairing the esophageal barrier, and increasing the epithelial permeability (11, 12).

In Western countries, the overall prevalence of *Helicobacter pylori* infection was decreased in the last decades, probably contributing to the rise of allergic diseases (65). Experiments in murine models demonstrated that the *H. pylori* infection early in life was protective against asthma through the induction of regulatory T cells (T-regs) (66). Furthermore, epidemiological data showed that the *H. pylori* infection was negatively associate with EoE, demonstrating the potential protective role in EoE pathogenesis (67–70). The decrease of H. *pylori* infection in Western countries might also be a consequence of better hygienic conditions; furthermore, its possible protective role might explain the lower prevalence of EoE in developing countries,

Abbreviations: AA, arachidonic acid; ADHD, attention deficit hyperactivity disorder; CAPN14, calpain 14; DHA, docosahexaenoic acid; EA, esophageal atresia; EoE, eosinophilic esophagitis; EPA, eicosapentaenoic acid; GERD, gastroesophageal reflux disease; HSV, herpes simplex virus; NICU, neonatal intensive care unit; OIT, oral immunotherapy; PPI, proton pump inhibitor; PUFA, polinsatured fatty acid; SLIT, sublingual immunotherapy; Th2, T helper type 2; TLSP, thymic stromal lymphopoietin; T-regs, regulatory T cells.

TABLE 1 | Risk factors of eosinophilic esophagitis [adapted from Dellon and Hirano (3)].

Male sex	Gene encoding for thymic stromal lymphopoietin (TLSP), a central mediator of eosinophilic inflammation, is located on a pseudo-autosomal region of the X and Y chromosomes (Xp22.3 and Yp 11.3). A single nucleotide polymorphism of this region predisposes male patients to develop EoE (4)
Family members of patients with EoE	Monozygotic twins had a 44% disease concordance, a 2-fold increase compared with dizygotic twins (5, 6). Also, the relative risk to develop this disease in dizygotic twins might increase more than 10-fold compared to siblings (5)
Genetic *loci*	Studies of Genome-wide association studies (GWAS) identified different genetic *loci* that are likely contributing to the development of EoE and mainly include thymic stromal lymphopoietin (TSLP), calpain 14 (CAPN14), EMSY, LRRC32, STAT6 and ANKRD27 (7). These genetic loci are mainly involved in T-helper 2 type inflammation (allergic inflammation) and epithelial barrier function and integrity
Non-atopic diseases	EoE prevails in patients with connective tissue disorders, coeliac disease, autoimmune diseases, autism, and ADHD (8)
Atopic diseases	EoE may be a late manifestation of the atopic march (9)
OIT for foods and aeroallergens	EoE is a complication of oral immunotherapy (OIT) in 3–5% of cases. EoE is also reported during sublingual immunotherapy (SLIT) for respiratory allergies (10)
Infectious Esophagitis (HSV)	HSV might impair the esophageal barrier and increase the epithelial permeability (11, 12)
GERD	GERD alters the esophageal barrier function, increases the epithelial permeability, and the passage of food allergens that might trigger EoE. Furthermore, GERD might induce the expression of inflammatory molecules and eosinophil chemoattractants (13–15)
Aeroallergens	Environment allergens might increase disease activity and explain the seasonal variation of EoE reactivations and diagnosis (16, 17)
Food allergens	Food allergens directly trigger EoE (1)
Cold climate regions	Higher exposition to aeroallergens (18)

TABLE 2 | Putative early risk factors of eosinophilic esophagitis (EoE).

Microbial gut dysbiosis	Microbial dysbiosis might arise from a modern lifestyle (limited physical activity, low intake of fibers, high saturated fats in the diet, and frequent use of antibiotics) and early life events (cesarean section, premature birth, early antibiotic exposure, and formula feeding) (25, 27–29)
Monogenic diseases	Hyper-IgE syndrome, Ehlers-Danlos syndrome, ERBIN deficiency, Loeys-Dietz syndrome, Netherton's syndrome, PTEN hamartoma tumor syndrome, severe atopy syndrome associated with metabolic wasting syndrome (7)
Esophageal atresia (EA)	EA and EoE might share same risk factors: genes, early life factors (prematurity, NICU admission), early exposure to acid suppressants and antibiotics, GERD and esophageal dysmotility and epithelial injury (30–33)
Esophageal injury in childhood, and fetal chest malformations	Caustic damage and diaphragmatic hernia might allow the development of EoE with mechanisms not well-understood and investigated (34, 35)
Western diet and obesity	A recent study in mice demonstrated that a high fat diet and obesity aggravated the immune histopathological characteristics and increased inflammatory cells in the EoE experimental model (36)
Low level of vitamin D	The supplementation of vitamin D *in utero* and early life seems to reduce the risk of atopy (37–43)
Early life exposures	Cesarean section, preterm birth, NICU admission, formula feeding, early prescription of PPI, and antibiotics might impair the host microbiome and the developing immature immune system (44–49)
Early prescription and long-term therapy with proton pump inhibitors (PPI)	PPIs prevent the digestion of food allergens, increase the gastric permeability, and alter the intestinal microbiome (27, 49–56)
Early prescription of antibiotics	Antibiotics might impair the immature gut microbiome, that is essential for the developing of immune system (27, 49, 57–59)
Formula feeding	Human milk shows potentially anti-allergic immune properties and is fundamental for the correct development of a well-balanced gut microbiome (27, 60, 61)

where the infection is usually acquired in childhood. On the other hand, Molina-Infante et al. recently published the results of a large prospective case-control study conducted in 23 centers, and showed that the prevalence of *H. pylori* infection was not different between EoE cases and controls (37 vs. 40%; $p = 0.3$; OR 0.97; 95% CI 0.73–1.30), neither in children (42 vs. 46%; $p = 0.1$) nor in adults (36 vs. 38%; $p = 0.4$) (71). Therefore, there are already insufficient and conflicting data to support the protective role of *H. pylori* infection, and several issues are still open.

Diseases of Modern Life and Phenotypes of EoE

Recent advances in disease pathogenesis and prognosis have demonstrated that EoE could be classified in different phenotypes based on specific comorbidities. Epidemiological data demonstrated that EoE is so strongly associated with atopic comorbidities (asthma, allergic rhinitis, IgE-mediated food allergy, atopic dermatitis) (3, 9, 72) to follow allergic conditions in the atopic march, as a late manifestation (73).

However, a significant number of EoE patients do not present allergic diseases, suggesting a possible non-atopic phenotype (2). Interestingly, several reports have suggested that EoE may be more frequently associated with some non-allergic disorders, including connective tissue disorders (74), autoimmune diseases (coeliac disease) (8), and contradictorily inflammatory bowel diseases (IBD) (8, 75–77), that are increased in the last decades, especially in Western countries (8). The pathogenetic mechanisms explaining the association between these non-atopic diseases and EoE are poorly understood and investigated. EoE and coeliac disease (CD) are two inflammatory diseases induced by food allergens. Although CD resulted more frequent in EoE patients than controls (5.6% of EoE, 0.9% of non-EoE, $P < 0.0001$) (8), Lucendo et al. did not find a common genetic basis between these two diseases (78). The frequency of the HLA DQ2 and DQ8 alleles predisposing to CD was not observed in adult EoE patients compared to controls (78). Also, type 1 diabetes, cystic fibrosis, adrenal insufficiency, autism, attention deficit hyperactivity disorder (ADHD) (8), and monogenic diseases (7) appear to be significantly associated with a non-atopic phenotype of EoE (2).

An increasing amount of evidence showed that children with esophageal atresia (EA) (30–32) or with diaphragmatic hernia (34) are at higher risk to develop EoE (33, 34, 79). Several risk factors have been associated with the development of EoE in children with EA, such as early life factors, early exposure to acid suppressants and antibiotics, GERD, esophageal dysmotility, and epithelial injury (79). Interestingly, Krishnan et al. demonstrated that children with EoE + EA share the same dysregulated genes (that encode for proteins involved in epithelial barrier functions and Th2 inflammation) compared to patients with EoE and without EA (33).

Although not widely demonstrated, another possible risk factor for EoE might be childhood exposure to caustic ingestion. Homan et al. reported a case of EoE development after caustic damage in a child with allergic comorbidity (35). The authors proposed two possible explanations for this association: (1) the caustic ingestion primarily triggered the eosinophilic inflammation of the esophagus or (2) after caustic damage the esophageal lesion might allow the trigger exposure (mainly food allergens) that might lead to EoE (35). Although fascinating, this report is characterized by some bias (child presented allergic diseases); however, further and extensive studies are required to confirm this data.

The diagnosis of gastroesophageal reflux disease (GERD) was also increased in the last two decades in Western countries (80), in parallel to allergic diseases, and, as a result of cow's milk allergy in the half of infants with refractory GER (81). Some authors reported that GERD might play a role in the pathogenesis of esophageal eosinophilia, more relevant in PPI-responsive cases (82). GERD, esophageal eosinophilia, and EoE are not mutually exclusive and may coexist in the same patient. However, there was no precise data about this association, and four mechanisms were proposed to explain it. (1) GERD causes esophageal eosinophilia in the absence of EoE, (2) GERD and EoE coexist but are unrelated, (3) EoE contributes to or causes GERD, (4) GERD contributes to or causes EoE (82). In patients with GERD, acid reflux alters the epithelial barrier of the esophagus, increasing the permeability and the passage of food allergens that might trigger EoE. Furthermore, acid reflux in GERD may induce the expression of inflammatory molecules and eosinophil chemoattractants (13, 83). On the other hand, eosinophilic inflammation produces different molecules (vasoactive intestinal peptide and interleukine-6) that might impair the esophageal peristalsis and delay the esophageal acid clearance (14). The subepithelial fibrosis, a delayed complication of EoE, might promote esophageal dysmotility (15). Further studies are needed to understand if this possible pathogenetic correlation might early predispose children with GERD to develop the EoE.

Interestingly, the 10–15% of children with EoE presented to the otolaryngologist before to be referred to the gastroenterologist (84), and the 33% of these patients required one or more otolaryngologic surgical interventions (20% bilateral myringotomy, 14% tonsillectomy, 18.5% adenoidectomy, 1.4% sinus irrigation, 3.3% bronchoscopy, and 1.4% laryngotracheoplasty), suggesting that EoE might overlap with otolaryngologic pathology (85).

Western Diet and Lifestyle

Although foods are the primary triggers of EoE, there are limited data about the role of the Western diet in the contribution of the EoE pathogenesis. Higher levels of fatty acids characterize the Western diet and could be related to the increased risk of developing allergic diseases. In a recent study in mice, Silva et al. demonstrated that high-fat diet and obesity aggravated the immune histopathological characteristics and increased inflammatory cells in the EoE experimental model (36). These fascinating data provide new insights about obesity as a possible risk factor, impairing EoE symptoms; however, further prospective studies are needed.

No studies evaluated tobacco exposure in children and adolescents with EoE. Only a recent case-control study of adult patients showed that smoking was inversely associated with EoE compared to controls (86).

Geographic Risk Factors and Vitamin D Levels

As previously reported and already described for other inflammatory gastrointestinal diseases, EoE prevails in specific geographic areas of the world. Prevalence rates of EoE were higher in Western regions of Europe, North America, and Australia than Asia and Africa (3). These geographic differences between Western countries (high prevalence) and Eastern countries (low prevalence) suggest that environmental factors might play a significant role in etiological mechanisms. The effects of people migration on the future development of EoE have not yet been investigated.

A few and conflicting studies evaluated the geographic distribution of EoE, based on the population density. An extensive US survey of Spergel et al. showed that EoE prevalence was higher in urban (0.58) and suburban (0.44) compared with rural settings (0.36, $P < 0.0065$) (87). Lee et al. demonstrated no significant difference in the incidence of EoE between people living in the rural area (50.9%) vs. patients from the urban

ones (49.1%) (88). On the other hand, more recently, Jensen et al. found a strong inverse association between the population density and development of esophageal eosinophilia or EoE, demonstrating that EoE was more common in rural areas, in contrast with the hygienic hypothesis (89). A possible explanation of these results might be the geographic variation of specific environmental allergens.

Eosinophilic esophagitis prevails in cold climate zones, suggesting a possible association with specific aeroallergens (tree or grass pollens) and with low serum vitamin D levels (18). Increasingly significant evidence showed a link between vitamin D deficiency (maternal diet during pregnancy, early childhood diet, lack of exposure to sunlight) and risk of atopy, as described for asthma, allergic rhinitis, food allergy, and atopic dermatitis (37–39). This association is generally strongest in early life; in fact, interventional studies showed that the supplementation of vitamin D *in utero* and early life reduces the risk of recurrent wheeze and asthma (40–43). Although vitamin D enhances antimicrobial pathways, promotes peripheral immunological tolerance, and maintains mucosal barrier integrity, no studies have evaluated its possible preventive role in EoE development or its help in disease remission.

Climate zones might also affect the season of EoE diagnosis. Several single-center studies have evaluated the seasonality of symptoms and new diagnoses of EoE. In pediatric cohort studies, the seasonal exposure to aeroallergens increased the esophageal eosinophilic inflammation in children with EoE and allergic rhinitis (90, 91). However, the association between EoE relapse and season is still unclear, and available results were contradictory (16, 17, 92–97).

EARLY LIFE RISK FACTORS OF EoE: STATE OF ART

Early life is a critical period during the immune system and microbiota mature, becoming susceptible to early environmental exposures. A well-balanced microbiome is fundamental for the correct development of the immune system (98–100), and numerous early life exposures, including prenatal (maternal diseases, mother diet, and lifestyle), intrapartum (cesarean section, maternal fever, and infections, prematurity), and postnatal factors (early antibiotic and acid suppressants use, formula feeding), might impair the gut microbiome, and predispose to allergic diseases (101–109). The association between early impaired microbiota and risk of atopy is widely described for asthma, allergic rhinitis and food allergy (44, 45, 110). A few studies postulated that early life exposures might also predispose to EoE in childhood (**Table 2**). However, few studies focalized on early life exposures and their effects on the future development of EoE (27, 46–49). The available studies reported that formula feeding (27, 60), neonatal intensive care (NICU) admission, prematurity (47, 49), maternal fever (47), antibiotic and acid suppressants use in infancy (27, 49), cesarean delivery (27, 47) were putative early risk factors of EoE. The antibiotic and proton pump inhibitor (PPI) use in infancy showed the most consistent evidence of a positive correlation with the future development of EoE.

Effect of Early-Life Use of PPIs and Antibiotics

Although PPIs are used to treat GERD and esophageal eosinophilia, some studies paradoxically showed that the early PPI use might predispose to the development of autoimmune gastrointestinal diseases (celiac disease) (60), food allergies (13), and EoE (50). Physiologically, digestion of food proteins–and potential food allergens–begins into the stomach through pepsin proteinases, that are activated by the gastric acid *milieu*. PPI therapy might inactive proteinases and facilitate the digestive escape of food allergens, increasing the gastric pH. Also, PPI might increase the gastric mucosal permeability and the passage of allergens through the gastric mucosa, allowing their exposure to immune cells and the activation of atopic inflammation (51–53). Finally, PPI might alter the esophageal microbiota, and the modulation of immune response (54, 55). The risk to develop EoE after PPI therapy later in life has minimally been evaluated and could be higher after a long-term therapy (56, 111, 112). However, these data suggest that the immune system of infants might be more susceptible to PPI exposure, which might trigger the allergen-mediated inflammation of EoE. Since 1989 when the first PPI (Omeprazole) has been introduced into clinical practice, a worldwide escalation of PPI prescriptions was described at any age. Surprisingly, a pediatric study documented an 11-fold increase of new PPI prescriptions under 12 months of age in the last two decades (113).

The use of antibiotics in pregnancy is related to the treatment of several infections, such as bacterial vaginosis and urinary tract infections. Also, *intrapartum* and *peripartum* antibiotic prophylaxis are fundamental to decrease the risk of Group B *Streptococcus* infection in positive mothers and newborns. However, antibiotics might alter the immature gut microbiome of the newborn. Studies in rodents demonstrated that the administration of antibiotics in pregnancy decreased the microbiota diversity and permanently altered the immunity (57, 58). In newborns, the early administration of antibiotics resulted in decreased *Bifidobacterium* and increased enterococci strains (59). The worldwide increase of antibiotics prescriptions, especially in infancy, might partially explain the rise of allergic diseases. Observational studies demonstrated that the early life antibiotic administration was associated with asthma, atopic dermatitis, and allergic rhinitis (114–116). As previously mentioned, Jensen et al. founded a significant association with early antibiotic use and the development of EoE in children (27). Although an exact cause-effect mechanism cannot be deducted, these data suggest that the early exposure to antibiotics potentially might alter the immature microbiome and the developing immune system, allowing the risk of EoE (117).

The worldwide increase of PPI and antibiotic prescriptions in early life, associated with their possible pathogenetic role in

allergic disease and EoE, suggests a conscious and rational use of these drugs, especially in childhood.

Breastfeeding and Timing of Food Introduction in Children

Breastfeeding might be a possible factor that could prevent the development of food allergy through different mechanisms. Human milk shows potentially anti-allergic immune properties; in particular, the presence of maternal antibodies might prevent exposure to food allergens and induce oral immuno-tolerance (118). However, there is limited evidence on the direct correlation between breastfeeding and the development of EoE. In a pediatric case-control study, Jensen et al. identified a strong interaction between the calpain14 (CAPN14) gene variant (rs6736278) and breastfeeding, suggesting the possible protective role of human milk against EoE. CAPN14 is a cysteine protease and plays a fundamental role in the integrity of the esophageal epithelial barrier. Furthermore, its expression is only limited to the esophageal mucosa (119). CAPN14 expression was almost 4-fold increased in EoE patients compared to controls. Higher levels of CAPN14 expression are associated with the downregulation of desmoglein 1, filaggrin, and zonulin, which are pivotal proteins of the epithelial barrier (119). Although the exact mechanism of interaction between breastfeeding and CAPN14 is still unknown, human milk with its immunological properties might protect the esophagus from the epithelial barrier impairment and the development of EoE in patients with specific genotypes (120).

Over the last decade, food allergy research mainly focused on the timing of food introduction and oral tolerance. Murine models well-explained the concept of oral tolerance, and previous works showed how early and regular oral exposure to food allergens induced clinical tolerance and immunological changes. A large amount of evidence demonstrated that an early introduction of allergens might protect against the risk to develop IgE-mediated food allergy (61, 121, 122). In the last years, an increasing scientific interest focused on the diagnosis of non-IgE mediated food allergy, which often presents with a delayed onset of gastrointestinal symptoms. The EAT study evaluated data of non-IgE mediated symptoms (colic, vomiting, regurgitation, diarrhea, and constipation), demonstrating that infants in the early intervention arm reported significantly more non-IgE type symptoms than children in the standard intervention arm. However, rates of non-IgE mediated symptoms were equivalent in both groups at any time point, suggesting that the reporting of these symptoms did not depend on the introduction of the specific food allergen (121, 123). Further research is needed to understand if early food introduction could prevent non-IgE mediated food allergies, including EoE. Although the understanding of the EoE pathogenesis achieved notable progress, there are no published studies about the timing of food introduction in infancy and the future development of EoE.

Genetic Risk Factors

EoE has a strong familiar hereditability pattern. Monozygotic twins had a 44% disease concordance, a 2-fold increase compared with dizygotic twins (5, 6). These data underly a complex interplay between genic loci and environmental exposures, through epigenetic mechanisms that are partially understood (6). Also, the relative risk to develop this disease in dizygotic twins might increase more than 10-fold compared to siblings. The increased rate of EoE development in dizygotic twins could be attributed to the same early-life environmental factors, previously mentioned.

The inheritance mechanism of EoE could be related to the effects of multiple single nucleotide gene polymorphisms (SNPs) that increase disease risk, depending on the environmental exposures and disease risk-modifying factors (119, 124). Several studies, including candidate-gene identification and genome-wide association studies (GWAS), have identified different genetic *loci* that are likely contributing to the development of EoE and mainly include thymic stromal lymphopoietin (TSLP), calpain 14 (CAPN14), EMSY, LRRC32, STAT6, and ANKRD27 (7). These genetic loci are mainly involved in T-helper 2 type inflammation (allergic inflammation) and epithelial barrier function and integrity. Interestingly, EoE is also associated with several monogenic inherited diseases, especially with connective tissue disorders and skin diseases. Connective tissue disorders, such as Marfan and Ehlers Danlos Syndromes, share a common pathogenic mechanism through the dysregulation of the TGF-β signaling. Children with autosomal dominant Hyper-IgE Syndrome (HIES) and Netherton Syndrome have also significantly increased the incidence of EoE (125, 126). Defects in PTEN, dehydrogenase E1, and transketolase domain–containing 1 (DHTKD1) genes are also associated with EoE (127, 128).

HOW COULD WE PREVENT EoE?

The rise of EoE diagnosis, especially in children, is an actual problem, and preventive strategies are needed to limit this phenomenon. Although there are no published studies about the prevention of EoE, we could speculate that possible strategies of primary prevention of EoE might be:

1. Sustaining breastfeeding in the first 6 months of life, especially in preterm babies and newborns from mothers that underwent cesarean section.
2. Limiting the uncontrolled prescriptions of acid suppressants and antibiotics only in specific and right circumstances.
3. Do not delay the introduction of food allergens in infants.
4. Providing adequate levels of vitamin D in infant and children, especially in those from cold climate regions.
5. Encouraging a well-balanced diet and a healthy lifestyle both in pregnant women both in children.

This work has several strengths. Firstly, this is a comprehensive review, summarizing the current knowledge on EoE risk factors, and focusing on the role of early exposures. Also, this review tried to answer to two main clinical issues: (1) the increased prevalence and incidence of EoE in Western countries, especially in children; (2) the lack of knowledge on early risk factors and possible preventive strategies.

There are several limitations. First of all, the lack of extensive and prospective studies evaluating the real burden of

environmental risk factors, particularly the pathogenetic role of early exposures. Secondly, the vast majority of genetic and epidemiological studies were realized in Western Countries and mostly in the US. Finally, a few studies evaluated the gene-environmental interactions and the possible preventive strategies for EoE. Therefore, the lack of prospective and extensive studies from Eastern and developing Countries did not allow to draw reliable conclusions on the role of early risk factors and preventive strategies in EoE.

In conclusion, EoE is an emerging atopic disease that affects people at any age and characterized by symptoms due to esophageal inflammation, dysmotility, and fibrosis. As described for allergic diseases, several environmental risk factors and early-life exposures might interfere with genes, alter tolerance mechanisms, and activate the Th2 inflammation of EoE. Further studies are needed to identify risk factors of EoE, understand the interaction between genes and environment, finally find possible early preventive strategies.

AUTHOR CONTRIBUTIONS

MV and MD reviewed the literature and wrote the manuscript. AL, SC, IB, and GM reviewed the literature and helped with the writing of the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work. Questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Food allergy: cause or consequence of pediatric eosinophilic esophagitis? Potential implications of ultraprocessed foods in prevention and management

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Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease characterized by eosinophilic infiltration, leading to esophageal dysfunction, inflammation, and fibrotic remodeling. In the last few decades, there has been an increased prevalence of EoE at an alarming rate in the pediatric age. The pathogenesis of EoE is still largely undefined, and this limits the definition of effective strategies for the prevention and management of this condition. EoE is considered a multifactorial disease arising from a negative interaction between environmental factors and genetic background, causing an impaired esophageal epithelial barrier with subsequent abnormal allergen exposure activating type 2 (Th2) inflammation. Food antigens have been suggested as key players in Th2 inflammation in pediatric patients with EoE, but emerging evidence suggests a potential role of other dietary factors, including ultraprocessed foods, as possible triggers for the occurrence of EoE. In this paper, we discuss the potential role of these dietary factors in the development of the disease, and we propose a new approach for the management of pediatric patients with EoE.

KEYWORDS

Th2 inflammation, esophageal barrier, advanced glycation end products, alarmins, ultraprocessed foods

Introduction

Food allergy (FA) in children is a major health concern, with an increased prevalence in the past two decades (1–4). Different clinical phenotypes of FA have been described, all deriving from the alteration of the mechanisms of immune tolerance to dietary antigens (5). Concomitantly, a similar increase in the prevalence of eosinophilic esophagitis (EoE) has been observed in the pediatric age (6–8). Children affected by FA present an increased risk of developing EoE later in life, and now EoE is considered as a component of the allergic march (9). EoE is a chronic disease characterized by an eosinophilic inflammation of the esophagus and symptoms of esophageal dysfunction (10, 11). Like FA, EoE is considered a condition deriving from a negative interaction between genetic

background and environmental factors, leading to esophageal barrier dysfunction. The esophageal barrier alteration facilitates an abnormal exposure to dietary antigens and the consequent activation of type 2 (Th2) inflammatory response (6, 12). EoE has evolved from a rare condition to a commonly encountered disease in pediatric clinical practice and a significant cause of upper gastrointestinal morbidity (13). The global prevalence of EoE is 0.5–1 cases/1,000 persons (13). In children, the pooled incidence of EoE is 6.6 cases/100,000 person years, whereas the pooled prevalence is 34 cases/100,000 children (14). During the last few years, several studies reported a dramatic increase in EoE prevalence, especially in children in Western Countries (7, 14–16). Although this evidence might be related to improved medical awareness and knowledge, it could also be related to the global increase in allergic disorders. Despite some genetic factors have been associated with an increased risk of developing EoE, environmental factors seem to be the most relevant players facilitating the occurrence of the disease (13). In the last few years, one of the most impressive changes in the exposure to environmental factors concerns dietary habits. The consumption of ultraprocessed foods (UPFs) rapidly spread in the last few decades among children living in Westernized countries (17, 18). Increased exposure to UPFs is considered a facilitating factor for the occurrence of several chronic non-communicable diseases, including FA (19, 20).

In this paper, we discuss the potential role of UPFs and FA in the development of the disease, and we propose a new approach for the management of pediatric patients with EoE.

Genetic and environmental factors: an intriguing interplay in the pathogenesis of EoE

The pathogenesis of EoE is still largely undefined. It is commonly considered a multifactorial disease in which genetic and environmental factors may play a role. These factors, through intricate and bidirectional interactions, are responsible for esophageal barrier impairment, with loss of cell-to-cell adhesion mechanisms (desmosomes, tight, and adherence junctions), increased permeability, and consequent abnormal exposure to dietary antigens (21, 22). Alteration of the esophageal barrier leads to the epithelial release of inflammatory molecules such as thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33, also called alarmins. These mediators drive the differentiation of Th2 effector cells, with the consequent production of several Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) and massive recruitment of eosinophils (23). Simultaneously, luminal antigens encountering antigen-presenting cells (APC), activate specific antigen Th2 differentiation, induce additional release of inflammatory cytokines, eosinophils recruitment, and plasma cell activation with specific IgE production (23).

Lessons from genetic findings

The role of genetic factors in EoE pathogenesis was postulated with the observation that disease prevalence varies among sex and ethnicity. Epidemiological studies show that EoE is most common in white males, in children, and in adults (24–26). Genetic susceptibility is also supported by the evidence that having a first-degree family member affected by EoE increases the risk for disease occurrence (OR, 16.3; 95% CI, 9.4–28.3) (27). The relevance of the genetic background has also been supported by the results of candidate-gene and genome-wide association studies (GWAS), highlighting the role of different *loci* involved in the Th2 inflammatory response, and in the regulation of epithelial barrier structure and function in patients with EoE (12, 28, 29). The integrity of the esophageal epithelial barrier is ensured by desmosomes, tight and adherence junctions, as well as by several genes involved in epithelial cell differentiation, including filaggrin (FLG) and desmoglein 1 (DSG1). A genetic variation in these genes was detected in patients with EoE (24). The most powerful association has been found in the alteration of calpain 14 (CAPN14) production, an enzyme involved in esophageal barrier regulation via the IL-13 pathway (30, 31). Lastly, two other variations in serine peptidase inhibitors, kazal type 5 and 7 (SPINK5 and SPINK7), were also detected in barrier integrity maintenance (12, 28, 29).

EoE is characterized by a Th2 inflammatory response and a high prevalence of other atopic comorbidities (32, 33). Several genetic alterations were detected in patients with EoE, mainly related to the Th2 response, resulting in the upregulation (up to 53-fold) of eotaxin-3 (CCL26), TGF-β, and Periostin (POSTN), respectively, involved in eosinophil chemotaxis and adhesion, with the consequent production of TSLP (12, 34). TSLP is considered a crucial mediator involved in the EoE inflammatory cascade. Although TSLP is also expressed in other atopic disorders, TSLP production seems unrelated to other concomitant allergic diseases in patients with EoE (28, 29).

Despite this evidence, twin studies reporting a low disease concordance in both monozygotic (41%) and dizygotic (22%) twins suggest the greater importance of environmental factors as a major driving force for the occurrence of EoE in genetically predisposed children (35, 36).

The potential role of environmental factors in facilitating the occurrence of EoE

Growing evidence underlines that early life exposure to several detrimental factors, as already reported for FA pathogenesis, could promote esophageal barrier dysfunction and Th2 inflammatory response in EoE (37–39). In contrast, several beneficial environmental factors, such as breastfeeding and the Mediterranean diet, showed a protective role against these conditions (40–42).

Several environmental agents could induce esophageal barrier dysfunction. This could be the case of the detergents that altering

the epithelial barrier, induced mucosal inflammation and the typical histological features of EoE in a preclinical model (43). Immortalized esophageal epithelial cells (EPC2) exposed to sodium dodecyl sulfate (SDS), a widely used detergent contained in domestic cleaning, cosmetic, pharmaceutical, and food products, showed a significant decrease in transepithelial electrical resistance and a significant increase of FITC-dextran flux. In addition, a proinflammatory IL-33 mRNA expression and a reduction of DSG1 expression were detected, with consequent alteration of epithelial barrier integrity. It was also observed that mice exposed to SDS showed a marked activation of proinflammatory cytokine pathways and esophageal eosinophilia compared with not-exposed controls (43).

Like FA, infections have also been proposed as potential risk factors for the occurrence of EoE. Some case series showed a direct association between herpes simplex virus esophageal infection and the development of EoE (44).

Data regarding different living areas are discordant. Some studies showed a positive association between EoE occurrence and suburban areas (36, 45, 46). It is well known that rural vs. urban or suburban areas are characterized by a considerable difference in pollution exposure, aeroallergen content, and climate temperature, which can modify the allergen air concentration. Living in a cold climate zone seems related to a higher risk of EoE occurrence, but more studies are needed to support this hypothesis (47). Aeroallergens have long been proposed as a trigger or worsening factor for EoE (48, 49), but their role in the pathogenesis of EoE is still controversial. Indeed, if it is well known that aeroallergens induce a Th2-orientated immune response in other allergic diseases (i.e., allergic rhinitis or asthma), their role in EoE occurrence or exacerbation needs to be better investigated (50–53). Recent studies on the role of seasonality were unable to demonstrate significant differences in EoE occurrence and disease course (54, 55).

New studies are now exploring the potential role of the Western diet as a trigger for non-communicable disease occurrence, including FA (19, 20, 56). Western diet is low in fibers and polyunsaturated fats and rich in UPFs (57). During the last few decades, the consumption of UPFs significantly increased in children living in Western countries. It was estimated that 65% of the total daily energy intake derives from UPF consumption in children in the US and EU (18, 19).

Smith and colleagues highlighted how dietary patterns could be related to FA occurrence in children (20, 56). They linked different types of foods consumed by US children and fast-food consumption by Australian pediatric subjects, with the increase in FA prevalence (58, 59).

Furthermore, countries with a huge increase in the EoE, FA, and anaphylaxis rates were also the countries where Western diet rapidly spread among the child population in the same period (7, 14–16, 60–65).

One of the main UPF-derived compounds are the advanced glycation end-products (AGEs), deriving from the non-enzymatic reaction between proteins and sugars via the Maillard reaction (66).

Dietary AGEs activate several inflammatory pathways, including the Th2 inflammatory response, through interaction with specific receptor (RAGE) expressed by epithelial cells, peripheral blood mononuclear cells, human esophageal mucosal cells, and by human eosinophils (17, 67–69). The activation of RAGE induces several intracellular pathways that activate the alarmins signal with increased production of TSLP, IL-33, and IL-25 (70). These inflammatory cytokines exert a pivotal role in EoE and FA pathogenesis, and they induce differentiation of innate lymphoid cells 2 in Th2 effector cells with a consequent production of IL-4, IL-5, IL-9, and IL-13 (12). AGEs also activate mast cells, via RAGE activation, with a consequent release of proinflammatory cytokines, and may induce the production of specific IgE against dietary antigens (71, 72). In addition, dietary AGEs increase oxidative stress levels, and may also act at the gastrointestinal (GI) level by impairing gut microbiome structure and function and tight junction protein expression (56, 73). These proteins are crucial in maintaining the esophageal and gut barrier integrity; thus, an increased epithelial permeability allows an abnormal antigen passage (56, 74). In summary, the alteration of the gut and esophageal barrier integrity, the abnormal antigen translocation, and the alarmin activation with a consequent Th2-orientated response, may allow an altered antigen presentation, resulting in a potentially harmful condition for the maintenance of immune tolerance to dietary antigens (75, 76).

Lastly, it has been demonstrated that proton pump inhibitors (PPIs) could modulate both esophageal barrier integrity and alarmin signal (77). This could be an additional mechanism of action of PPIs in EoE treatment.

Altogether, these data, from the epidemiological and immunological points of view, add plausibility to the potential role of UPFs in facilitating the occurrence of EoE and FA.

Food allergy-EoE links

As EoE is characterized by Th2 inflammatory response, most pediatric patients have other coexisting atopic comorbidities, such as FA, allergic oculorhinitis, and asthma (32, 33). This clinical picture demands multidisciplinary management involving pediatric allergy, gastroenterology, and nutrition expertise (78). Observational studies have demonstrated that the risk of developing EoE increases in allergic children, especially in those with ≥1 allergic disease, and to date, EoE has been proposed as a component of the allergic march (9). Moreover, allergic sensitization has been reported in most pediatric patients with EoE (79). According to recent FA classification, EoE can also be considered a mixed (IgE- and non-IgE-mediated) FA, where food antigens have been proposed as triggers for esophageal Th2 inflammation in genetically susceptible patients (80). In 2017, a systematic review with the meta-analysis by Gonzalez-Cervera et al. reported that the frequency of FA in patients with EoE, compared with healthy controls, ranged from 0% to 44%, with a relevant clinical heterogeneity in FA definition (81). Thereafter, Capucilli and Hill, assessing the prevalence of allergic diseases in patients with EoE, reported a 24%–68% prevalence from 2015 to 2019 (33). A more recent literature revision confirmed that the prevalence of IgE-mediated FA varies between 25% and 70% (31).

The *primum movens* in allergic diseases is the epithelial barrier alteration, as in the case of FA (21). After this, the loss of immune tolerance against allergens is crucial for FA development (33). In the context of IgE-mediated disease, specific IgG4 are generally increased and considered a marker of immune tolerance. Evidence shows that patients with EoE may also present high levels of IgG4, but their role in EoE pathogenesis and diagnosis is unclear. In fact, EoE shares some clinical features not only with IgE-mediated FA but also with IgG4-related disease, characterized by progressive fibrosis (82). In 2014, Clayton et al. showed increased IgG4-positive plasma cells (IgG4-PC) in the lamina propria and granular extracellular IgG4 deposits in adults with EoE. In addition, the authors reported high IgG4 serum levels against milk, wheat, egg, and nuts in these patients, demonstrating that the esophageal deposition of IgG4 was associated with food-specific IgG4 antibodies (83). Recent studies confirmed the presence of total specific IgG4 high serum level in pediatric patients with EoE compared with healthy controls (84, 85). Unfortunately, despite this evidence, the pathogenetic role of IgG4 in EoE is still unclear and requires further research.

FA and EoE have also been linked by the response to the elimination diet (32, 86–88). However, despite the fact that a complete clinical response to the elimination diet is observed in all children with FA, as this is mandatory for making a definite diagnosis of FA (89), the response to the elimination diet has not been reported in all children with EoE (90). The first evidence that foods were the triggers of esophageal inflammation were reported by Kelly et al. (91). The authors highlighted the link between FA and EoE by showing that children treated with an exclusive elemental (amino acid–based) formula completely recovered from GI symptoms and showed a drastic decrease in esophageal eosinophilia (91). The elemental diet is effective in up to 90% of pediatric patients with EoE (90).

The most frequently implied foods in pediatric patients with EoE are cow's milk, wheat, soy and/or legumes, egg, tree nuts, and shellfish. The elimination of these food allergens showed different efficacy rates, depending on the number of foods removed and the rationale used to eliminate them from the diet (empirical vs. targeted) (92, 93). The empirical elimination of all these six food antigens produced effective results in approximately 72% of patients, and the targeted one could induce a similar remission rate in patients with EoE when a combination allergy screening tests is performed [skin-prick tests (SPT), atopy patch tests (APT), and/or specific IgE] (90, 94). The four-food elimination diet (cow's milk, wheat, soy, and egg) induces histological remission in above 53% of patients, with higher efficacy in children than in adults (60% vs. 46%) (90). Kagalwalla et al. performed a prospective observational study in children with EoE treated with a four (cow's milk, wheat, egg, and soy)-food elimination diet finding that after food reintroduction, the most common food triggers that induced histologic inflammation were cow's milk (85%), egg (35%), wheat (33%), and soy (19%) (93). Therefore, since milk and wheat are the most allergenic foods, Molina-Infante et al. proposed starting with an empirical 2-food elimination diet, finding that this approach was effective in 43% of treated patients (95). The authors thus proposed a step-up approach that avoids unnecessary dietary restrictions and spare GI endoscopies to assess histologic remission (96). A recent prospective study in children with EoE found that the single milk elimination diet was effective in more than 50% of patients, suggesting that this dietary intervention may be proposed as first-line treatment because of the ease of implementation and adherence (96). More recently, de Rooij et al. proposed a mixed dietary treatment in adults with active EoE, combining the empirical four-food elimination diet with an amino acid–based formula. The authors found that, although the combined dietary treatment significantly improved the quality of life in adult patients with EoE, it did not lead to a more considerable decrease in the peak of eosinophil count at 6-week follow-up (97). As already reported in patients with atopic dermatitis, children with EoE may develop IgE-mediated hypersensitivity to food antigens (98, 99). On the other hand, children who outgrow IgE-mediated FA and reintroduce the culprit food(s) in their diet, can later develop EoE for the same food (100).

Unfortunately, the response to the food-elimination diet is not complete or sustained over time in many children with EoE (90). Several factors impacting clinical or histologic response should be considered in patients with EoE who are unresponsive to the elimination diet (**Table 1**) (101).

TABLE 1 Established and possible causes of unresponsiveness to food elimination diets and suggested solutions.

Causes of unresponsiveness	Solutions
Low diet compliance	
Poor palatability of amino acid-based formula	Discuss with patient and his/her family all possible therapeutic strategies
Several dietary restrictions	Modified elemental diet (amino acid-based formula + one or two less allergenic foods, generally vegetables or fruits)
Expensive cost of amino acid-based formula or dietary alternatives	Nasogastric tube or gastric tube in candidate children*
Psychosocial isolation with negative impact on the quality of life	Nutritional and psychological counseling
Desire to consume trigger foods	
Food contamination	Patient and family education
Persistent fibro-stenotic disease with esophageal stricture	Esophageal dilatation
Persistent high exposure to other environmental/ dietary factors (ultraprocessed foods, detergents)	Patient and family education Nutritional counseling

*Toddlers and young children with active disease complicated by severe failure to thrive and malnutrition.

Discussion

In the last few decades, the increased incidence and prevalence of pediatric EoE paralleled with the increased incidence, prevalence, and severity of the clinical manifestations of FA, in the pediatric age. The origin of these parallel epidemiologic patterns is still largely undefined, but it could be the target for innovative preventive and therapeutic strategies against both conditions.

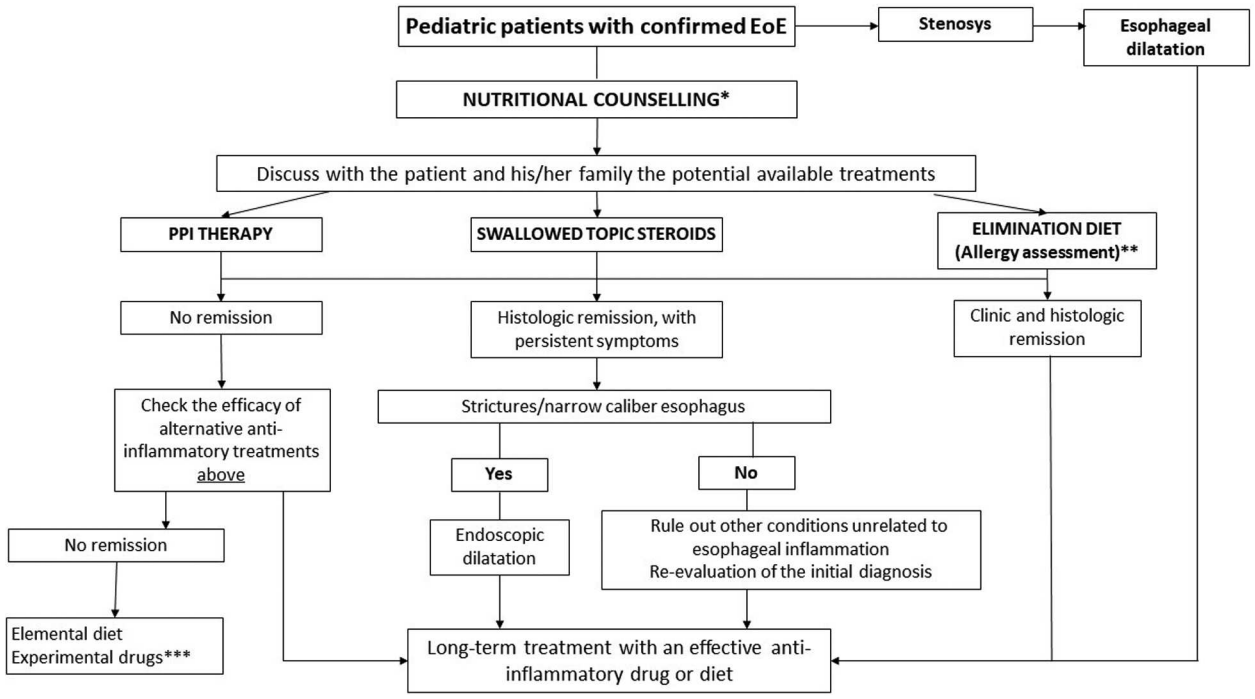

FIGURE 1
Toward an innovative strategy for the management of pediatric EoE. EoE, eosinophilic esophagitis; PPI, proton pump inhibitors. *Nutritional counseling aims to assess the patient's diet, eating habits, potential nutritional deficiencies, and reduces exposure to ultraprocessed foods. **Skin prick test, specific IgE, and atopy patch test + nutritional counseling. ***Consider biological treatment (dupilumab was approved by the FDA in patients >12 years with EoE).

The role of dietary factors in EoE pathogenesis has been long considered only from the FA point of view, in which food antigens are considered triggers for the esophageal barrier dysfunction, for the occurrence of Th2 inflammatory response and the consequent clinical and histological features of EoE (10). It is now time to speculate that the abnormal food antigen exposure could be just the consequence of a first hit, which could be mainly responsible for the occurrence of EoE in genetically predisposed individuals (21). Thus, defining which environmental factor could elicit the first hit could be paramount for designing disrupting strategies against EoE.

The activation of alarmins is one of the initial signals in EoE pathogenesis, driving a Th2 inflammatory response and esophageal barrier alteration (79, 102). Recent data suggest that selected environmental factors could induce alarmins signal and esophageal barrier dysfunction (20, 103). Among these factors, the UPF detrimental compounds, AGEs, seem to be relevant candidates able to directly "switch on" EoE inflammation (20). AGEs directly activate the production of alarmins. Then, esophageal barrier impairment could be responsible for increased epithelial permeability and abnormal exposure to food allergens, with subsequent sensitization of food antigens (24). This could explain why sensitization of food antigens is commonly observed in pediatric patients with EoE. In the light of this, sensitization of FA and food antigens cannot be the trigger but just an epiphenomenon in several pediatric patients with EoE. This could justify why the response to the food-elimination diet may be ineffective in a number of children with EoE.

Altogether, it is possible to hypothesize that UPFs, and in particular dietary AGEs, could act as the *primum movens* for the esophageal barrier dysfunction, mimicking the innate alarmin pathways and facilitating the occurrence of EoE in genetically predisposed children. This hypothesis could drive innovative preventive measures to limit UPFs/AGEs exposure in the pediatric age and provide a new strategy for EoE management. This could be a reasonable, affordable, and easily applicable strategy against EoE.

Thus, we propose a new approach for pediatric EoE management, in which nutritional counseling aimed to reduce exposure to UPFs/AGEs could facilitate better therapeutic outcomes in pediatric patients with EoE (Figure 1). Future preclinical and clinical studies are advocated to explore the potential of this approach.

Author contributions

LC and MV analyzed the literature, wrote the manuscript, and read the manuscript. RC designed and structured the review, wrote the manuscript, and read the manuscript. AL and GM analyzed the literature and read the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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REVIEW ARTICLE

Primary eosinophilic gastrointestinal disorders and allergy: Clinical and therapeutic implications

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Abstract

Primary eosinophilic gastrointestinal disorders (EGID) are increasingly prevalent, immune-mediated, chronic conditions which primarily affect pediatric and young adult patients, leading to substantial disease burden, and poor quality of life. EGID may either involve single portions of the gastrointestinal tract (i.e., esophagus, stomach, small bowel, and colon) or a combination. Their strong association with allergic disorders has been recently recognized, and although their shared pathophysiological basis remains partly elusive, this feature greatly impacts the diagnostic and treatment work-up. We herein critically discuss the current knowledge on the association of EGID and allergic disorders, including atopic dermatitis, allergic rhinitis, allergic asthma, and food or drug allergy. In particular, we reviewed the literature focusing on their epidemiology, pathophysiological basis and mechanisms, and diagnostic strategies. Finally, we discuss the currently ongoing clinical trials targeting EGID and allergic diseases, including, among others the monoclonal antibodies dupilumab, mepolizumab, benralizumab, and lirentelimab.

KEYWORDS
allergy, asthma, atopic dermatitis, food allergy, rhinitis

1 | INTRODUCTION

Primary eosinophilic disorders of the gastrointestinal tract (EGID) encompass a spectrum of diseases characterized by prominent eosinophilic inflammation affecting different regions of the gut that occur in the absence of secondary causes (e.g., infections, drug reactions).[1,2] Eosinophils typically show an activated phenotype, and their infiltration leads to symptoms related to organ dysfunction. EGID include some major entities according to the topographical localization of the inflammation, namely eosinophilic esophagitis (EoE), eosinophilic gastritis/gastroenteritis, and eosinophilic colitis, and both the pediatric and adult populations can be affected by these conditions, although with different manifestations in the pediatric and adult populations.[3,4]

Eosinophilic gastrointestinal disorders are increasingly recognized conditions, the prevalence of which has been probably underestimated so far due to poor awareness and lack of standardized diagnostic criteria.[5,6] Also, given that endoscopic examinations are needed for making a definitive diagnosis, the entity of underdiagnosis in pediatric patients is probably more relevant. More in depth, EoE,

Abbreviations: EGID, eosinophilic gastrointestinal disorders; EoE, eosinophilic esophagitis.

with a prevalence of 0.5 to 1/1000 individuals in the general population, is the most frequent among EGID, and hence it is the most studied.[7] It represents the most common cause of chronic dysphagia in children and the most common cause of dysphagia with bolus impaction in adults.[8] In a recent study by Cianferoni et al. conducted in the United States, the prevalence of concomitant atopic diseases was significantly higher in both adults and children, compared to non EoE patients.[9]

Due to their supposed rarity and the paucity of data, the prevalence of the other disorders belonging to the EGID spectrum is more difficult to ascertain. According to a recent US registry-based study by Dellon et al., the prevalence of eosinophilic gastritis, gastroenteritis and eosinophilic colitis, after the introduction of specific ICD-9 codes, can be estimated to be as high as 6.3/100,000, 8.4/100,000, and 3.3/100,000, respectively.[10] However, this figure is probably underestimated, as this commonly occurs in administrative data-driven studies.[11] As recently reported in a systematic review with meta-analysis, non-esophageal EGIDs affect about 2% of patients referred to the hospitals for gastrointestinal symptoms and the prevalence of atopic comorbidities ranges from 25% to 54% of affected patients.[12]

Eosinophilic esophagitis is a chronic immune-mediated, antigen-driven, disease, and results from the complex interplay between genetic and environmental factors, also including early life exposures to certain factors, leading to epithelial barrier dysfunction, allergic sensitization, and prominent Th2 inflammation.[8,13,14] On the contrary, the pathogenesis of EGID not affecting the esophagus is still largely uncertain. Some cellular and molecular features of Th2 inflammation have been demonstrated, particularly with reference to eosinophilic gastroenteritis, but autoimmune factors are also believed to exert a role.[15,16] However, a comprehensive view of their pathogenesis is still lacking, and this contributes, along with other factors, to the substantial diagnostic delay and therapeutic uncertainty.[17,18] Moreover, the association with allergic disorders must be considered when managing patients with EGID, as they may share a common etiopathological background and hence some clinical features.[2,9,17] In fact, some patterns of disease association are common in these patients, such as the co-occurrence of allergic asthma, rhinitis, and esophageal symptoms, or the occurrence of gastrointestinal symptoms in patients receiving oral immunotherapy for food allergy, or else the occurrence of isolated diarrhea in atopic patients.[6,19,20] All these clinical patterns should raise the suspicious of EGID.

Apart from the common association with allergic manifestations, the clinical features of EGID vary according to the gut segment and the layer of the gut wall involved, that is, the mucosa, the muscular layer, or the serosa, and the diagnostic work-up of EGID is primarily based on endoscopy and histopathology.[21] The main clinical features, diagnostic criteria, and currently available therapies for EGID are summarized in Table 1.

The aim of the present review is to provide in a narrative and concise fashion an updated overview about the association between EGID and the whole spectrum of allergic disorders in adults and children, in order to improve diagnosis and treatment of allergic comorbidities in patients with EGID. We also provide a critical update of the ongoing clinical trials regarding therapies for EGID, highlighting potential advantages for concomitant allergic disorders.

2 | METHODS

In June and September 2021, we performed a computer-assisted literature search for relevant studies using PubMed. The aim of the search was to find papers dealing with the association of EGID with allergic disorders, focusing on the clinical and therapeutical implications. The research was restricted to papers published in English. The medical subject heading terms used were “EoE,” “eosinophilic gastritis,” “eosinophilic gastroenteritis,” “eosinophilic colitis,” and “atopy,” “asthma,” “allergic rhinitis,” “atopic dermatitis,” “drug allergy,” “eczema,” “environmental allergy.” By using these terms, we found more 3000 papers. Of these, most were unrelated to the review topic and hence were discarded by all authors. We focused on the original, review articles, and case reports/series since database inception, dealing with the association of allergic disorders in EGID, in both the pediatric and the adult settings. We also searched for relevant papers cited in authoritative reviews dealing with EGID in relation to other allergic disorders. Given the narrative, expert-based, nature of the review we did not carry out a systematic review of the literature.

2.1 | Eosinophilic esophagitis

Eosinophilic esophagitis has proteiform manifestations and symptoms, which vary with age.[4] While young children and toddlers usually experience vomiting, regurgitation, abdominal pain, feeding refusal, and failure to thrive, adolescents and adults often report dysphagia and food impaction that may be the expression of advanced tissue remodeling.[22–24] EoE may affect people of any age and gender, but it is more common in young male individuals. It is characterized by the presence of esophageal infiltration in both the proximal and distal esophagus. The disrupted function of the muscolaris mucosa layer, which can be shown by ultrasonography, results in symptoms of esophageal dysmotility.[25]

Most of the studies considering the relationship between EGID and asthma are focused on EoE, probably because EoE is the most frequent form of EGID, paralleling the epidemiologic surge of allergic diseases.[7,26] Several studies have shown that patients with EoE suffer from a significant burden of allergic comorbidities, such allergic rhinitis, asthma, atopic dermatitis, and IgE-mediated food-allergy.

The prevalence of asthma in adult series of EoE patients varies from 25% to 50%, and reaches 60% in pediatric series.[26–28] Moreover, in a previous meta-analysis considering a large number of individuals it was found that patients with EoE had a significantly increased probability of having asthma (OR 3.01, 95% CI 1.96–4.62, OR 5.09, 95% CI 3.91–8.90, respectively) and allergic rhinitis compared to controls.[29] This strong association has led some authors to consider EoE as “the asthma of the esophagus.”[30]

TABLE 1 Clinical and endoscopic features, diagnostic criteria, current therapeutic options in eosinophilic gastrointestinal disorders

	Eosinophilic esophagitis	Eosinophilic gastritis/enteritis	Eosinophilic colitis
Clinical features	Symptoms vary with age Gastroesophageal reflux disease (heartburn, acid regurgitation), epigastric/chest pain, dysphagia, food impaction, vomiting, weight loss	Mucosal form: vomiting, abdominal pain, diarrhea malabsorption, protein-losing enteropathy, iron-deficient anemia, failure to thrive (children), melena Muscolaris layer form: obstructive symptoms Serosal form: eosinophil-rich ascites	Abdominal pain Diarrhea Weight loss Anorexia
Endoscopic features	Edema Linear oriented creases (furrowing) Mucosal rings (feline esophagus) Exudates and whitish papules Polyps Strictures	Micronodules Erosion Mucosal hyperemia	Erythema Loss of vascularity Lymphonodular hyperplasia
Diagnostic criteria	≥15 Eo/HPF from at least one site (distal, mid, or proximal esophagus)	≥30 Eo/HPF in ≥5 HPF or ≥70 Eo/HPF in ≥3 HPF (stomach) ≥52 Eo/HPF (duodenum) ≥56 Eo/HPF (ileum)	≥100 Eo/HPF (cecum/ascending colon) ≥84 Eo/HPF (transverse/descending colon) ≥64 Eo/HPF (sigma/rectum)
Histopathological features	Eosinophilic inflammation, eosinophil abscess, eosinophil surface layer, basal zone hyperplasia, dilated intercellular spaces, dyskeratotic epithelial cells, lamina propria fibrosis. Immunostaining for MCP, ECP, IgE, tryptase	Eosinophilic inflammation in different layers Blunt villi Immunostaining for MCP, ECP, IgE, tryptase	Eosinophil cryptitis/crypt abscesses, crypt architectural abnormalities, increased intraepithelial eosinophils, and eosinophils in muscularis mucosa and submucosa Immunostaining for MCP, ECP, IgE, tryptase
Laboratory parameters	Peripheral blood eosinophilia (not always present)	Peripheral blood eosinophilia (not always present)	Peripheral blood eosinophilia (not always present)
Differential diagnoses	Infection HES Neoplasm CTD/SS Small vessel vasculitis Drug reaction	Infection HES Celiac disease Crohn's disease CTD/SS Small vessel vasculitis Systemic mastocytosis Drug reaction	Infection HES Ulcerative colitis Crohn's disease CTD/SS Small vessel vasculitis Systemic mastocytosis Drug reaction
Association with allergic disorders	+++	++	+
Predominant allergic phenotype	IgE T-cell	IgE T-cell	T-cell
Therapeutic options	Elemental diet, 6, 4, and 2 FED Topical glucocorticoid Proton pump inhibitors	Elemental diets Topical and systemic glucocorticoid	Elemental diet Topical and systemic glucocorticoid
Evolution	Esophageal stenosis, bleeding, perforation/rupture, especially if left untreated	Poorly characterized in the long term	Poorly characterized in the long term

Abbreviations: CTD, connective tissue disease; FED, food elimination diet; HES, hyper-eosinophilic syndrome; HPF, high power field; SS, systemic sclerosis.

Food allergy has been traditionally linked to EoE, given the strong epidemiologic link between these disorders, the clinical and histological response of EoE to elemental diets, and, more recently, the increased recognition of EoE in patients being treated with oral immunotherapy.[8] The prevalence of IgE-mediated food allergy varies between 25% and nearly 70%.[29,31] The most frequently implied foods are milk, wheat, soy, egg, nuts, and shellfish. Eczema was also significantly more frequent in patients than controls, (OR 2.85, 95% CI 1.87–4.34).

Finally, in a large cross-sectional, population-based survey conducted in the US, a high prevalence of allergic disorders was observed among 74 EoE children and 89 EoE adults, namely 32.4%

TABLE 2 Studies describing the association between eosinophilic gastrointestinal disorders and allergic disorders in adults

Author, year, country	Study type	Population	Pathology	Allergy disease	Comments	References
Wright et al., 2018 United States	Prospective Patients with peanut allergy (n = 21)	Adults	EoE	Food allergy	EoE common in adults with IgE-mediated peanut allergy before OIT	50
Eckmann et al., 2018 United States	Pilot, prospective, open-label. EoE (*n* = 8)	Adults	EoE	Food allergy	Only four patients with a positive atopy patch test. No concordance between atopy patch test and EoE	51
Burk et al., 2017 United States	Prospective EoE patients with peanut allergy (*n* = 13)	Adults	EoE	Food allergy	Two patients pretreated with omalizumab developed EoE	52
Dellon et al., 2015 United States	Prospective, case-control EoE (n = 81), controls (n = 144)	Adults	EoE	Asthma Rhinitis Atopic dermatitis Food allergy	Food allergies more common in EoE while atopy disease had not statistical significance	27
Sealock et al., 2013 United States	Prospective, case-control. EoE patients (*n* = 31), esophageal eosinophilia without EoE (*n* = 7), controls (*n* = 1319)	Adults	EoE	Asthma	Seasonal allergies and esophageal strictures associated with esophageal eosinophilia. Asthma not significantly associated with esophageal eosinophilia or EoE	53
Joo et al., 2012 Korea	Prospective. EoE patients(*n* = 8) and controls (*n* = 114)	Adults	EoE	Asthma Rhinitis Atopic dermatitis Food allergy	A history of allergic rhinitis and atopic dermatitis significantly common in EoE patients	54
DeBrosse et al., 2011 Unites States	Retrospective, nested case-control. EoE patients (*n* = 42), chronic esophagitis (*n* = 67), controls (*n* = 100)	Adults	EoE	Rhinitis Food allergy	Food impaction more common in patients with food allergy. Eczema associated with history of esophageal dilation Allergic rhinitis, asthma, and food allergy associate with dysphagia Food allergy more frequent in EoE patients than chronic esophagitis	55
Garcia-Compean et al., 2011 Mexico	Prospective. EoE patients (*n* = 6) and controls (*n* = 144)	Adults	EoE	Atopy	Atopy as an independent predictor of EoE	56
Ravi et al., 2011 United States	Retrospective. EoE patients (*n* = 418) and controls (*n* = 59)	Adults	EoE	Asthma Rhinitis	Atopy (asthma and allergic rhinitis) more common in patients with ≥15 eos/HPF	57
Foroutan et al., 2010 Iran	Cross-sectional. EoE patients (*n* = 6),	Adults	EoE	Asthma Rhinitis	Atopy was more common in EoE, while asthma, urticaria, atopic dermatitis, rhino-conjunctivitis, and	58

TABLE 2 (Continued)

Author, year, country	Study type	Population	Pathology	Allergy disease	Comments	References
	controls (n = 62)			Atopic dermatitis Food allergy Atopy	food allergy had not significant values	
Veerappan et al., 2009 United States	Prospective. EoE patients (n = 25) controls (n = 360)	Adults	EoE	Asthma	Higher asthma rates in patients with EoE than controls	59
Mackenzie et al., 2008 United States	Prospective. EoE patients (n = 31) and non-EoE patients (n = 230)	Adults	EoE	Asthma Food allergy	12% of patients had EoE pathological criteria. EoE more common in patients with asthma and self-reported food allergy	60

Abbreviations: EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; OIT, oral immunotherapy.

and 37.3%, respectively, had ≥1 current IgE-food allergy, 27.8% and 47.8%, respectively, had asthma, 27.5% and 22.9%, respectively, had atopic dermatitis/eczema, and 43.5% and 41.6%, respectively, had seasonal rhinitis.[9]

Overall, these findings have led many researchers to include EoE in the spectrum of disorders making up the atopic march, often representing the final step of this progression.[32] Of note, the association between food allergy and EoE has been found to be the strongest.[32]

Several pathophysiological theories have been put forward to explain the association between EoE with atopic disorders, however a consistent picture is still lacking.[33] A possible role of aeroallergens in terms of EoE diagnosis/exacerbation has been suggested by clinical studies, showing an association between pollen season and incidence of EoE diagnosis.[34] Besides, cases of EoE after sublingual immunotherapy for respiratory allergies have also been observed.[20,35,36] The exact mechanistic interpretation of these findings is still incomplete. A direct effect of pollen allergens, but also of food allergens that are cross-reactive to pollens, could be present.

A common pathophysiologic feature of EoE and food allergy could be the presence of a shared allergen-restricted Th2 specificity. However, despite these similarities, these conditions display peculiar features, as EoE is usually a life-long disease, whereas food allergy is usually transitory, so it is not uncommon to encounter patients with EoE with a history of food allergy. Moreover, the anti-IgE therapy seems to exert a marginal role in EoE.[37,38] These findings imply that the eosinophilic inflammation in EoE is independent of a classical Th2-response and other still unknown factors play a role.

2.2 | Eosinophilic gastritis and gastroenteritis

Gastritis, enteritis, and gastroenteritis are usually considered as a whole nosologic entity given their clinical similarities and paucity of pathogenetic knowledge. They may show concomitant eosinophilic infiltration of other gut regions, such as the esophagus and the large intestine. Clinical manifestations are proteiform, as already shown in Table 1, depending on which layer of the gut wall is mostly affected. Symptoms could be mild and often overlooked, or could be serious and potentially life-threatening, including abdominal pain, diarrhea, and frank malabsorption.[39]

Asthma and other allergic diseases, such as allergic rhinitis, have also been described in patients with eosinophilic gastritis or gastroenteritis, but with less convincing evidence compared to EoE. Nonetheless, the frequency of self-reported allergic rhinitis and asthma is still relevant, as high as 63% and 39%, respectively, in a questionnaire-based registry study assessing the prevalence of atopic conditions in 107 patients, adults and children, with these conditions.[40]

More recently, some case reports have described the association between asthma and eosinophilic gastritis in a few patients with severe asthma, treated with dupilumab or mepolizumab.[41,42] Few data pertaining the association between eosinophilic gastritis with food allergy are available, while the majority of the studies has

TABLE 3 Studies describing the association between eosinophilic gastrointestinal disorders and allergic disorders in children

Author, year, country	Study type	Population	Pathology	Allergy disease	Comments	References
Votto et al., 2021 Italy	Retrospective	Children and adolescents	EGIDs	Asthma Rhinitis Atopic dermatitis Food allergy	Allergic comorbidities in approximately 30% of enrolled patients, more frequently observed in children with EoE (36.5%)	61
Leung et al., 2015 Canada	Prospective. EoE (n = 23), GERD (n = 20), normal superior endoscopy with gastrointestinal symptoms (n = 14) and controls (n = 26)	Children	EoE	Asthma Rhinitis Atopic dermatitis Food allergy	Rhinitis more common in EoE group	62
Fuentes-Aparicio et al., 2013 Spain	Randomized clinical trial. Patients with egg allergy (*n* = 40)	Children	EoE	Food allergy	One patient developed EoE after egg OIT	63
Slae et al., 2013 Canada	Cross-sectional, case-control study. EoE patients (*n* = 102) and controls (*n* = 167)	Children	EoE	Asthma Rhinitis Atopic dermatitis Food allergy	Food allergy, (peanuts and tree nuts) allergy to pollen (tree and grass) significantly higher among EoE than controls	64
Jensen et al., 2013 United States	Case-control. EoE patients (*n* = 31), GERD (*n* = 26), and siblings of non-syndromic cleft lip/palate patients (*n* = 26)	Children	EoE	Asthma Food allergy	The frequency of food allergies, environmental allergies, and asthma higher for cases with EoE than controls	65
Sanchez-Garcia et al., 2012 Spain	Retrospective. Patients with milk allergy (*n* = 110)	Children	EoE	Food allergy	Three patients developed EoE after milk OIT	66
Ridolo et al., 2011 Italy	Case report	Children	EoE	Food allergy	A child with acute EoE after egg OIT	67
Cassel et al., 2009 United States	Retrospective charts review. EoE patients (*n* = 35) and controls (*n* = 7)	Children	EoE	Asthma Atopic dermatitis	Atopy, asthma, and eczema were more common in EoE patient than in GERD	68
Aceves et al., 2009 United States	Prospective, case-control. Patients with EoE (*n* = 35), GERD (*n* = 27), allergic patients without EoE (*n* = 24), and non-allergic patients (*n* = 14)	Children	EoE	Asthma Rhinitis Food allergy	Food allergy more common in patients with EoE while asthma and allergic rhinitis were more common in allergic controls	69

TABLE 3 (Continued)

Author, year, country	Study type	Population	Pathology	Allergy disease	Comments	References
Hofmann et al., 2009 United States	Retrospective. Patients undergoing oral immunotherapy (OIT) (n = 28)	Children	EoE	Food allergy	One patient developed EoE after OIT	70
Sugnaman et al., 2007 Australia	Prospective. EoE patients (n = 45) and controls (n = 33)	Children	EoE	Asthma Rhinitis Atopic dermatitis Anaphylaxis	Atopic eczema, asthma, and rhinitis significantly increased in EoE patients than controls. Incidence of anaphylaxis 24%	71

Abbreviations: EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; OIT, oral immunotherapy.

evaluated mainly sensitization to food allergens alone. Another limitation is represented by the inclusion of cases of concomitant EoE. The presence of food allergy was ascertained in a pediatric US series in one-ninth of patients with isolated eosinophilic gastritis and one-third in those with eosinophilic gastritis with duodenal eosinophilia.[43] in an another US study including 44 patients, children and adults, with eosinophilic gastroenteritis (associated EoE in 30% of the cases) the prevalence of food allergy was 42%. Interestingly, drug allergy was also found in 31% and eczema in 16%.[44]

Overall, the prevalence of atopic disorders in patients with eosinophilic gastritis and gastroenteritis appears to be high, being estimated at 38.5% and 45.6%, respectively.[10]

2.3 | Eosinophilic colitis

Primary eosinophilic colitis is the least frequent disorder among EGID. The absence of internationally agreed diagnostic criteria, including a clear eosinophilic infiltrate threshold, has hampered its identification for a long time. Eosinophilic colitis frequently presents with diarrhea, abdominal pain, anorexia, and weight loss. It has a bimodal age presentation, namely in infancy (at approximately 60 days of age) and during adolescence and early adulthood.[45] Also, it has been associated with a wide range of atopic disorders, including drug allergy, allergic rhinitis, asthma, and food allergy.[46,47]

In a US administrative database study, Jensen et al. evaluated 404 adult patients with eosinophilic colitis, finding that co-existing allergic conditions were common, being present in 41.8% of the patients.[10] The most commonly reported allergic condition was allergic rhinitis (30%). Asthma was reported in 15% and atopic dermatitis in 6.2% of the patients. In a smaller series of adult patients (n = 22), a lower incidence of both asthma and allergic rhinitis (18%) was reported.[47]

The prevalence of atopic conditions seems to be high also in children, according to the only case series available, which includes almost 50 individuals, and reports that 40% displayed one or more signs of atopy.[48] The same estimate of comorbid atopic conditions has been calculated by Dellon et al. in the aforementioned register-based study.[10]

3 | OUTLOOK

Allergic manifestations are a frequent comorbidity in patients with immune-mediated disorders of the gastrointestinal tract, including classical autoimmune diseases and EGID.[49] The current evidence of the association between EGID and allergic disorders, as discussed above, is summarized in Tables 2–4, for adults, children, and both, respectively.

Allergens can lead to disease exacerbation and allergen elimination results in disease control in a significant proportion of patients. Besides, the control of atopic conditions is important to control EoE.[77] Patients living with EGID should be carefully

TABLE 4 Studies describing the association between eosinophilic gastrointestinal disorders and allergic disorders in both adults and children

Author, year, country	Study type	Population	Pathology	Allergy disease	Comments	References
Duffey et al., 2016 United States	Retrospective, administrative data. EoE and their relatives (n = 4.009) and controls (n > 100.000)	Children and adults	EoE	Asthma	Significant familial clustering of asthma and atopic disease (anaphylaxis, atopic dermatitis, allergic rhinitis, and conjunctivitis) in distant relatives of EoE proband	72
Peterson et al., 2015 United States	Retrospective, case-control. EoE (n = 4423) and controls (first- and second-degree relatives, first cousin and spouses of patients) (n = 22.627)	Children and adults	EoE	Asthma Rhinitis Atopic dermatitis Food allergy Anaphylaxes	Atopy diseases including anaphylaxes more common in EoE patients and relatives	73
Mansoor et al., 2016 United States	Administrative data. EoE patients (n = 7840), whole population controls (n = 30,301,440)	Children and adults	EoE	Asthma Rhinitis Atopic dermatitis Food allergy Drug allergy	Allergic diseases (drug allergy, food allergy, rhinitis, IgE mediated disorder, asthma, sinusitis, dermatitis, eczema, and urticaria) more common in EoE patients	74
Mulder et al., 2013 Canada	Retrospective, case-control. EoE patients (n = 44) and controls (n = 44)	Children and adults	EoE	Asthma Rhinitis Atopic dermatitis Food allergy Drug allergy	Atopy more common in EoE patients than controls	81
Zafra et al., 2013 Spain	Prospective, case-control. EoE (n = 25) and controls (n = 17)	Children and adults	EoE	Rhinitis Food allergy	EoE patients more likely to have sensibilization to aeroallergens, rhino conjunctivitis, and food allergy	75
Dellon et al., 2009 United States	Retrospective case-control. EoE patients (n = 151), GERD (n = 226)	Children and adults	EoE	Asthma Rhinitis Atopic dermatitis Food allergy	Atopy (allergic rhinitis/dermatitis, food allergy, and asthma) was more common in EoE patients and food allergy was considered a reliably predictor factor to discriminate EoE from GERD	76

Abbreviations: EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease.

TABLE 5 The currently ongoing clinical trials for the treatment of primary eosinophilic gastrointestinal disorders

Agent	Route of administration	Mechanism of action	Condition	Clinical trial number	Phase
Antihistamines (loratadine and famotidine)	Oral	Histamine-1 (H1) and Histamine-2 (H2) receptor antagonists	EoE	NCT04248712	2
Febuxostat	Oral	Non-purine-selective inhibitor of xanthine oxidase	EoE	NCT02873468	2
Omeprazole	Oral	PPI	EoE	NCT04149470	4
Fluticasone and omeprazole versus fluticasone alone	Oral	Anti-inflammatory PPI	EoE	NCT03781596	4
Budesonide	Oral	Anti-inflammatory	EoE	NCT03245840	3
Fluticasone propionate	Oral	Anti-inflammatory	EoE	NCT04281108	3
Mometasone furoate	Oral	Anti-inflammatory	EoE	NCT04849390	2
Mepolizumab	s.c.	Anti-IL5 mAb	EoE	NCT03656380	2
Benralizumab	s.c.	Anti-IL5Rα mAb	EoG EoGE	NCT03473977	2–3
Benralizumab	s.c.	Anti-IL5Rα mAb	EoE	NCT04543409	3
Dupilumab	s.c.	Anti-IL4/13 mAb	EoG EoGE	NCT03678545	2
Dupilumab	s.c.	Anti-IL4/13 mAb	EoE	NCT03633617	3
Dupilumab	s.c.	Anti-IL4/13 mAb	EoE	NCT04394351	3
Cendakimab	s.c.	Anti-IL3 mAb	EoE	NCT04753697	3
CALY-002	i.v.	Anti-IL15 mAb	EoE Celiac disease	NCT04593251	1
Lirentelimab	i.v.	Anti-Siglec-8 mAb	EoE	NCT04322708	2–3
Lirentelimab	i.v.	Anti-Siglec-8 mAb	EoG EoGE EoD	NCT04322604	3
Lirentelimab	i.v.	Anti-Siglec-8 mAb	EoG EoGE EoD	NCT03664960	2
Lirentelimab	i.v	Anti-Siglec-8 mAb	EoG EoGE EoD	NCT04620811	3
Lirentelimab	i.v.	Anti-Siglec-8 mAb	EoGE EoD	NCT04856891	3
Etrasimod	Oral	Sphingosine 1-phosphate (S1P) receptor	EoE	NCT04682639	2
Benzimidazolylpicolinoyl	Oral	Active lanthionine synthetase C-like 2 (LANCL2)	EoE	NCT04835168	1

Abbreviations: EoD, eosinophilic duodenitis; EoE, eosinophilic esophagitis; EoG, eosinophilic gastritis; EoGE, eosinophilic gastroenteritis; mAb, monoclonal antibody; PPI, proton pump inhibitor.

evaluated from a multidisciplinary team, made up by an allergist, a pediatrician, and a gastroenterologist, considering all aspects of Th2 inflammation. Treatment modalities should possibly be tailored to tackle shared molecular pathways.

Notably, a number of clinical trials regarding treatment modalities for EGID are currently ongoing (Table 5). Apart from a few unspecific, non-biologic, molecules, most of the drugs under investigations are monoclonal antibodies, all of them targeting different pathogenic

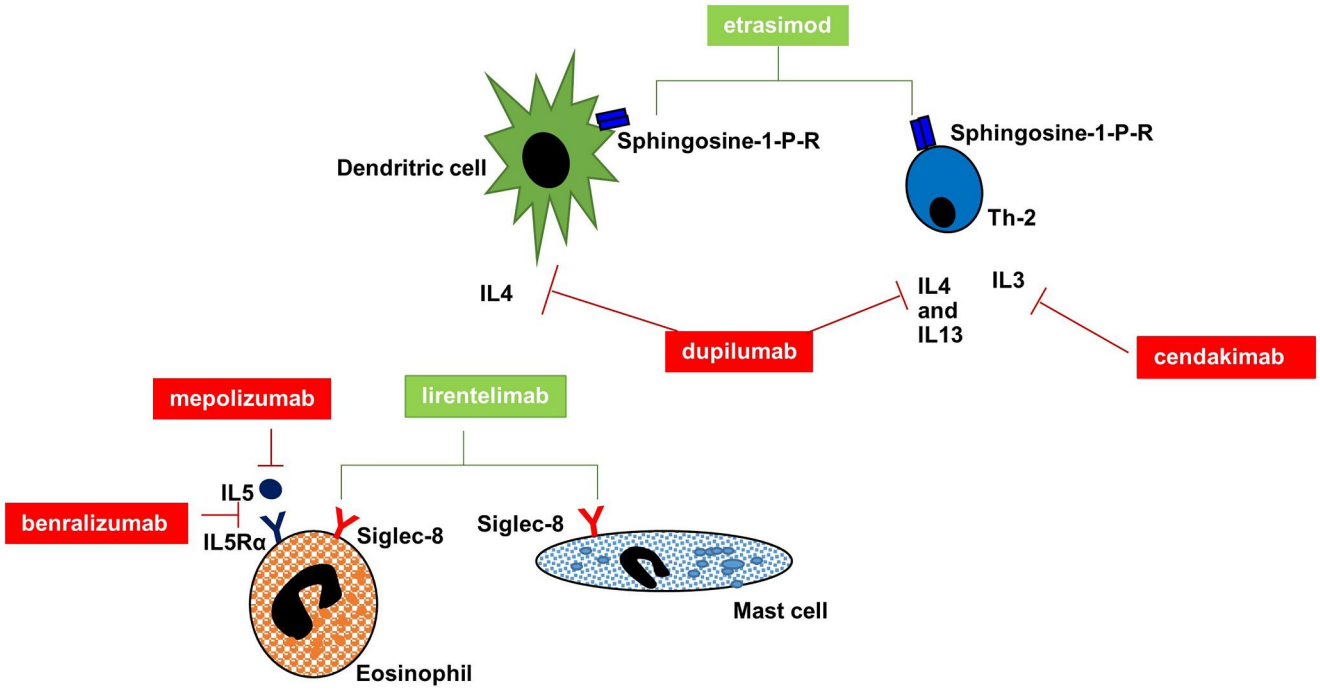

FIGURE 1 Main molecular targets of monoclonal antibodies in primary eosinophilic gastrointestinal disorders (EGID). Monoclonal antibodies (mAbs) available in clinical practice for other Th2 disorders and under evaluation in clinical trials in EGID are shown along with the main cellular effectors of Th2 response (i.e., dendritic cells, mast cells, Th2 cells, and eosinophils). The red lines denote an inhibitory action, such as for mAbs against interleukin (IL)5 (mepolizumab) or IL5 receptor (benzalizumab), IL4/IL13 (dupilumab), and IL3 (cendakimab), whereas the green lines denote a modulatory effect, such as for etrasimob on sphingosine 1-P receptor and lirentelimab on Siglec-8

TABLE 6 Key messages

1. A multidisciplinary approach for the diagnosis and treatment of EGID is warranted to tackle all the diverse organ manifestations of Th2 inflammation (i.e., skin, nose, and lungs, gastrointestinal tract).
2. The identification of the causal allergen(s) improves disease control.
3. Pathogenesis-targeted therapies aimed at controlling the whole burden of allergic comorbidities within the same patient should be considered.
4. Non-invasive diagnostic biomarkers to enable early diagnosis are needed.

pathways that, in some cases, are shared with allergic diseases. For example, dupilumab, an anti-interleukin 4 (IL4) receptor alpha monoclonal antibody, has already been approved for the treatment of atopic dermatitis and allergic asthma, while mepolizumab, an anti-IL5 monoclonal antibody, has already been approved for allergic asthma.[78,79] Moreover, lirentelimab, a monoclonal antibody targeting an inhibitory receptor Siglec-8, could represent an interesting therapeutical agent targeting both the allergic disorders and EGID, since this receptor is present only on mastcells, basophils, and eosinophils, all key players in both disease groups.[18,80,81] The main molecular targets of monoclonal antibodies are shown in Figure 1.

We do feel that EGID and allergic disorders should be better managed by a multidisciplinary team, given their complex nature, which is not only confined to their possible shared pathophysiological bases, but also includes (i) the high clinical burden, due to their potentially long diagnostic delay and poor quality of life, (ii) the difficult diagnostic work-up, and (iii) the need for specific expertise and competences for their diagnosis. The future clinical research agenda should focus on the identification of non-invasive biomarkers for their diagnosis and their early recognition. The main key messages mentioned in the outlook are summarized in Table 6.[82]

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CONFLICT OF INTEREST

None to disclose for all authors.

AUTHOR CONTRIBUTIONS

All authors significantly participated in the drafting of the manuscript or critical revision of the manuscript for important intellectual content and provided approval of the final submitted version.

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REVIEW ARTICLE

WILEY

Eosinophilic gastrointestinal disorders and allergen immunotherapy: Lights and shadows

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Abstract

Allergic diseases, such as IgE-mediated food allergy, asthma, and allergic rhinitis, are relevant health problems worldwide and show an increasing prevalence. Therapies for food allergies are food avoidance and the prompt administration of intramuscular epinephrine in anaphylaxis occurring after accidental exposure. However, allergen immunotherapy (AIT) is being investigated as a new potential tool for treating severe food allergies. Effective oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT) induce desensitization and restore immune tolerance to the causal allergen. While immediate side effects are well known, the long-term effects of food AIT are still underestimated. In this regard, eosinophilic gastrointestinal disorders (EGIDs), mainly eosinophilic esophagitis, have been reported as putative complications of OIT for food allergy and sublingual immunotherapy (SLIT) for allergic asthma and rhinitis. Fortunately, these complications are usually reversible and the patient recovers after AIT discontinuation. This review summarizes current knowledge on the possible causative link between eosinophilic gastrointestinal disorders and AIT, highlighting recent evidence and controversies.

KEYWORDS

allergen immunotherapy (AIT), eosinophilic esophagitis (EoE), eosinophilic gastrointestinal disorders (EGIDs), food allergy (FA), oral immunotherapy (OIT), sublingual immunotherapy (SLIT)

1 | INTRODUCTION

Eosinophilic esophagitis (EoE), the most studied eosinophilic gastrointestinal disorder (EGID), is a chronic antigen-mediated disease which affects people of any age.[1] The eosinophilic inflammation leads to a progressive esophageal dysfunction, characterized by feeding and swallowing issues and recurrent vomiting in children. In contrast, dysphagia and food bolus impaction prevail in adolescent and adult patients.[1] The diagnosis of EoE requires (i) chronic symptoms, (ii) suggestive endoscopic findings, such as esophageal rings, furrows, edema, stricture, narrowing, and crepe-paper mucosa, (iii) more than 15 eosinophils/high-power field (HPF) in esophageal biopsy specimens, and (iv) the exclusion of other causes of esophageal eosinophilia.[2,3] The overall prevalence of EoE has considerably

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increased in the last few decades and is currently estimated to be 0.5-1/1000 subjects.[4,5] However, EoE is detected in 2.4%-6.6% of patients undergoing endoscopy for any gastrointestinal (GI) indication, and in about 50%, of patients showing food bolus impaction.[5] EoE is a multifactorial disorder which results from the combination of genetic predisposition, epithelial barrier dysfunction, environmental risk factors, and allergen sensitization. All these factors lead to the type 2 inflammation of the esophagus.[6] Non-esophageal EGIDs are uncommon inflammatory diseases caused by allergic and possibly autoimmune inflammation, which affects the GI tract distally to the esophagus. The diagnostic work-up of these conditions requires ruling out other causes of intestinal eosinophilia.[7,8] Based on the GI tract involved, non-esophageal EGIDs can be distinguished in eosinophilic gastritis (EoG), gastroenteritis (EoGE), and colitis (EoC). Unlikely EoE, non-esophageal EGIDs currently represent a clinical enigma for clinicians, and standardized guidelines for their diagnosis and treatment are still lacking.[8]

IgE-mediated food allergy is a global health issue, affecting from 2% to 8% of the US population and increasing in prevalence.[9] The classical therapeutical approaches for food allergy include allergen avoidance and the prompt administration of intramuscular epinephrine in case of anaphylaxis. However, food avoidance significantly impacts the allergic patients' quality of life, mainly due to the fear of experiencing severe symptoms; moreover, life-threatening accidental exposure to the causal allergen limits its efficacy. In this context, oral allergen immunotherapy (AIT), such as the administration *per os* of the culprit allergen (oral immunotherapy), is being investigated as a new potential tool for treating severe food allergies. In January 2020, the oral immunotherapy (OIT) treatment for peanut allergy received approval from the US Food and Drug Administration (FDA). Although the desensitization schedules vary according to the individual Centers' clinical experience, the OIT is generally based on an initial rapid dose escalation phase followed by a buildup phase lasting several weeks or months in order to reach the maintenance dose.[10-12] The aim of the OIT is the achievement of a temporary state (immune tolerance) in which the patient can safely assume a specific amount of the culprit food allergen without life-threatening reactions (desensitization).[10-12] To maintain the desensitization state, patients should continue consuming the tolerated final dose of the food allergen regularly. Mild-moderate side effects typically occur during the administration and escalation of the initial doses and usually require no treatment or antihistamine.[10-12] The medium- and long-term complications of OIT are still unknown and little studied. However, food OIT has been suggested as one of the possible risk factors of EGIDs, mostly EoE; namely, 2.7% of patients who have received OIT for food allergy developed esophageal inflammation.[6,13]

Both subcutaneous AIT (SCIT) and sublingual (SLIT) have emerged as an effective and safe alternative treatment in patients with allergic rhinitis and well-controlled asthma and have been shown to modify the underlying cause of these diseases with long-term benefits.[14] To date, the connection between SLIT for allergic rhinitis and asthma and the subsequent development of EGIDs was described in a few case reports.[15,16]

Key Message

Allergen immunotherapy has proven to be an effective treatment for IgE-mediated diseases, including food allergy, allergic rhinitis, and asthma. Eosinophilic gastrointestinal disorders are rare disorders that might complicate oral and—in anecdotal cases—sublingual immunotherapy protocols. However, significant esophageal eosinophilia has been reported in allergic patients prior to the beginning of oral immunotherapy. According to the current state of knowledge, clinicians should always consider the risk of EGIDs in patients treated with allergen immunotherapy and promptly perform diagnostic tests, in order to rule out these conditions.

A scoping review of articles was performed via the online database PubMed, combining the terms "allergen immunotherapy" AND "eosinophilic gastrointestinal disorders" OR "allergen immunotherapy" AND "eosinophilic esophagitis." The review of literature was performed in October 2020, including the publication years 1990-2020. All studies that met the following criteria were included:

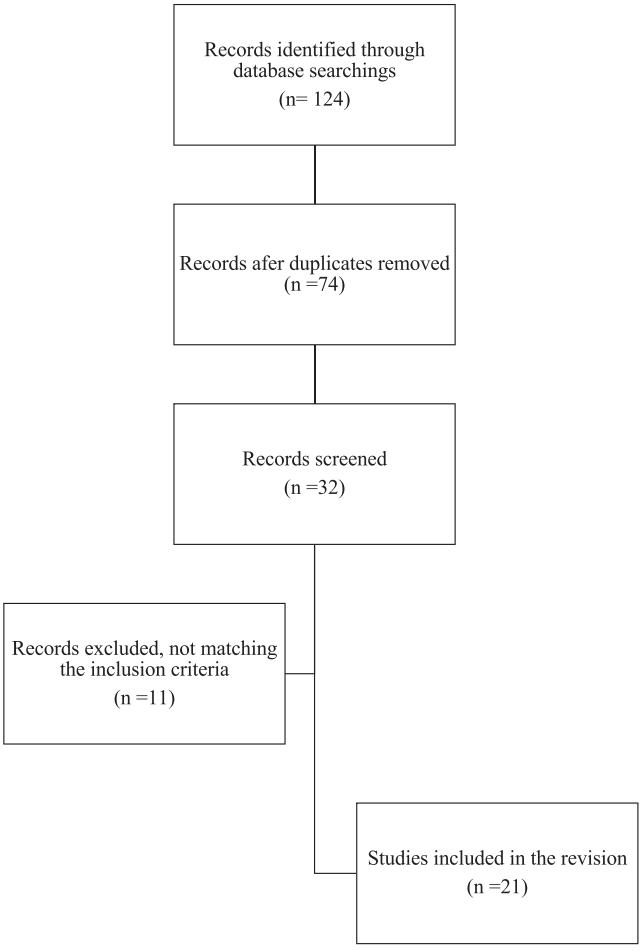

FIGURE 1 Inclusion criteria and search strategy

TABLE 1 Articles reporting clinical cases of EGID development during oral immunotherapy for IgE-mediated food allergy

Author and year	Country	Sample size	Patients with EGIDs	Age (years)	Sex	Allergen	Way to administer AIT	Duration of OIT treatment
Afinogenova et al, 2020[27]	USA	783	9	n.a.	n.a.	Peanut	OIT	n.a.
García-Rodríguez et al, 2020[26]	Spain	90	3	n.a.	n.a.	Egg	OIT	2.5-4.5 y
Yee et al, 2019[78]	USA	13	1	8	M	Peanut	OIT	50 mo
Bushyhead et al, 2019[79]	USA	1	1	34	F	Peanut	OIT	3 mo
Gómez Torrijos et al, 2017[25]	Spain	57	3	n.a.	n.a.	Milk	OIT	3 y
García Rodríguez et al, 2017[80]	Spain	1	1	55	F	Egg	OIT	3 y
Babaie et al, 2017[24]	Iran	18	1	3	F	Milk	OIT	n.a.
Burk et al, 2017[69]	USA	13	2	17-18	F and M	Peanut	OIT	8 mo and 1.5 y
Echeverría-Zudaire et al, 2016[23]	Spain	128	8	3-14	M > F	Milk and Egg	OIT	15-48 mo
Semancik and Sayej, 2016[22]	USA	3	3	6-11	M	Peanut	OIT	2 wk
Morais Silva et al, 2014[21]	Portugal	1	1	3 y and 9 mo	F	Milk	OIT	6 wk
Fuentes-Aparicio et al, 2013[20]	Spain	40	1	7	n.a.	Egg	OIT	6 wk
Sanchez-Garcıa et al, 2012[19]	Spain	110	3	3-14	M	Milk	OIT	29-39 wk
Ridolo et al, 2011[18]	Italy	1	1	11	M	Egg	OIT	5 mo
Hofmann et al, 2009[17]	USA	28	1	n.a.	n.a.	Peanut	OIT	n.a.

Note: EoGE, Eosinophilic Gastroenteritis; EoE, Eosinophilic Esophagitis; OIT, Oral Immunotherapy; PPI, Proton Pump Inhibitor.
*All EGID diagnoses were performed with upper and lower endoscopy with biopsy.

(i) case reports, clinical trials, cross-sectional and cohort studies published in English in peer-reviewed journals, and (ii) participants were children and adult patients with a diagnosis of EGIDs histologically confirmed. Potentially eligible publications were manually screened and reviewed, and nonrelevant publications were excluded (Figure 1).

2 | ORAL IMMUNOTHERAPY AND EGIDS: THE CHICKEN OR EGG: WHICH CAME FIRST?

The first case of EoE during OIT for peanut allergy was reported by Hofmann et al in 2009 (Table 1).[17] Among 28 children enrolled in the US study, one patient developed EoE and achieved disease remission after discontinuing peanut OIT.[17] Two years later, Ridolo et al described the first Italian case of an 11-year-old boy who developed dysphagia for solid foods and dyspepsia 5 months after completing the OIT protocol and recovered after an egg-free diet and oral steroid therapy.[18] A large retrospective study of 110 Spanish children undergoing milk OIT reported three cases of EoE that recovered after a complete milk-free diet combined with proton pump inhibitors (PPI) and swallowed corticosteroids.[19] A randomized clinical trial comparing the efficacy of the OIT and elimination diet for egg allergy showed that in the OIT group, one developed EoE and stopped the immunotherapy.[20] The first Portuguese case report concerned a 3-year-old girl who developed EoE during milk OIT and recovered after the OIT discontinuation and administration of

Symptoms	Diagnosis of EGIDs*	Intervention	Outcome
n.a.	EoE	n.a.	n.a.
n.a.	EoE	Egg-free diet	Egg was not the culprit food. Patients achieved remission with milk-free diet and swallowed corticosteroids
Vomiting and dysphagia	EoE	OIT discontinuation	Initial disease remission.
Dysphagia to solids	EoE	OIT was stopped, and patient started viscous budesonide	Disease remission
Dysphagia to solids and chest pain	EoE	OIT discontinuation and milk-free diet	Disease remission
Dysphagia and heartburn upon eating any food	EoE	OIT discontinuation and PPI	Disease remission
Recurrent abdominal pain.	EoE	OIT discontinuation	n.a.
Dysphagia and heartburn. One patient had weight loss	EoE	OIT discontinuation	Disease remission. After a period of disease remission, one patient experienced EoE relapse and started swallowed corticosteroids
Abdominal pain, vomiting and dysphagia. The two patients with EoGE experienced more intense symptoms, with diarrhea	EoE was diagnosed in 6 patients; 2 had EoGE	In 3 patients, OIT was discontinued. The other 5 patients were treated with PPIs and swallowed steroids without OIT discontinuation	Histological remission in 7 patients
Emesis and dysphagia	EoE	OIT discontinuation and PPI therapy.	Disease remission.
Emesis	EoE	Topical swallowed fluticasone and a milk-free diet.	Disease remission.
Abdominal pain, vomiting	EoE	OIT discontinuation.	n.a.
Retrosternal pain and dysphagia	EoE	PPI, oral fluticasone, and OIT discontinuation.	Disease remission
Dysphagia for solid food and dyspepsia	EoE	Egg-free diet and 3 mo of oral steroid therapy	Disease remission
n.a.	EoE	OIT discontinuation	Disease remission

swallowed corticosteroids.[21] Semancik and Sayej described three pediatric cases of EoE during peanut OIT.[22] Those children presented gastrointestinal symptoms a few weeks after the beginning of the peanut OIT, with clinical improvement after OIT discontinuation.[22] A prospective Spanish study of 128 children undergoing milk and egg OIT reported eight cases of EGID.[23] Six patients with EoE developed vomiting and dysphagia, and two children with EoGE presented severe gastrointestinal symptoms and diarrhea.[23] A cohort study of 18 children undergoing OIT for milk allergy reported the first Iranian case of EoE in a 3-year-old girl.[24] In a case series of 57 Spanish children undergoing milk OIT, EoE was diagnosed in 3 patients, who achieved remission after OIT discontinuation.[25] A recent prospective study of 90 children who underwent egg OIT reported EoE in three patients.[26] OIT discontinuation was not effective, and patients were successfully treated with a milk-free diet and swallowed corticosteroids.[26] Finally, in a large retrospective US study of 783 patients aged 3.5 to 48.3 years who were treated with peanut OIT, only nine patients developed EoE during the buildup and maintenance phase.[27]

EoE is a disease characterized by symptoms related to esophageal dysfunction and eosinophilic inflammation.[28] Although esophageal symptoms are required for the diagnosis of EoE, they may not accurately reflect endoscopic and/or histologic findings, and possible inconsistency between clinical and pathological findings has been observed.[29] During the desensitization schedule, immediate and delayed GI symptoms are commonly reported, while the diagnosis of EoE, endoscopically confirmed, only occurs in 5.3% of OIT patients.[16] GI symptoms associated with peripheral eosinophilia were described

TABLE 2 Articles reporting clinical cases of EoE development during sublingual immunotherapy for allergic rhinitis and asthma

Author and year	Country	Sample size	Patients with EGIDs	Age (years)	Sex	Allergen	Way to administer AIT
Kawashima et al, 2018[57]	Japan	1	1	53	F	Japanese cedar pollen	SLIT
Wells et al, 2018[50]	UK	1	1	10	M	Grass pollen	SLIT and after SCIT
Rokosz et al, 2017[56]	USA	1	1	9	M	Grass pollen and Dust mite	SLIT
Béné et al, 2016[49]	France	1	1	10	F	Dust mites	SLIT
Antico and Fante, 2014[48]	Italy	1	1	23	F	Dust mites and Grass pollen	SLIT
Miehlke et al, 2013[47]	Germany	1	1	44	F	Hazelnut, Birch, Alder	SLIT

Note: EoE, Eosinophilic Esophagitis; PPI, Proton Pump Inhibitor; SCIT, Subcutaneous Immunotherapy; SLIT, Sublingual Immunotherapy.
*All EGID diagnoses were performed with upper and lower endoscopy with biopsy.

as adverse responses to OIT for different foods in 8% up to 14% of children and have been defined as OIT-induced gastrointestinal and eosinophilic responses (OITIGER). In addition to the most known immediate IgE-mediated reactions, recurrent non-IgE-mediated GI symptoms, mostly vomiting, during the OIT individualized regimen have been reported 2-6 hours after the oral dose administration.[30-32] OITIGER symptoms appear in the first 2-3 months of OIT treatment and are reversible or transient in most children, modifying the protocol with an individualized and slower dosing regimen.[31] Although OITIGER patients may develop EoE, most of them can continue the desensitization protocol with complete remission of the GI symptoms without requiring further endoscopies. Patients and their parents were generally reluctant to perform GI endoscopies, because the reduction or discontinuation of dosing improves the symptoms, and children do not show dysphagia or food impaction. Evaluation at baseline, during symptom flares, and in the remission phase should be performed to fully characterize this clinical entity and its possible pathogenetic relationship with EoE.

Although EoE is a possible long-term complication in about 3% of patients undergoing OIT for food allergies,[13] a preexisting esophageal eosinophilia was recently found before the beginning of the desensitization in adults with IgE-mediated peanut allergy.[33] Moreover, a recent randomized placebo-controlled trial (clinicaltrials.gov no: NCT02103270) reported esophageal eosinophilia in most patients who underwent peanut OIT at week 52, that resolved at the end of the maintaining phase.[34]

Despite different etiological mechanisms, IgE-mediated food allergy and eosinophilic GI disorders are strongly related.[35] Patients with IgE-mediated food allergy have a significantly increased risk (118 times) of developing EoE subsequently in their life, as a late manifestation of the atopic march.[36,37] On the contrary, it has been proposed that after a period of a food elimination diet, patients with EoE might develop IgE-mediated hypersensitivity when the food is reintroduced.[38] Interestingly, a common pathogenic mechanism between EoE and food allergy is the intestinal epithelial barrier disruption.[39] Eosinophils are multifunctional cells that generally colonize the GI tracts, with the exception of the esophagus.[40] Also, intestinal eosinophils are involved in pivotal homeostatic functions and play essential regulatory roles in epithelial barrier maintenance through mucus and IgA production, tissue repair, and remodeling.[41-43] In addition to EGIDs, several chronic diseases can be characterized by increased GI eosinophils, such as inflammatory bowel disease, celiac disease, malignancy, vasculitis, and connective tissue disorders.[8] It is still unclear if esophageal or intestinal eosinophilia might eventually progress to EoE or non-esophageal EGIDs without OIT or whether or not the chronic exposure to the food allergen might increase the preexisting eosinophilic inflammation.

The immunological effects of OIT are complex and concern changes in cytokine responses (switch on the IL-10 pathway), reduced levels of allergen-specific IgE, increased levels of allergen-specific IgG4 and regulatory T cells, and the downregulation of the type 2 inflammation.[24] The increase of food-specific IgG4 and its subsequent deposition in the esophagus was the most studied mechanism of EoE pathophysiology during OIT.[44] The immune complexes are produced when the patient is exposed to high amounts of relevant antigens, as is likely the case in EoE because of local barrier dysfunction.[44] Whether or not these immune complexes further bind food allergens or other antigens or decrease inducing disease remission is currently unknown. Moreover, IL-10, released by tissue eosinophils, might play a central role in driving

Reason to administer AIT	Duration of treatment	Symptoms	Diagnosis of EGIDs*	Intervention	Outcome
Severe allergic rhinitis	13 d	Severe dysphagia and frequent vomiting	EoE	SLIT discontinuation; PPI (20 mg/die)	Histological remission after 8 wk
Allergic rhinitis and well-controlled asthma	1 wk	GERD-like symptoms	EoE was diagnosed histologically at age 8	SLIT and SCIT discontinuation. Oral steroid therapy and elemental formula	Clinical improvement
Perennial allergic rhinoconjunctivitis	17 mo	Complete feeding refusal	EoE	SLIT discontinuation	Histological remission
Asthma, allergic rhinitis	6 wk	Reflux vomiting, retrosternal chest discomfort and weight loss	EoE	SLIT discontinuation; PPI	Histological remission after 12 wk
Allergic rhinoconjunctivitis and asthma	4 wk	Retrosternal constriction, retrosternal pain and dysphagia	EoE	SLIT discontinuation	Histological remission
Asthma	4 wk	Dysphagia	EoE	SLIT discontinuation	Histological remission after 4 wk

IgG4 class-switch.[44] In the setting of chronic antigen stimulation situations, such as those occurring in allergic epithelial barrier diseases and conditions characterized by impaired gastrointestinal mucosa, levels of IL-10 and IgG4 tend to be high.[44] Otherwise, IgG4 could represent an epiphenomenon linked to the immune response that leads to the esophageal inflammation.[44] Therefore, the pathogenetic role of IgG4 in EoE is still controversial and requires further research.

No studies have assessed the rate of non-esophageal EGIDs in children and adults undergoing the OIT for food allergy. To date, only anecdotal case reports have been described. The pathogenesis of non-esophageal EGIDs is still unknown. However, non-esophageal EGIDs can be considered a type 2 inflammatory disease, driven by allergen exposure that leads to the pathological eosinophilic intestinal inflammation.[8,45] Indeed, empirical elimination and elemental diets effectively improve GI symptoms and intestinal inflammation, suggesting that exposure to food allergens might be the possible trigger in most affected patients.[8,45] A significant group of patients with non-esophageal EGIDs shows a history of concomitant allergic diseases, including IgE-mediated food allergy.[46] In this context, the initial treatment of non-esophageal EGIDs is usually the dietary approach, but oral corticosteroids have been reported as a second therapeutic choice.[8,45]

3 | THE CONTROVERSIAL RELATIONSHIP BETWEEN AEROALLERGENS AND EGIDS

The first report of EGIDs following SLIT was described in 2013 by Miehlke et al[47] A 44-year-old woman with asthma and allergic rhinitis developed EoE during SLIT for birch, hazelnut, and alder allergies (Table 2).[47] Clinical manifestations and histological findings resolved 4 weeks after the discontinuation of SLIT.[47] In another similar report, Antico and Fante described a 23-year-old female who developed heartburn, retrosternal pain, and dysphagia 4 weeks after the initiation of SLIT for dust mite and grass allergies.[48] The esophageal biopsy confirmed the diagnosis of EoE, and symptoms resolved after the cessation of SLIT.[48] A 10-year-old girl with asthma and allergic rhinitis developed severe GI symptoms (vomiting and retrosternal chest discomfort) and weight loss 6 weeks after the beginning of SLIT for dust mites allergy.[49] Upper endoscopy and histological findings were suggestive of EoE.[49] After discontinuation of the SLIT, the patient achieved a complete resolution of symptoms and esophageal inflammation.[49] More recently, Wells et al described a case of a 10-year-old boy with a previous diagnosis of EoE, who developed a new disease flare after only 1 week of grass pollen SLIT for allergic rhinitis and well-controlled asthma.[50]

The real incidence rate of EoE following SLIT is still underestimated.[51] However, in the US, contraindications for SLIT also include a history of EoE. SLIT may induce EoE with the same pathogenetic mechanism of OIT that is related to the chronic antigenic exposure in patients with a robust allergic susceptibility. While attenuating the IgE-mediated immune reactions, the progressive entrance of the culprit allergen might induce a chronic stimulation of the immune system with the consequent activation of tissue eosinophils and Foxp3-expressing T cells, and the release of cytokines, such as IL-10 and IL-5.[24,47,49,52,53] Although most EoE patients achieve disease remission with a food elimination diet, the lack of an adequate diet response in a significant number of subjects may suggest that aeroallergens other than food antigens can play a pathogenic

role.[54,55] Aeroallergens can trigger and exacerbate EoE; in fact, the SLIT discontinuation improves esophageal inflammation.[47-50,56-59] Several single-center studies have evaluated the seasonality and the potential role of aeroallergens in EoE development and reactivation.[60-62] Cohort studies reported that children and adolescents with EoE might develop exacerbations in esophageal inflammation during the pollen season depending on the specific aeroallergens to which they are sensitized.[63,64] However, patients' follow-up data are not available, rendering the real cause-effect mechanism inconsistent. Furthermore, the association between EoE relapse and season is still controversial, and available results were contradictory.[6,60,65-69]

Moreover, the latency between the inflammatory effects of ingested allergens and the appearance of GI symptoms can be exceptionally variable. Whether SLIT is the real trigger of EoE or whether asymptomatic eosinophilic inflammation is already present before the desensitization protocol is still unknown. Also, no clinical trials have currently assessed a latent esophageal inflammation in patients before the beginning of SLIT for allergic rhinitis and well-controlled asthma.

4 | EPIT A NEW POTENTIAL TOOL TO TREAT EoE

The cornerstone of pediatric EoE therapy is the off-label use of oral topical steroids and the elimination of the culprit antigen(s) from the diet. Swallowed steroids are generally effective in inducing EoE remission in 53%-95% of patients.[1] However, patients may develop new EoE flares when the therapy is suspended. No data on the long-term safety of swallowed steroids are currently available. Potential growth retardation, bone demineralization, and adrenal suppression have been reported as potential side effects of swallowed steroid treatment.[1] Food elimination diets are equally effective and are generally based on avoidance of the most common food allergens (milk, wheat, soy, egg, fish and shellfish, nuts) or the prescription of an exclusive elemental formula. The compliance to the elemental diet is significantly impaired by taste, restricted meal variety, and lack of insurance coverage.[70] Furthermore, restrictive diets may compromise the patients' growth and nutritional status, lead to nutritional deficiencies, and decrease patients' quality of life.[70]

Epicutaneous immunotherapy (EPIT) is an experimental immunotherapy based on a low dose of allergen exposure through the skin to induce desensitization and reduce cell activation in response to food antigens. In animal models of EGIDs, the EPIT treatment for peanut allergy effectively prevented intestinal inflammation due to chronic exposure to peanuts.[71,72] The EPIT protocol has been successfully used to desensitize children with cow's milk and peanut IgE-mediated food allergies.[73] Recently, EPIT was proposed as a new treatment of EoE, showing exciting and encouraging results in children.[74] In a phase 2 double-blind controlled trial, Spergel et al reported that EPIT for milk allergy was safe and reduced esophageal inflammation (<15 eos/HPF) in 47% of EoE enrolled children.[74] The same research group recently reported that children could tolerate milk without developing GI symptoms 2 years after the discontinuation of the EPIT protocol.[75] These data suggest that EPIT may also be safe and effective in treating non-IgE-mediated food diseases, and its immunological effects may be sustained and persistent.

5 | CONCLUSION

The prevalence of IgE-mediated allergic diseases is increasing worldwide. These conditions significantly impact the patients' and their caregivers' quality of life. To date, AIT is the only treatment that could modify the natural history of allergic diseases, favoring the transition from the immediate IgE-mediated disease mechanism to immune tolerance. Current evidence suggests that EoE could be a complication of OIT or SLIT for food and respiratory allergies, respectively. Non-esophageal EGIDs are currently reported as an infrequent side effect of OIT. However, available data are insufficient to demonstrate AIT's causative role in the development of EGIDs.

The specific phase (dose escalation or maintenance therapy) of OIT or SLIT in which patients become at the highest risk for EGIDs development needs to be defined. It is still unknown whether EoE has been previously developed or is a consequence of the prolonged allergen exposure during the maintenance phase or if it eventually resolves.[15] Providers should be aware of the risk of developing EGIDs, mostly during OIT. When recurrent gastrointestinal symptoms are observed during food AIT or SLIT, the diagnosis of EGIDs should be promptly considered, and patients should undergo GI endoscopy or less invasive diagnostic tools, such as the esophageal string test.[76,77] Fortunately, these complications seem to be reversible by early diagnosis and cessation of OIT and SLIT. However, a strict and prolonged follow-up of the patients undergoing OIT is recommended to detect possible long-term adverse events.

Three possible hypotheses could explain the occurrence of EGIDs during OIT and should be investigated: (i) The subclinical eosinophilic inflammation might exist before the desensitization procedure, (ii) EGIDs might develop regardless of OIT, and (iii) OIT might induce EGIDs.[31] Further studies are required in order to assess the natural history and the specific management options of EGIDs in patients who previously underwent AIT.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTION

Martina Votto: Validation (equal); Writing-original draft (equal). **Maria De Filippo:** Investigation (equal); Writing-original draft (equal). **lucia Caminiti:** Methodology (equal); Supervision (equal). **Carella Francesco:** Validation (equal); Visualization (equal). **Giovanna De Castro:** Data curation (equal); Supervision (equal). **Massimo Landi:** Supervision (equal); Visualization (equal). **Roberta Olcese:** Formal analysis (equal); Supervision (equal). **Vernich Mario:** Supervision

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Eosinophilic esophagitis as a side-effect of allergen immunotherapy: protocol for a systematic review and meta-analysis

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ABSTRACT

Background; Sensitization to food and airborne allergens is common in the majority of patients with eosinophilic esophagitis (EoE). Although there is not a direct cause-effect relationship of IgE-mediated allergy with the pathogenesis of EoE, there is a growing evidence that oral desensitization to food and sublingual immunotherapy (SLIT) may induce the development of EoE as an adverse effect. As part of the 'EoE and Allergen Immunotherapy (AIT)' Task Force funded by the European Academy of Allergy and Clinical Immunology (EAACI), a systematic approach will be followed to review the evidence from the published scientific literature on the development of EoE in children and adults under any type of AIT.

Methods; This systematic review will be carried out following the PRISMA statement guidelines. Studies will be assessed for inclusion in the review according to the Population-Interventions-Comparators-Outcomes (PICO) criteria.

Results; Expected outcomes will provide evidence on the AIT-EoE development connection.

Conclusion; The findings from this review will be used as a reference to provide useful guidelines for physicians treating patients with EoE and/or are practicing AIT.

PROSPERO registration ID: CRD42023425917

Keywords: eosinophilic esophagitis, allergen immunotherapy, oral desensitization.

Impact Statement

A continuously increasing incidence of eosinophilic esophagitis (EoE) is noticed during the last 2 decades. In the same timeframe, protocols of food desensitization (oral tolerance induction with the use of fresh food and immunotherapy with food extracts) have been developed for patients suffering of food allergy. Many cases of EoE development in patients following food desensitization protocols have been reported in the literature, as well as cases of EoE following sublingual immunotherapy to airborne allergens. A Task Force has been funded by EAACI to examine this association. The presentpaper, describes the methodology adopted to examine the association and is the first one produced by the relevant TF.

BACKGROUD

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease clinically characterized by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation (>15 eosinophils per high power field)(1). Various EoE phenotypes have been proposed, based on response to therapy, atopic status and natural history of the disease, while three different endotypes have also been identified, based on histological, endoscopic and molecular features(2). Although EoE is not etiologically caused by an IgE-mediated pathomechanism, sensitization to airborne and food allergens is common in these patients with an underlying T-helper 2 (Th2) cell-mediated pathophysiology (3,4).

Food allergens are considered common triggers for EoE, and this hypothesis has been sustained by the fact that elimination diets are often an effective treatment option. However, their effectiveness is not noticed in all EoE patients. It appears that EoE is a multifactorial disease caused by a combination of genetic predisposition, epithelial barrier dysfunction,environmental risk factors and allergen sensitization (5).

Airborne allergens have also been implicated in the pathogenesis of EoE, although there is no strong evidence of a cause-effect relationship. EoE has been developed experimentally in a murine model by initial intranasal sensitization to *Aspergillus fumigatus,* followed by challenging mice with the relative airborne allergen (6). Several single-center clinical observations have also found correlations between the onset or worsening of EoE symptoms with seasonal aeroallergen exposure (7–10). These findings have not been confirmed by other studies and no significant variations in the seasonal distribution of either the diagnosis of EoE or its clinical recrudescence throughout the year was reported by a systematic review and meta-analysis on this topic (11).

Regular contact of the esophageal mucosa with large amounts of food allergens and the minuscule exposure to airborne allergens have been involved in the development of EoE (12). This potential cau relationship poses the question on whether allergen immunotherapy (AIT) administered *per os* may represent a risk factor for the onset of EoE. There are case reports of biopsy-confirmed EoE developed in patients undergoing sublingual immunotherapy (SLIT) to pollen or house-dust mites, but the incidence rate is unknown (13–17).

The involvement of oral immunotherapy (OIT) to food allergens in the development of EoE has also been described (18,19). OIT has emerged as a promising therapy for patients with IgE-mediated food allergy, with various tolerance induction protocols being developed and a variety of food allergens being addressed. The incidence of confirmed newly developed EoE as a side-effect of OIT has been reported in approximately 2.7-5.3% of patients, with a 5.6% OIT discontinuation rate due to a diagnosis of EoE (or symptoms possibly related to EoE) (18–20). The clinical and histological remission of EoE reported in case-series after the discontinuation of OIT is a further clue of this interaction.

Given the overarching principles of the European Academy of Allergy and Clinical Immunology (EAACI) to promote effective and safe medical care, EAACI created a Task Force (TF) to investigate the causal relationship between EoE and AIT, conducting a systematic review and meta-analysis. Subjects with active EoE would rather rarely undergo SLIT or OIT, so the systematic review aims to evaluate the ab initio manifestation of EoE in patients undergoing such treatments and to provide useful guidelines for physicians treating patients with EoE and/or practicing AIT. The protocol of the systematic review on the development of EoE as a side-effect in patients treated with AIT to airborne and food allergens is presented here.

METHODS

Study design

In this systematic review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines will be followed (21,22). The methodology has been reviewed and approved by all authors in a TF meeting held on December 2022.

Search strategy

The electronic search of the literature will be performed in three engines: Pubmed, Scopus, and Embase. Grey literature (e.g., conference abstracts) will also be searched, and the list of references of full-text articles will be screened to identify further relevant studies.

All databases will be searched from inception to March 31st, 2023. The following Medical Subject Heading (MeSH) terms and text words will be used in the queries: "eosinophilic esophagitis" OR "eosinophilic oesophagitis" OR "EoE" combined with ("AND") "Allergen immunotherapy" OR “Specific immunotherapy” OR "desensitization" OR "AIT" OR "Sublingual immunotherapy" OR "SLIT" OR "specific oral tolerance induction" OR "SOTI" OR "oral immunotherapy" OR "OIT" OR "airborne allergen" OR "respiratory allergen" OR "food allergen" OR “Epicutaneous immunotherapy” (“AND”) "side effect" OR “adverse effect”.

Eligibility criteria

Studies will be assessed for inclusion in the review according to the Population-Interventions-Comparators-Outcomes (PICO) criteria:

Population

Human studies, without age, gender, or origin limits, will be included.

Intervention(s) / Exposure(s)

Any type of AIT (probably only oral or sublingual) reported to cause or exacerbate, histologically and clinically diagnosed EoE, will be considered. Modalities used for AIT may include any protocol of food desensitization or sublingual AIT and any fresh food or extract used for these purposes.

Comparator(s) / Control(s)

Studies comparing the assessment of EoE before and after AIT will be considered. A comparator can also be a group of AIT-treated patients that have been histologically and clinically assessed for the development of EoE, in parallel with the ones that developed EoE.

Main Outcome(s) / Additional outcome(sThere are two similar but not identical questions that will be addressed, both regarding the development of EoE after starting AIT. The first is the connection of EoE development after sublingual AIT using extracts of airborne allergens and the second is the

connection of EoE development during oral desensitization to food allergens. The primary outcome for both will be any evidence on AIT-EoE development connection. Indicating AIT and OIT as the causal factor of EoE can be done with certainty only if patients have undergone an endoscopy prior to desensitization. The extended use of the non-invasive technique of sponge test, performed during endoscopy, has started facilitating the diagnostic procedure. Triggering the exacerbation of pre-existing EoE after AIT can be examined as a secondary outcome. Another secondary outcome is the course of EoE after the discontinuation of the culprit AIT, for both branches of the study.

Inclusion criteria

Observational (prospective and retrospective) and interventional studies examining the correlation of AIT with the development of EoE in humans will be included in this systematic review. Any type of AIT, including different protocols of food desensitization and any extract of SLIT, should have been performed in the primary studies. In order to confirm AIT as the trigger of EoE, confirmed histological diagnosis of EoE (>15 eosinophils/high-power field) developed after the start of AIT will be considered. There will be no restrictions in terms of age, sex, and race. No language restrictions of the studies will be imposed.

Exclusion criteria

- Case reports, Case series, Reviews, Opinion articles, Editorial articles
- Studies on laboratory animals
- *In vitro – ex vivo studies* not directly referring to clinical data (EoE symptoms)
- Studies that do not include AIT as described in the inclusion criteria and refer to other procedures; for example, the use of food supplements or herbal infusions.
- Studies on the use of AIT for the treatment of EoE are subject of another project of our TF.

Study selection and Risk of Bias assessment strategy

Two investigators will independently scrutinize the eligibility of the identified titles and abstracts based on the elements of the "EoE as a side-effect of SLIT with airborne allergens" question. A third author will help resolve disagreements between the first two authors and reach consensus. Two investigators will also work on the identified search results on "EoE due to the specific oral tolerance induction / food immunotherapy" question, with a third investigator helping as a referee. The Rayyan QCRI web tool will be used to assist in the study selection (23). Data extraction will be done twice. Excluded papers will be published as an online supplementary Appendix.

Detailed information on the included studies will be provided in a table describing study participants (number and age groups), research designs, interventions (allergy testing), comparators, and outcomes. The sources of funding for the studies included in the review will be reported.

Two investigators will carry out an independent quality assessment on each eligible study of the final list. AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews) will be used to assess the quality of all studies that will be extracted from the literature research, offering an accurate and comprehensive summary of the results (21,22). Moreover, different assessment tools will be used for different study designs. The risk of bias (RoB) of the included randomized controlled trials will be

evaluated using the Cochrane Collaboration RoB Tool (24). To assess the quality of evidence in non-randomised interventions, ROBINS-I will be used (25). Two investigators will review the results.

Data extraction, analysis and synthesis

Separate analyses for each one of the outcomes will be undertaken. When possible, subgroup analyses by age group, food allergens, airborne extracts, study design and risk of bias will be performed to investigate potentially different effects on risk.

The heterogeneity of pooled results will be examined using the Cochran's Q test, with a 0.10 level of significance and the I^2 statistic, which describes the percentage variation across studies due to heterogeneity rather than chance (26,27). A narrative synthesis of the data will also be done.

DISCUSSION

There are still unmet needs regarding the development of EoE as a side-effect of AIT; age as a risk factor, the implication of each of the two different food desensitization modalities (sublingual and oral) to the development of EoE, the possibility that the practice of spitting (not swallowing) the allergen during SLIT is a safer (still efficacious) option, whether preliminary anamnesis of symptoms posing the suspicion of EoE is enough or whether endoscopy should be performed before the start of desensitization protocols and if the treatment protocols of EoE in the cases related to AIT should be the same with the already followed ones.

In a meta-analysis regardingpatients undergoing OIT the overall rates per patient for symptoms possibly related to EoE were 34% for general gastrointestinal symptoms, including 32% of reported symptoms related to abdominal pain and 12% of reported vomiting. The overall rate of OIT discontinuation was 14%, with 4.7% of these reporting symptoms potentially attributable to EoE (19). In general, EoE clinically and histologically resolves after food OIT discontinuation. Food desensitization protocols are proposed in cases of IgE-mediated food allergy, mainly to patients that have a history of anaphylaxis, so it is clear that a decision to stop OIT has to be followed by an updated anaphylaxis action plan.

It is certainly important to offer evidence-based guidelines on whether EoE related to AIT prohibits any future effort to desensitization, either to food or to airborne allergen, using the oral route. Although it appears apparently irrelevant, it should be clear whether desensitization can be performed using other AIT routes for the same patients.

In this paper, we describe the protocol of the systematic review that has been planned. This systematic review will mainly focus on existing evidence i) on whether the severity and frequency of EoE presented during AIT is similar to a comparator population without AIT and ii) how cessation or prolongation of AIT affects the clinical course of EoE. The described option to treat EoE (with proton pump inhibitors and swallowed corticosteroids) and continue the desensitization protocol will be also assessed (20).

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ETHICS
Ethical approval and consent were not required as this study was based on publicly available data.

CONTRIBUTIONS OF EACH AUTHOR
This protocol was conceptualized by CP, CMR, IT AC and the search strategy was developed by GKN. The initial draft was prepared by EA and CP and initially revised following critical review by

GKN, GNK, OP, MV and AD-D, and then by all co-authors. All authors read and approved the final version to be published.

CONFLICT OF INTERESTS

CP, CMR, IT, EH, MV, AA-P, AB, EA, DA-A**,** GKN, GNK and AC have no conflict of interest to declare relative to this project.

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Chapter 3

CLINICAL FEATURES OF EGIDs

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Alimentary Tract

Eosinophilic gastrointestinal disorders in children and adolescents: A single-center experience

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ABSTRACT

Background: To date, few studies have been conducted in Italy on pediatric eosinophilic gastrointestinal diseases (EGIDs).

Aims: To assess clinical features of pediatric patients with EGIDs who are followed in a tertiary pediatric center.

Methods: From January 2015 to December 2019, we retrospectively enrolled patients with EGIDs, and collected clinical, endoscopic, and histological data.

Results: We enrolled 112 patients, 75.8% were male. Mean age was 9.3 ± 4.8 years. Diagnosis of EGIDs has increased in the last two years, with non-esophageal EGIDs more prevalent than eosinophilic esophagitis (EoE) (5.1% vs. 4.4%). Approximately 30% of patients had allergic comorbidities, which prevailed in children with EoE. Autism spectrum disorders were common in patients with non-esophageal EGIDs ($p = 0.007$), a statistically significant finding. In addition, esophageal atresia was associated with EoE ($p = 0.04$). Most EGIDs patients had normal findings or an inflammatory endoscopic phenotype. Patients with EoE were mainly treated with proton pump inhibitors (PPIs) alone or in combination with swallowed steroids. PPIs, oral steroids, and food-elimination diets were prescribed to patients with non-esophageal EGIDs.

Conclusion: This is the first Italian study revealing an increased frequency of EGIDs in a pediatric population. Further studies are needed to characterize patients with these emerging diseases.

1. Introduction

Primary eosinophilic gastrointestinal disorders (EGIDs) are chronic inflammatory diseases of unknown etiology, which may involve any part of the gastrointestinal (GI) tract, and lead to eosinophilic mucosal infiltration in the absence of secondary causes of intestinal eosinophilia [1,2]. Although their pathogenic mechanisms are mostly unknown, EGIDs seems to be commonly associated with atopy and, to a lesser extent, autoimmunity [2]. While pediatric eosinophilic esophagitis (EoE) is a well-defined disease with established guidelines [3,4], non-esophageal EGIDs, including eosinophilic gastritis (EoG), gastroenteritis (EoGE), and colitis (EoC), remain a clinical enigma [1]. EGIDs are increasingly prevalent over the past decade, and have a substantial impact on the patients' quality of life [5–7]. However, few observational studies have been conducted in Europe on the clinical and epidemiological features of pediatric EGIDs. Specifically, the handful of published European and Italian studies have reported epidemiological data on non-esophageal EGIDs in pediatrics [8]. In this context, our retrospective study attempted to evaluate the epidemiological, clinical, and endoscopic features of Italian children and adolescents

Abbreviations: ASD, Autism Spectrum Disorder; CD, Ceeliac Disease; EA, Esophageal Atresia; EGID, Eosinophilic Gastrointestinal Disorder; EoC, Eosinophilic Colitis; EoE, Eosinophilic Esophagitis; EoEn, Eosinophilic Enteritis; EoG, Eosinophilic Gastritis; EoGE, Eosinophilic Gastroenteritis; GERD, Gastroesophageal Reflux Disease; GI, Gastrointestinal; HPF, High Power Field; PPI, Proton Pump Inhibitor.

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with EGIDs, and characterize initial provider management of these patients.

2. Materials and methods

2.1. Study design, patient cohort, and data extraction

We retrospectively analyzed all pediatric patients who underwent digestive endoscopies for GI symptoms from January 2015 to December 2019 at our Pediatric Clinic in Pavia, Italy. Upper and lower GI endoscopies were performed by pediatric endoscopists working in the Surgery Division.

Gastroscopy protocol required at least one tissue sample in the distal, middle and proximal esophagus, one in the corpus and gastric antrum, and two biopsies in the duodenum. Among patients who underwent ileocolonoscopy, endoscopists took a single biopsy from the distal ileum, cecum, right colon, transverse colon, left colon, sigma, and rectum.

The diagnosis of EoE was made based on current guidelines put forth by the American Academy of Allergy, Asthma & Immunology [3], and a Working Committee of several European gastroenterology and allergy organizations [4]. The European group considered the histological threshold of ≥15 eosinophils/high power field (eos/HPF).· As there are no consensus guidelines for the diagnosis of non-esophageal EGIDs, pathology reports were reviewed based on the pathological cut-offs proposed by Licari et al. (stomach ≥30 eos/HPF, small intestine ≥50 eos/HPF, right colon ≥100 eos/HPF, transverse and left colon ≥80 eos/HPF, and rectosigmoid colon ≥60 eos/HPF) [1,9,10]. The term eosinophilic gastroenteritis (EoGE) was used to define patients with intestinal involvement (duodenum and/or ileum) and diffuse pathological eosinophilic inflammation of the stomach, small bowel, and colon. Exclusive small bowel (duodenum and/or ileum) involvement was diagnosed as eosinophilic enteritis (EoEn). For EoE, histological remission was achieved when esophageal eosinophil count was < 5 eos/HPF [11].

Patients < 19 years with a diagnosis of primary EGIDs were enrolled. All patients with a secondary cause of pathological eosinophilic inflammation of the GI tract were excluded (Table S1). Data collected from EGIDs patients included demographics (date of birth, age at diagnosis, gender, and ethnicity), medical history of atopic and other coexisting diseases, symptoms at diagnosis, and laboratory tests (serum total immunoglobulin E [IgE] and peripheral blood eosinophil count). Endoscopic and histological findings were also reported. Data regarding treatments started at the time of diagnosis were also collected, including medications (i.e., swallowed steroids, biological therapy, proton pump inhibitors, other drugs), food elimination diets, or combined therapies. Finally, we analyzed and assessed treatment responses by examining follow-up clinical records and endoscopic and histologic reports at one, three, and five years of follow-up. All data were extracted from electronic medical records from Policlinico San Matteo (Ormaweb™ and Fenix™, Software) and entered into a spreadsheet. We replaced every patient identifier (patient name) with a specific numeric code. The Ethical Committee of the Policlinico San Matteo approved this study (Approval Number: P_20,210,023,100) and written informed consent was obtained from parents or legal guardians.

2.2. Statistical analysis

Continuous variables were expressed as means and standard deviation (SD), while categorical variables were reported as numbers and percentages. Frequencies were tabulated for categorical variables. Bivariate analysis of categorical variables was conducted with the chi-square test or Fisher's exact test. The Student's *t*-test was used to compare continuous variables. A p value less than 0.05 was considered significant. All analyses were performed using GraphPad Prism 8 for Mac, Version 8.4.3 (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Epidemiological and clinical features

A total of 1184 GI endoscopies (1122 with biopsies) were performed at the Pediatric Surgery Division of our Hospital throughout the study period. One hundred twelve (112) (9.5%) patients met the diagnostic criteria of EGIDs. Notably, the diagnosis of non-esophageal EGIDs was obtained in 60 (5.1%) patients, while EoE was diagnosed in 52 (4.4%) subjects. In the cohort of patients with non-esophageal EGIDs, 43 (71.7%) subjects had a diagnosis of EoC, 12 (20%) had EoEn, four (6.7%) had EoGE, and only one (1.6%) child had gastric involvement. The EGIDs cohort included 75.8% male subjects with a mean age of 9.3 ± 4.8 years (Table 1). The prevalence of Caucasian subjects was significantly high (92.0%, $p = 0.016$) compared to other ethnicities.

From 2015 to 2019, there was a 65.6% increase in new EGID diagnoses (30.5% per year). In the same period, the rise of GI biopsy was 26.0% (8.0% per year). When analyzing time trends, the overall EGIDs diagnosis frequency increased throughout the study period, especially in the last two years ($p = 0.06$) (Table 2 Fig. S1).

Common presenting symptoms at diagnosis included abdominal pain (54.4%), chronic diarrhea (35.7%), symptoms of GERD (27.7%), and nausea/vomiting (11.6%). Abdominal pain and chronic diarrhea significantly prevailed in children with non-esophageal EGIDs (p <0.0001 and $p < 0.0001$, respectively). As for EoE, GERD-like symptoms (heartburn, epigastric/chest pain, gastric pyrosis, regurgitation), food impaction, and dysphagia were significantly prevalent in patients with EoE ($p < 0.0001$, $p = 0.008$, and $p = 0.02$, respectively). Functional chronic diarrhea was also reported in five patients with EoE who showed normal findings at ileocolonoscopy and histology. None of the EGIDs patients developed protein-losing enteropathy, intestinal obstruction, and GI bleeding.

EGIDs patients had a high frequency of atopy, with approximately 30% of subjects having a history of atopic conditions. Allergic rhinitis was the most common atopic disorder in all EGIDs patients, while the history of food allergy and asthma prevailed in patients with EoE. Surprisingly, other medical histories included autism spectrum disorders (ASDs) (23.5%), which significantly prevailed in children with non-esophageal EGIDs ($p = 0.007$). Four (7.7%) children with EoE reported a history of congenital esophageal atresia ($p = 0.04$), while three (5.0%) patients with EoC had a previous diagnosis of celiac disease (CD). Ten (8.9%) patients had congenital malformations, such as *situs viscerum inversus*, polycystic and horseshoe kidney, diaphragmatic hernia, esophageal atresia, pontocerebellar hypoplasia, and lung cystic adenomatoid malformation.

Full allergic assessment with skin prick tests and specific serum IgE levels was performed in 62 (55.4%) EGIDs patients (31 children with EoE and 31 with non-esophageal EGIDs). Although not statistically significant, the prevalence of children with peripheral eosinophils ≥ 500 mm^3 and IgE levels ≥ 100 kU/L was higher in EoE than non-esophageal EGIDs (Table S2). The four patients with EoGE showed high levels of IgE (mean 640.0 kU/mL, min 15 kU/mL, max 2458 kU/mL), and peripheral eosinophils (mean 754.4/mm^3, min 200/mm^3, max 1810/mm^3) (Table S3).

3.2. Endoscopic and histological findings

Most EGIDs patients underwent both upper and lower GI endoscopies (56.3%). Also, 48 (80%) patients with non-esophageal EGIDs

Table 1
Demographic and clinical features of EGIDs patients.

Demographic features	EGIDs	EoE	Non-esophageal EGIDs	*p* value
Sample size, *n* (%)	112 (100.0)	52 (46.4)	76 (53.6)	–
Age at diagnosis, *mean* ± SD	9.3 ± 4.8	9.7 ± 5.0	8.9 ± 4.7	0.5*
Male, *n* (%)	85 (75.8)	45 (86.5)	40 (66.7)	**0.011**
Caucasian, *n* (%)	103 (92.0)	44 (84.6)	59 (98.3)	**0.016**
Symptoms at onset	**EGIDs**	**EoE**	**Non-esophageal EGIDs**	***p* value**
Abdominal pain, *n* (%)	61 (54.4)	17 (32.7)	44 (73.3)	**< 0.0001**
Anemia, *n* (%)	3 (2.7)	1 (1.9)	2 (3.3)	> 0.99
Bloating, *n* (%)	2 (1.8)	1 (1.9)	1 (1.7)	> 0.99
Chronic constipation, *n* (%)§	4 (3.8)	1 (1.9)	3 (5.0)	0.62
Chronic diarrhea, *n* (%)§	40 (35.7)	5 (9.6)	35 (58.3)	**< 0.0001**
Dysphagia, *n* (%)	5 (4.5)	5 (9.6)	0	**0.02**
Failure to thrive, *n* (%)	4 (3.8)	2 (3.8)	2 (3.3)	> 0.99
Food impaction, *n* (%)	6 (5.4)	6 (11.5)	0	**0.008**
GERD-like symptoms, *n* (%)°	31 (27.7)	25 (48.1)	6 (10.0)	**< 0.0001**
Loss of appetite, *n* (%)	1 (0.9)	1 (1.9)	0	0.46
Nausea and vomiting, *n* (%)	13 (11.6)	9 (17.3)	4 (6.7)	0.13
Weight loss, *n* (%)	4 (3.8)	0	4 (6.7)	0.12
Atopic comorbidities	**EGIDs**	**EoE**	**Non-esophageal EGIDs**	***p* value**
History of atopic diseases, *n* (%)	33 (29.5)	19 (36.5)	14 (23.3)	0.15
Allergic rhinitis, *n* (%)	30 (26.8)	16 (30.8)	14 (23.3)	0.40
Anaphylaxis, *n* (%)	2 (1.8)	1 (1.9)	1 (1.7)	> 0.99
Asthma, *n* (%)	8 (7.4)	6 (11.5)	2 (3.3)	0.14
Atopic dermatitis, *n* (%)	6 (5.4)	4 (7.7)	2 (3.3)	0.41
Food allergy, *n* (%)	9 (8.0)	7 (13.5)	2 (3.3)	0.08
Non-atopic comorbidities	**EGIDs**	**EoE**	**Non-esophageal EGIDs**	***p* value**
Autism spectrum disorders, *n* (%)§§	30 (23.4)	6 (11.5)	20 (33.3)	**0.007**
History of celiac disease, *n* (%)	3 (2.7)	0	3 (5.0)	0.25
Congenital malformations°°, *n* (%)	10 (8.9)	7 (13.5)	3 (5.0)	0.18
Connective tissue disorders, *n* (%)	1 (0.9)	0	1 (1.7)	> 0.99
Epileptic encephalopathy, *n* (%)	5 (4.5)	4 (7.7)	1 (1.7)	0.18
Esophageal atresia, *n* (%)	4 (3.8)	4 (7.7)	0	**0.04**
Genetic disorders°°°, *n* (%)	4 (3.8)	2 (3.8)	2 (3.3)	> 0.99
Obesity, *n* (%)	3 (2.7)	1 (1.9)	2 (3.3)	> 0.99
Prematurity, *n* (%)	4 (3.8)	3 (5.8)	1 (1.7)	0.33

EGID: Eosinophilic Gastrointestinal Disorder; EoE: Eosinophilic Esophagitis; GERD: Gastroesophageal Reflux Disease; GI: Gastrointestinal; SD: Standard Deviation.
* unpaired *t*-test.
° Heartburn, epigastric/chest pain, gastric pyrosis, regurgitation.
°° *Situs viscerum inversus*, polycystic and horseshoe kidney, diaphragmatic hernia, esophageal atresia, ponto-cerebellar hypoplasia, and lung cystic adenomatoid malformation.
°°° Chr5q35.1 duplication, Cornelia De Lange Syndrome, Down Syndrome, and Ehlers Danlos Syndrome.
§ Diagnosis of chronic constipation and diarrhea was made according to the Rome IV Criteria [37,38].
§§ Diagnosis of autism spectrum disorder was made according to the DSM-5 guidelines [39].

Table 2
Annual prevalence of EGIDs diagnosis through the study period compared to the number of GI endoscopies performed from 2015 to 2019 at our Pediatric Clinic. The overall diagnosis of EGIDs was increased through the study period (Chi-square test for trend $p = 0.06$).

Diagnosis	< 2015	2015	2016	2017	2018	2019	Total
EoE, ***n* (%)**	8 (-)	6 (3.0)	7 (3.2)	8 (3.2)	9 (3.8)	14 (5.1)	52
Non-EoE EGIDs, ***n* (%)**	0	5 (2.5)	11 (5.1)	11 (4.4)	15 (6.1)	18 (6.6)	60
EGIDs, ***n* (%)**	8 (-)	11 (5.4)	18 (8.8)	19 (7.6)	24 (9.8)	32 (11.7)	112
GI endoscopies, ***n* (%)**	n.a	202 (17.0)	216 (18.2)	249 (21.0)	244 (21.0)	273 (23.0)	1184

EGIDs: eosinophilic gastrointestinal disorders; EoE: eosinophilic esophagitis; GI: gastrointestinal.

and 15 (29.0%) with EoE underwent a complete endoscopic assessment. Upper GI endoscopy was performed in 37 (71.2%) EoE children and adolescents with suggestive symptoms of refractory gastroesophageal reflux disease (GERD) or food impaction. Twelve (20%) patients with EoC only underwent ileocolonoscopy because of their exclusive history of persistent change in bowel movements.

In patients with EoE, endoscopic findings included mucosal edema and hyperemia (30.8%), furrowing (23.1%), esophageal rings and trachealization (19.2%), and white exudates (13.5%) (Table 3). Upper endoscopic findings were completely normal in 18 (34.6%) patients, with none of the enrolled patients showing esophageal strictures.

Endoscopic findings were reported in all patients with non-esophageal EGIDs. As shown in Table 3, normal endoscopic findings prevailed in patients with non-esophageal EGIDs (70.0%). Intestinal edema with mucosal hyperemia was reported in four (25.0%) patients with EoGE and 3 (7.0%) with EoC. Nodular lymphoid hyperplasia of colonic mucosa was the second most common endoscopic finding in EoC patients (20%). Median values of intestinal eosinophils are reported in Tables S3 and S4 of Supplemental Digital Content.

3.3. Therapeutic management

Data on therapy were available for 40 (77.0%) patients with EoE, and 36 (60%) with non-esophageal EGIDs. For subjects with EoE, the most commonly used medications were PPIs (46.2%) and swallowed corticosteroids (21.2%), also in combination (Table 4).

Table 3
Endoscopic findings in patients with EGIDs at diagnosis.

Eosinophilic esophagitis		Non-esophageal EGIDs					
Endoscopic findings	Results	Endoscopic findings	Overall	EoG	EoEn°	EoGE	EoC
Normal endoscopic findings, *n* (%)	18 (34.6)	Normal endoscopic findings, *n* (%)	42 (70.0)	1 (100)	9 (75)	2 (50.0)	31 (72.1)
Edema and hyperemia, *n* (%)	16 (30.8)	Lymphoid nodular hyperplasia, *n* (%)	12 (20.0)	0	1 (8.3)	0	11 (25.6)
Esophageal furrows, *n* (%)	12 (23.1)	Edema and hyperemia, *n* (%)	7 (11.7)	0	1 (8.3)	1 (25.0)	3 (7.0)
Esophageal rings and trachealization, *n* (%)	10 (19.2)	Ulcers and erosions, *n* (%)	3 (5.0)	0	1 (8.3)	1 (25.0)	2 (4.6)
White exudates, *n* (%)	7 (13.5)	Mucosal bleeding, *n* (%)	3 (5.0)	0	0	0	2 (4.6)
Strictures, *n* (%)	0	Intestinal polyp, *n* (%)	2 (3.3)	0	0	0	2 (4.6)

EoC: Eosinophilic Colitis; EoD: Eosinophilic Duodenitis; EoEn: Eosinophilic Enteritis; EoG: Eosinophilic Gastritis; EoGE: Eosinophilic Gastroenteritis; SD: Standard Deviation.
° All patients with EoEn had a specific duodenal involvement.

Table 4
Therapies of EGIDs patients.

Eosinophilic esophagitis		Non-esophageal EGIDs					
Therapies	Results	Therapies	Overall	EoG	EoEn	EoGE	EoC
PPI, *n* (%)	24 (46.2)	PPI, *n* (%)	11 (18.3)	0	8 (66.7)	0	0
Swallowed steroids, *n* (%)	2 (3.8)	Oral steroids, *n* (%)	10 (16.7)	1 (100)	1 (8.3)	0	7 (16.3)
Empiric elimination diet, *n* (%)	1 (1.9)	Empiric elimination diet, *n* (%)	6 (10.0)	0	1 (8.3)	0	5 (11.6)
Elemental formula, *n* (%)	0	Elemental formula, *n* (%)	0	0	0	0	0
Biological therapy, *n* (%)	0	Biological therapy, *n* (%)	0	0	0	0	0
Combination therapy, *n* (%)	13 (25.0)	Combination therapy, *n* (%)	12 (20.0)	0	0	3 (75.0)	2 (4.7)
PPI + swallowed steroids, *n* (%)	9 (17.3)	PPI + steroids, *n* (%)	1 (1.7)	0		3 (100.0)	0
PPI + elimination diet, *n* (%)	0	PPI + elimination diet, *n* (%)	0	0		0	0
Swallowed steroids + elimination diet, *n* (%)	4 (7.7)	Steroids + elimination diet, *n* (%)	2 (3.3)	0		0	2 (4.7)
		Probiotics, *n* (%)*	9 (15.0)	0	0	0	8 (18.6)
		Mesalamine, *n* (%)	3 (5.0)	0	0	0	3 (7.0)
		Montelukast, *n* (%)	1 (1.7)	0	0	0	1 (2.3)
No therapy, *n* (%)	0	No therapy, *n* (%)	0	0	0	0	0
Data not available, *n* (%)	12 (23.1)	Data not available, *n* (%)	23 (38.3)	0	2 (16.7)	1 (25.0)	20 (46.5)

EoC, Eosinophilic Colitis; EoD, Eosinophilic Duodenitis; EoEn, Eosinophilic enteritis; EoG, Eosinophilic Gastritis; EoGE, Eosinophilic Gastroenteritis; PPI, Proton Pump Inhibitor.
* Probiotics were always prescribed in combination with other treatments.

Thirteen children with EoE (25.0%) received combination therapies, whereas only one (1.8%) patient was treated with a food elimination diet. None of the EoE enrolled patients was on biological therapy or elemental diet.

Most patients with EoEn (66.7%) were on PPI therapy. Three (75.0%) patients with EoGE were treated with PPI and oral steroids. For EoC, oral budesonide (16.3%) and food elimination diets (11.6%) were the most commonly prescribed treatments. Multiple concomitant treatments were used in 4.7% of these patients. Therapeutic data were not available for 23 (38.3%) patients with non-esophageal EGIDs.

3.4. Remission rate

Of the 52 subjects with EoE, 30 (57.7%) had follow-up within one year of the diagnosis (Table S5). Twenty-one (40.4%) subjects had an endoscopic evaluation, and nine (43.0%) patients reported a histological response to treatments. At three years of follow-up, 11 (21.2%) patients underwent an upper endoscopy, and four (36.4%) were in remission. Only four (7.7%) patients with EoE were scoped at five years of follow-up. PPIs were the first-line treatment and were most effective in inducing clinical and histologic remission or response in 57.1% of EoE patients (Table S6).

Eight (13.3%) patients with non-esophageal EGIDs had follow-up within one year of starting their diagnosis, and four (50.0%) had a response to treatment (Table S5). Twenty-five (41.7%) subjects had clinical evaluation without endoscopy. Only one child with EoEn was in remission at three years of follow-up. None of the patients with non-esophageal EGIDs had a follow-up endoscopy beyond five years from diagnosis.

4. Discussion

This single-center retrospective study examined, for the first time, the epidemiological, clinical, and endoscopic features of a cohort of Italian children and adolescents with EGIDs. There were several notable findings, starting with the primary result, which showed that the overall frequency of EGIDs increased through the study period, and mostly in the last two years, despite a lesser rise of the GI endoscopy rate (65.6% vs. 26.0%). Since the first case identified in the mid-1990s [12], EoE has evolved from a rare condition to a commonly encountered disease in clinical practice, and a significant cause of upper gastrointestinal morbidity and rising health care costs [13,14]. Overall prevalence of EoE is 0.5–1 cases/1000 persons [15]. Most of the estimates in the United States ranges from 40 to 90 cases/100,000 persons, with similar data reported from Australia (89/100,000), Switzerland (43/100,000), Spain (45/100,000), and Canada (34/100,000) [14]. However, the frequency of EoE might be orders of magnitude higher in patients who underwent an endoscopy for GI symptoms, as reported in our work (4.4%). Studies with a similar design found a high prevalence of EoE diagnosis, ranging from 2.4 to 6.6% [15,16].

Although the exact epidemiology is still unclear, the diagnosis of non-esophageal EGIDs has also increased in the last decade [6]. In our cohort, the prevalence of non-esophageal EGIDs was 5.1%, much higher than previously reported. A recent meta-analysis found that non-esophageal EGIDs might affect approximately 2% of symptomatic patients, highlighting the growing incidence of these emerging conditions [8]. Most of the patients with non-esophageal EGIDs had colonic and intestinal involvement with a high prevalence of EoC. We found only one case of pediatric EoG, unlike a report from a recent multi-center US

study, in which this disorder was more common than EoGE and EoC [6]. This discrepancy could reflect differences in the two study populations in terms of age, country, diagnostic accuracy, and differing exposure to environmental and genetic risk factors.

EGIDs patients had a remarkable prevalence of atopic diseases, mainly allergic rhinitis, asthma, and food allergy. Recent studies demonstrated that EoE might arise after atopic dermatitis, food allergy, asthma, and allergic rhinitis, as a late manifestation of the allergic march [17,18]. In our cohort, patients with EGIDs also had higher rates of other coexisting non-allergic diseases, even confirming the existence of a possible non-atopic phenotype of EGIDs.

ASDs were significantly described in children and adolescents with non-esophageal EGIDs. In children with ASDs, GI symptoms are widespread, and as shown in different studies, the prevalence of feeding dysfunction, chronic diarrhea, recurrent abdominal pain, constipation, vomiting, gastroesophageal reflux, intestinal infections may range from 17 to 86% [19,20]. Although a significant prevalence of ASDs was recently found in 7.5% of children with EoE participating in a large retrospective study, to date, only a few reports describe this putative relationship, especially in patients with non-esophageal EGIDs [21,22]. Several pathogenetic mechanisms occur in the onset of GI disorders in children with ASDs, and might involve high intestinal dysbiosis and increased gut permeability associated with immune-mediated response to luminal allergens [20]. We acknowledge a possible selection bias in these findings. Namely, children with ASDs undergo more frequent endoscopic evaluation for GI disorders, feeding disorders, or altered bowel habits, resulting in a more likely diagnosis for EGIDs.

Three patients with EoC had a previous diagnosis of CD [21]. Although the exact relationship remains unclear, EGIDs might be associated with autoimmune diseases, such as CD [21]. Moreover, a high prevalence of EoE has been described in patients with esophageal atresia (EA), and several putative pathogenetic mechanisms have been assumed, such as prematurity, Cesarean section, admission to the neonatal intensive care unit, early administration of antibiotics and PPIs, and the exposure to risk factors affecting the mucosal barrier and the normal esophageal motility [23,24].

In children and adolescents with EoE, normal mucosa and inflammatory lesions were the most common endoscopic findings [25,26]. The second most common was the intestinal nodular lymphoid hyperplasia [1,6,8], which is a common finding during lower GI endoscopy in children. Its clinical significance has not yet been clearly established, so starting from a recent retrospective study by Raffaele et al., we focused on a possible classification of nodular lymphoid hyperplasia based on morphological characteristics, and assigning a score to each specimen [27].

Diagnosis of non-esophageal EGIDs was made according to Collins's cut-offs [9]. Pediatric colonic eosinophilia represents a confounding finding with a broad differential diagnosis. It is often difficult to determine which children may progress to IBD, have EoC, or may have no underlying pathology or functional disorders, suggesting that repeat colonoscopies may be required to reach the final diagnosis, especially in doubtful cases [28]. In our cohort, four patients had EoGE characterized by an extensive intestinal inflammation and high levels of total serum IgEs and peripheral eosinophils. Reed et al. reported that 30% of EoGE patients had esophageal involvement, and 28% had colonic involvement [29]. Choi et al. described 24 children with EoGE and noted concomitant esophageal involvement in 13%, colon involvement in 29%, and multiple segments in 54% [30]. Caldwell et al. found that 87% of EoG patients had eosinophilia at other GI sites [31]. Other studies have found rates of eosinophilic inflammation at multiple sites varying from 20 to 88% [32–34]. Despite these reports, the overall prevalence of this phenomenon is still unknown. Our finding suggests that diagnostic workup should include: (1) esophagogastroduodenoscopy and ileocolonoscopy, even in patients presenting only with upper or lower GI symptoms, (2) a complete allergic assessment (skin prick tests and serum IgE, and (3) the exclusion of hypereosinophilic syndrome in selected cases.

At diagnosis, most patients with EoE were on PPIs alone or in combination with swallowed corticosteroids. Empiric elimination diets were reported in a small number of patients with EoE, and no children with EoE were treated with elemental formula or biologics. Several limitations may impair the efficacy of dietary treatment [7]. These include the ways to identify food triggers, issues of cross-contact and dose of food allergen required to trigger a flare, costs, patient and family burden, long-term efficacy, risk of developing subsequent IgE-mediated reactions, child's compliance, repeated endoscopies, and availability of expert nutritionists [7,35]. As for topical steroids, barriers are potential side effects on growth, costs, and preferring a medication-free approach, especially in adolescents [35]. Moreover, the immediate effects of elimination diets and swallowed steroids are well described, but relatively little is known about their long-term effectiveness [36].

After one year of follow-up, PPIs induced disease remission in about 57% of EoE patients. Laserna-Mendieta et al. recently reported that PPIs provided the most significant benefits for inducing remission in inflammatory EoE phenotype compared to the stricturing phenotype [11]. Our findings confirm the effectiveness of PPIs in young patients who show a prevalent inflammatory phenotype.

While clinical follow-up was achieved in more than 57% of EoE patients, endoscopic follow-up occurred in only about 40%. Most of the enrolled patients were followed in primary and secondary pediatric centers inside and outside our region, and came to our hospital only for the GI endoscopy. We also experienced a high rate of follow-up loss, especially in the adolescent group, illustrating the need for proactive education on the importance of treatments and regular monitoring with endoscopies. Finally, many diagnoses were performed in the last year of the study period, meaning patients were waiting for the revaluation scope at the time of data collection.

Considering the absence of standardized guidelines, the therapeutic management of non-esophageal EGIDs should consider various clinical factors, such as disease severity, presence of complications (anemia, GI bleeding, protein-losing enteropathy, weight loss and growth impairment, intestinal obstruction), patient and family compliance, and physician's experience [10]. If feasible, we generally start by proposing a food elimination diet to patients, and reserve steroid therapy for non-responsive or severe diseases [10]. However, in our experience, food elimination diets are generally less accepted by patients and their caregivers. Therefore, PPIs alone or with oral budesonide were mainly administered in EoEn and EoGE, while steroids were mostly prescribed for children with EoC.

Conclusions drawn from the analysis of treatment responses were limited by the low follow-up rates, mainly due to the diagnoses of non-esophageal EGIDs being performed in the last year of the study period. Pesek et al. reported that only 29% of patients had a follow-up endoscopy after six months from the diagnosis, and 65–89% of these achieved disease remission, confirming the high drop-out rate [6].

4.1. Limitations

There are several limitations to this research (Table 5). First, this was a retrospective study with the limitations inherent in this design. The increased prevalence of EGIDs diagnosis could be influenced by the number of GI endoscopies performed at our Pediatric Hospital during the study period. Although most of the enrolled patients underwent a complete endoscopic assessment (with

Table 5
Limitations, strengths, and future directions.

Limitations	Strengths	Future directions
Retrospective and monocentric pediatric study.	**First Italian pediatric study** to assess epidemiological, demographic, clinical, and pathological features of EGIDs.	Prospective study to determine epidemiology, natural history and response to therapies, especially for patients with multiple eosinophilic inflammation sites (ongoing).
The number of GI endoscopies could influence the prevalence of new EGIDs diagnoses.	**EGIDs are not such rare disorders** in our clinical practice.	Italian multi-center study (in progress).
The different number of esophageal and gastric biopsies taken in EoE patients versus the number of those taken in non-EoE EGID subjects.	EGIDs symptoms depend on the site of intestinal eosinophilic inflammation. EoE patients mainly show an **inflammatory endoscopic phenotype**.	Complete endoscopic assessment in every patient with a new diagnosis of EGIDs (ongoing).
Lack of consensus criteria for the diagnosis and therapy of non-esophageal EGIDs.	Patients with doubtful diagnosis, secondary causes of intestinal eosinophilia, and without a precise histological diagnosis were excluded from the analysis. Identification of a **potential score for intestinal nodular lymphoid hyperplasia**, commonly observed in patients with non-esophageal EGIDs [27].	Shared protocol for the management of affected patients in our Pediatric Clinic (ongoing). Multidisciplinary approach (pediatric allergists, gastroenterologists, endoscopists, nutritionists) (ongoing).
Limited number of patients who underwent a complete allergic assessment.	EGIDs are common in patients with allergies but also in children with ASD, EA, and other congenital or genetic disorders, suggesting **different clinical phenotypes** (atopic and non-atopic phenotype).	Complete allergic assessment (skin prick tests and serum IgE) in every patient with a new diagnosis of EGIDs (ongoing). Provide a disease classification, stratifying subjects into phenotype subgroups having potential significance in prognosis, and response to therapy (ongoing).
High rates of patients lost to follow-up and missing data on response to therapies.	**PPIs are effective in inducing disease remission**, especially in patients with an inflammatory phenotype of EoE.	Proactive education of affected patients and their caregivers (ongoing). Phone calls to assess response to therapy (ongoing). Identification of non-invasive biomarkers (ongoing).

ASD: Autism Spectrum Disorders; EA: Esophageal Atresia; EGIDs: eosinophilic gastrointestinal disorders; EoE: eosinophilic esophagitis; PPIs: Proton Pumps Inhibitors.

esophagogastroduodenoscopy and ileocolonoscopy), another potential bias could be the difference between the number of upper GI biopsies taken in EoE patients versus the number taken in subjects with non-esophageal EGID.

Diagnosis of non-esophageal EGIDs was also limited by the absence of standardized guidelines and pathological cut-offs of intestinal eosinophils. All unclear diagnoses were excluded to reduce the potential risk of bias, mainly if intestinal eosinophils were not counted and the number of intestinal biopsies proved inadequate. However, these subjects could have met the criteria for this diagnosis. In other published studies, diagnosis of non-esophageal EGIDs was made according to pathological cut-offs of intestinal eosinophils different from those we arbitrarily decided to use in our study. Therefore, patients with a potential diagnosis of non-esophageal EGIDs may be lost or misdiagnosed.

The high rate of non-available data on therapies and the limited number of patients assessed at follow-up did not allow us to perform statistical and comparative analysis and obtain more information on the disease course. As the therapeutic approach to non-esophageal EGIDs is not standardized and mainly results from physicians' experience, we did not obtain comparable data on treatments at diagnosis and during the follow-up. Finally, this study collected data from one Pediatric Center, so more general conclusions on clinical and epidemiological features of EGIDs require multi-center studies.

4.2. Strengths

This study has several strengths, starting with being the first attempt to assess epidemiological, demographic, clinical, and pathological features of Italian children with EGIDs at diagnosis and through a five year follow-up period. To limit overdiagnoses and obtain more reliable data, we excluded patients with doubtful diagnosis, secondary causes of intestinal eosinophilia, and without a precise histological diagnosis. Although the results cannot be generalized, we reported that EGIDs:

1. Are not rare disorders.
2. Are more common in male Caucasian children and adolescents, not only with atopic comorbidities, but also in children with ASD, history of esophageal atresia, and other congenital or genetic disorders, suggesting different potential phenotypes.
3. Present with symptoms depending on the site of intestinal eosinophilic inflammation.

In our cohort, children and adolescents with EoE mainly showed inflammatory endoscopic phenotype, confirming that esophageal strictures are generally complications of adult patients. This finding may explain the sustained response to PPI therapy at one year of follow-up.

5. Conclusion

EGIDs are an emerging spectrum of heterogeneous GI disorders that might include different disease subgroups with various inflammatory patterns and potentially different clinical phenotypes (atopic and non-atopic). Although intestinal inflammation might sometimes involve more than the GI tract, EGIDs mainly show normal findings or an inflammatory endoscopic phenotype. Finally, EGIDs have a chronic/remittent course with a high impact on patients' quality of life, including several limitations from impaired adherence to therapies and follow-up visits [7]. The long-term and restrictive therapies, need for repeated endoscopies, and small number of Italian pediatric reference centers with a multidisciplinary expert team could be the main limitations to follow-up and excellent response to treatments. Future studies are needed to:

1. Find non-invasive tools to assess intestinal inflammation and response to therapy,
2. Standardize pathological values of intestinal eosinophils to apply in the diagnostic workup of non-esophageal EGIDs and identify specific treatments for their management,

3. Provide a disease classification, stratifying subjects into phenotype subgroups with potential significance in prognosis, and response to therapy (Table 5).

Declaration of Competing Interest

All authors declared no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.06.027.

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nutrients

MDPI

Review

Malnutrition in Eosinophilic Gastrointestinal Disorders

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Abstract: Primary eosinophilic gastrointestinal disorders (EGIDs) are emerging chronic/remittent inflammatory diseases of unknown etiology, which may involve any part of the gastrointestinal (GI) tract, in the absence of secondary causes of GI eosinophilia. Eosinophilic esophagitis is the prototype of eosinophilic gastrointestinal disorders and is clinically characterized by symptoms related to esophageal inflammation and dysfunction. A few studies have assessed the nutritional status of patients with eosinophilic gastrointestinal disorders, showing conflicting results. This review summarizes the current evidence on the nutritional status of patients with EGIDs, focusing on the pediatric point of view and also speculating potential etiological mechanisms.

Keywords: children; adolescents; eosinophilic esophagitis; eosinophilic gastrointestinal disorders; growth; failure to thrive; malnutrition; undernutrition; obesity; vitamin

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1. Introduction

Primary eosinophilic gastrointestinal disorders (EGIDs) are emerging chronic/remittent inflammatory diseases of unknown etiology, which may involve any part of the gastrointestinal (GI) tract, leading to eosinophilic mucosal infiltration in the absence of secondary causes of intestinal eosinophilia [1–3]. While eosinophilic esophagitis (EoE) is a well-characterized disease with established guidelines [4,5], nonesophageal EGIDs, including eosinophilic gastritis, gastroenteritis, and colitis, remain a clinical enigma [1]. Although their pathogenic mechanisms are still unknown, EGIDs seems to be commonly associated with atopy and, to a lesser extent, autoimmunity [1,2]. EoE pathogenesis has been more extensively studied, and advances concerning the genetic and environmental contributors and cellular and molecular etiology have been achieved [6]. EGIDs seem to be multifactorial diseases resulting from genetic predisposition, environmental risk factors, and intestinal dysbiosis, leading to the activation of T-helper type 2 (Th2) inflammation and impaired epithelial barrier [1,7]. To date, no studies have extensively assessed malnutrition in patients with EGIDs.

In all its forms, malnutrition includes undernutrition, inadequate intake of vitamins and/or minerals, overweight, and obesity [8]. Undernutrition is a common complication of several chronic inflammatory GI diseases, mainly coeliac disease (CD) and Crohn's disease, often associated with weight loss, failure to thrive, malabsorption, and vitamin deficiency. However, obesity and overweight are the main comorbidities of gastroesophageal reflux

disease (GERD) and functional GI disorders, and are well-known risk factors of hepatic steatosis [9,10].

This review aims to summarize the current evidence on the nutritional status and malnutrition in patients with EGIDs, mainly focusing on the pediatric patients' population and highlining the lack of nutritional management algorithms.

A review of articles was performed via the online database PubMed (Table 1), following PRISMA guidelines [11]. The literature review was performed in December 2020, including all publication years. All studies that met the following criteria were included: (1) case reports, case series, and cross-sectional and cohort studies published in English in peer-reviewed journals; (2) participants were children and adult patients diagnosed with EGIDs. Potentially eligible publications were manually screened and reviewed, and nonrelevant publications were excluded (Figure 1).

Table 1. Search strategy.

PubMed: "Eosinophilic gastrointestinal disorders" AND "malnutrition." Publication date: all years.
PubMed: "Eosinophilic gastrointestinal disorders" AND "obesity." Publication date: all years.
PubMed: "Eosinophilic gastrointestinal disorders" AND "vitamin." Publication date: all years.

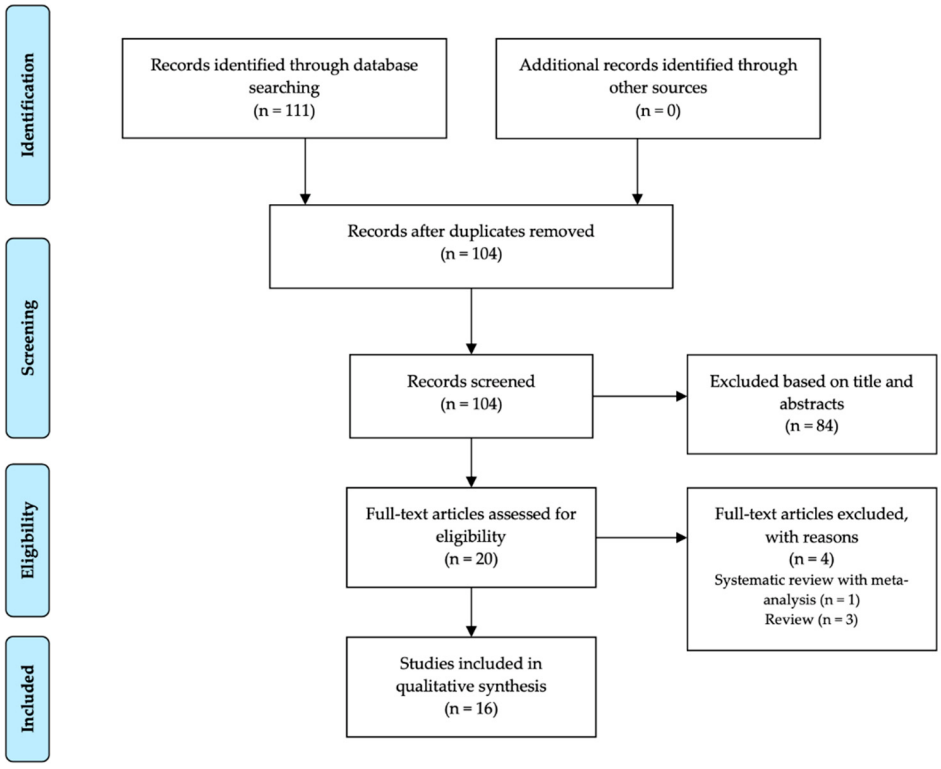

Figure 1. Process of literature screening.

2. Obese and Overweight EGID Patients

Obesity is a global public health problem associated with many chronic diseases, including type 2 diabetes, arterial hypertension, cardiovascular diseases, and asthma [12]. Growing evidence supports the association between obesity and immune disorders, such as cancer, autoimmunity, and atopy [13]. Some studies have suggested that pediatric obesity epidemy and obesity-related inflammation might at least in part be responsible for the significantly raised prevalence of allergic diseases [13]. The relationship between asthma and obesity in children is widely demonstrated, and several observational studies have reported that obese children are more frequently affected by a severe phenotype of asthma,

refractory to conventional therapies [14–17]. Additionally, data from the National Health and Nutrition Examination Study III (NHANES III) have described a positive association between body mass index (BMI) and atopy rates [17]. However, a real link between obesity and other allergic disorders, such as allergic rhinitis, atopic dermatitis, as well as EGIDs, has not yet been extensively established [18]. A few studies have assessed the role of body weight and BMI in children and adolescents with EoE, and no articles were published on EGIDs distal to the esophagus (Table 2). There is evidence that most adults with EoE mainly have a good nutritional status and expected BMI values [19–27]. Despite feeding or swallowing issues, EoE children did not generally report nutritional deficiency or impaired growth [23]. Rezende et al. found that 82.8% of the enrolled EoE children had a good nutritional state, 11.4% were overweight, whereas 5.7% were underweight [27]. Moreover, Jensen et al., 2019 reported that EoE children might present a slight impairment of height at diagnosis and achieve their expected growth, regardless of treatment modality [21]. Finally, children with GERD and EoE had a weight-for-length (WFL) Z score at the 18th–13th percentiles; thus, they did not meet the criteria for failure to thrive (FTT) [24].

Table 2. Studies reporting a normal or high BMI of children and adult patients with EoE. No study has been published on non-esophageal eosinophilic gastrointestinal disorders (EGIDs).

Author, Year	Country	Study Design	Sample Size	Population	Outcomes
Zdanowicz et al., 2020 [19]	Poland	Single-center retrospective study	36 EoE patients	Children	No difference was observed in the prevalence of failure to thrive between children with EoE and controls (30.6% vs. 19.14%).
Alexander et al., 2020 [20]	U.S.A.	Retrospective cohort study	223 EoE patients	Adults	PPI non-responding EoE patients were younger ($p = 0.001$), had a lower BMI (27.3 vs. 28.6 kg/m^2, $p = 0.04$), and higher peripheral eosinophil count ($p = 0.006$) than responders, suggesting that these variables might be risk factors for PPI non-response in EoE.
Jensen et al., 2019 [21]	U.S.A.	Retrospective multicenter study	409 EoE patients	Children (<18 years)	Children with EoE had a slight impairment of height at diagnosis; thus, they were not malnourished. Additionally, they generally maintained their expected growth regardless of treatment modality. Subtle changes were noted for patients treated with elemental diets in combination with other therapeutical approaches.
Kovačić et al., 2019 [22]	Croatia	Cross-sectional study	32 EoE patients	Children (<18 years)	Most of the enrolled patients were well-nourished, and a normal BMI Z score was found in 75% of the patients. There was no difference in BMI Z score between baseline and 12 months follow-up (median −0.3 vs. −0.3 SD, $p = 0.862$).
Tanaka et al., 2019 [23]	Japan	Cross-sectional study	27 EoE patients	Adults	Subjects with EoE had higher BMI values than those without EoE (23.4 kg/m^2 vs. 22.3 kg/m^2, $p = 0.005$). Additionally, they had a higher proportion of bronchial asthma and hiatal hernia compared to controls (25.9% vs. 5.2%; $p < 0.00129.6\%$ vs. 14.7%; $p = 0.049$).
Mehta et al., 2018 [24]	U.S.A.	Prospective study	91 patients (GERD = 38, EoE = 53)	Children (0–7 years)	Children with GERD and EoE had greater eating issues than healthy controls and did not report nutritional deficiency or impaired growth. Additionally, children with GERD and EoE had a WFL Z score at the 18th and 13th percentiles; thus, they did not meet FTT criteria.

Table 2. *Cont.*

Author, Year	Country	Study Design	Sample Size	Population	Outcomes
Wolf et al., 2017 [25]	U.S.A.	Prospective case-control study	417 patients (EoE = 120, healthy controls = 297)	Adults	BMI was lower in EoE cases than controls (25 kg/m^2 vs. 28 kg/m^2, $p = 0.002$), but it was not in the underweight range. Additionally, BMI was lower in EoE patients with esophageal narrowing, suggesting that a low weight in a patient suspected of having EoE should raise concern for esophageal remodeling.
Lee et al., 2015 [26]	U.S.A.	Cross-sectional study	57 EoE patients	Adults	The median BMI was 25.5 kg/m^2, defined as overweight. There was no significant difference between the mean ages at diagnosis and different BMI categories (<25, 25–30, and >30 kg/m^2). Rural and urban adult groups did not differ in BMI categories (24 kg/m^2 $\pm$ 8.2 vs. 27 kg/m^2 $\pm$ 11.7, $p = 0.271$).
Rezende et al., 2014 [27]	Brazil	Cross-sectional study	35 EoE patients	Children (<18 years)	A good nutritional state was observed in 82.8% of the enrolled children. In particular, 11.4% of enrolled children were overweight, whereas 5.7% were underweight.

BMI, body mass index; EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; WFL, weight-for-length.

To date, no research has investigated the possible pathogenetic role of obesity in EGID development. Putative explanations could probably be found in environmental and genetic risk factors and EGID-related comorbidities. The overall prevalence of EGIDs seems to higher in developed Western countries, where childhood obesity and atopic diseases were significantly increased through time [7,28]. Indeed, obesity and the Western lifestyle, mainly characterized by high calorie/fat consumption and reduced physical activity, might be directly related to the increased risk of developing allergic diseases, such as EGIDs [13]. In a study in mice, Silva et al. demonstrated that obesity aggravated the immune histopathological characteristics of the EoE experimental model, reducing the regulatory cytokines profile (low expression of forkhead box P3, FOXP3, and interleukin 10, IL-10), increasing the inflammatory mediators (IL-5 and thymic stromal lymphopoietin, TSLP), and promoting tissue remodeling [29]. These fascinating data might provide new insights about obesity as a possible EoE risk factor that might impair esophageal inflammation and symptoms.

Another possible pathogenetic mechanism might be the relationship between EoE and GERD. Diagnosis of GERD has also increased, especially in developed countries [7]. In half of the infants with refractory vomiting and regurgitation, GERD was also expressed in the underlying cow's milk allergy, and improved with a hydrolyzed formula [30]. Several studies reported that GERD might play a possible pathogenetic role in esophageal eosinophilia, more relevant in PPI-responsive patients [31]. Indeed, EoE and GERD are not mutually exclusive and might coexist [4]. Although there are no exact data, four mechanisms have been proposed to explain this association: (1) GERD only causes esophageal eosinophilia; (2) GERD and EoE coexist but are independent phenomena; (3) EoE induces GERD; (4) GERD contributes to or induces EoE [7,31]. Acid reflux alters the esophageal epithelial barrier, leading to high intestinal permeability, with a subsequent passage of food allergens and release of inflammatory and eosinophil chemoattractant molecules might trigger EoE in susceptible subjects [32].

On the other hand, the esophageal eosinophilic inflammation is also associated with the production of different proinflammatory cytokines that might impair peristalsis and the esophageal acid clearance [7,33]. The subepithelial fibrosis, a delayed complication

of EoE, might also promote esophageal dysmotility and GERD-related symptoms [31]. It is well described that being overweight and obese contribute to the development and worsening of GERD frequency and symptoms [34,35]. Obesity is notoriously involved in the pathogenesis of GERD [23]. Visceral fat might mechanically induce reflux events, increasing the intra-abdominal pressure [36]. Additionally, abdominal fat is metabolically active, activating macrophages, increasing and releasing proinflammatory cytokines and adipokines such as leptin [23,36].

Genes, obesity, and atopic diseases are linked. This association is well described in asthma patients, whereas no studies have been reported on EGID subjects. The β2-adrenergic (ADRB2) and glucocorticoid (NR3C1) receptor genes have been involved in the development of asthma and obesity [13]. Similarly, polymorphisms of the fractalkine receptor gene (CX3CR1) have been associated with asthma, atopy, and obesity [16]. However, no studies have described a genetic correlation between obesity/overweight and EGIDs.

Finally, EoE is characterized by chronic inflammation, specifically affecting the esophagus and generally sparing other GI tracts. This feature could clarify why EoE is not related to intestinal malabsorption and does not affect the bodyweight of adult patients.

The relationship between EGIDs, overweight, and obesity is still speculative, and further studies are required to confirm these clinical findings.

3. Undernutrition and Failure to Thrive in EGIDs Patients

Although poorly investigated, EGIDs may also be complicated by undernutrition and FTT for pathogenetic mechanisms similar to those reported in inflammatory bowel disease (IBD) patients [37]. FTT is one of the most commonly described clinical complications in children with EoE [3,38], although the exact prevalence has never been documented. Retrospective studies have reported that the prevalence of FTT ranges from 10.5% to 24% of EoE patients with different age-related rates (Table 3) [39–44]. In a large retrospective study, Spergel et al. demonstrated that FTT mainly characterized young children (2.8 ± 3.2 years) [44]. Moreover, Alhmoud et al. reported FTT and weight loss only in children with EoGE, and 15% of these had severe mucosal involvement leading to malabsorption [41].

Table 3. Studies reporting underweight and failure to thrive in children and adult patients with EGIDs.

Author, Year	Country	Study Design	Sample Size	Population	Outcomes
Hoofien et al., 2019 [39]	Europe	Multicentric retrospective study	410 EoE patients	Children	The most frequent indications for endoscopy were dysphagia (38%), gastroesophageal reflux (31.2%), food impaction (24.4%), and FTT (10.5%).
Chehade et al., 2018 [40]	U.S.A.	Multicentric study	705 EoE patients	Children and adults	FTT was present in 21.3% of enrolled subjects and was significantly common in children. Common pediatric comorbidities were neurological/developmental disorders, gastric tube placement, prematurity, atopic dermatitis, and food allergy.
Alhmoud et al., 2016 [41]	U.S.A.	Retrospective study	13 EoGE patients	Children and adults	FTT and weight loss were observed only in children. Two children (15%) had severe mucosal involvement leading to malabsorption, FTT, and weight loss.
Paquet et al., 2016 [42]	Canada	Retrospective study	62 EoE patients	Children	Sixty-two children were enrolled. Of these, 15 (24%) met at least one criterion for FTT.
Colson et al., 2014 [43]	France	Retrospective study	59 EoE patients	Children	Most children had negative WFH z scores, and 10% had nutritional indices compatible with moderate malnutrition. Nutrition therapy (elemental and six food elimination diets) did not impair nutritional status.
Spergel et al., 2009 [44]	U.S.A.	Retrospective study	620 EoE patients	Children	FTT/feeding issues and GERD-like symptoms were the most common presentations in the youngest children. (118 patients).

EoE, eosinophilic esophagitis; EoGE, eosinophilic gastroenteritis; FTT, failure to thrive; GERD, gastroesophageal reflux disease; WFL, weight-for-length.

Several factors may negatively impact the nutritional status of EGIDs patients (Table 4), mostly children. Firstly, children with EoE more likely present feeding disorders, recurrent vomiting, or regurgitation due to the esophageal inflammation and dysfunction, which can severely impair the adequate intake of foods and nutrients [2,3]. EGIDs are emerging GI disorders, therefore the diagnostic delay was often reported in adolescents and adults, who can consequently develop esophageal strictures due to the chronic inflammation and fibrous tissue deposition, prolonging clinical symptoms and patient feeding discomfort [45].

Table 4. Potential factors that may negatively influence the nutritional status of patients with EGIDs.

Chronic esophageal inflammation leading to typical GI symptoms: recurrent vomiting and regurgitation, loss of appetite, food impaction, GERD-like symptoms
Diagnostic delay may increase the risk of esophageal stricture and prolong GI discomforting symptoms
The low compliance to therapies may sustain esophageal inflammation, also allowing a low grade of antigen exposure
Swallowing disorders and fear of food impaction may compromise feeding behavior, allowing the development of food avoidance, anorexia, and anxiety
Restrictive food-elimination diets may reduce adequate food oral intake and lead to low levels of vitamins
Atopic (IgE mediated food allergy, atopic dermatitis) and non-atopic comorbidities (CD, IBD, type 1 diabetes mellitus, ASDs, CF) may be associated with FTT, low growth, reduced food oral intake, vitamins deficiency, and undernutrition
Multisite GI eosinophilic inflammation with subsequent abnormal permeability may be a possible reason for nutrients loss and higher caloric and protein requirements in patients with EGIDs distal to the esophagus

ASDs, autism spectrum disorders; CD, coeliac disease; CF, cystic fibrosis; FTT, failure to thrive; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IBD, inflammatory bowel disease.

Secondly, low compliance to treatment is one of the main reasons for therapeutic failure and persistent active EoE, especially in adolescents and adults [46]. Chronic GI symptoms and impaired oral food intake, due to the sustained esophageal inflammation and continued low-grade antigen exposure, through limited dietary compliance are other possible explanations for undernutrition.

Thirdly, children, adolescents, and adults with previous food impaction episodes may have a high risk of developing anxiety and eating disorders, such as nervous anorexia and food avoidance, leading to an inadequate nutrient intake [46,47]. In a case-control study, Wu et al. found that most children with EGIDs had feeding behavioral problems compared to healthy controls [48]. Another study showed that 16.5% of EGID children had feeding issues, such as food refusal, low volume, and variety of intake, grazing, and spitting food out [49]. Moreover, 21% of these children were also complicated by FTT, suggesting that feeding issues may impair the regular childhood oral intake contributing to undernutrition and growth failure [49].

Additionally, a retrospective multicentric U.S. study of Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) reported that 41% of children and adolescents with nonesophageal EGIDs might have a multisite GI inflammation [50]. This finding suggests that the persistent GI inflammation and subsequent abnormal intestinal permeability may be possible reasons for nutrients loss and higher caloric and protein requirements in patients with EGIDs distal to the esophagus [24].

Moreover, the association between EoE and other allergic conditions is well established and might be a potential further reason for FTT and undernutrition in EGIDs children. Children with EGIDs have an excessive prevalence of atopic dermatitis, IgE-mediated food allergy, asthma, and allergic rhinitis, potentially affecting the expected growth [51]. Moreover, several reports have suggested that EGIDs may also be frequently associated with chronic non-allergic comorbidities that might compromise adequate child growth,

feeding behavior, and quality of life [46]. In a cross-sectional study, Capuccilli et al. demonstrated that children with EoE also had higher rates of coexisting non-atopic diseases, including IBD (0.7%) and CD (5.6%), as well as a higher prevalence of autism spectrum disorders (ASDs) (7.5%), type 1 diabetes mellitus (1.2%) and cystic fibrosis (0.9%) [52].

Finally, an important unanswered question is whether therapies can influence FTT. Paquet et al. have reported that EoE-related FTT resolved in 62% of affected children, suggesting that medical interventions might be helpful not only for disease-remission but also for clinical complications [42]. However, these results cannot be generalized because this study was retrospective and based on a small number of patients (15 patients with EoE + FTT). On the other hand, it was widely described that impaired growth and inadequate intake of macro- and micronutrients are possible complications of restrictive food elimination diets, which are pivotal therapeutical approaches of several pediatric illnesses, including EGIDs [1]. Several clinical factors might induce protein–calorie malnutrition and impaired food intake with weight loss, FTT, and delayed puberty. These findings underly the importance of assessing potential risk factors that may bring dietary limitations and normal growth of children with EGIDs.

4. Vitamin D Deficiency in EGIDs

Low serum vitamin D levels have been proposed to explain the increased prevalence of atopic and autoimmune diseases in Western countries [53]. Several efforts have focused on the role of vitamin D in the contribution of chronic dysregulated inflammation and its modulation [53]. Prevalence of EoE is higher in Western countries and cold climate zones, suggesting a possible association with low serum vitamin D levels [7]. Increasingly, significant evidence has shown a consistent link between vitamin D deficiency—due to the quality of diet, lack of exposure to sunlight—and the risk of atopy, as already described for asthma, allergic rhinitis, food allergy, and atopic dermatitis [7].

A systematic review has reported that low vitamin D prevalence varied widely in enrolled studies (0–52%) and did not improve with therapy [24,54] (Table 5). Low levels of vitamin D were described in 42% of adults and 50% of children with EoE, prevailing in patients with symptoms of food impaction [54,55]. In a case-control study of 69 children, Waterhouse et al. reported that patients with EoE and GERD had low vitamin D levels compared to normal controls, but without a significant difference [56]. To date, no study assessed other vitamins in EGIDs and serum vitamin D in patients with EGIDs beyond the esophagus.

Table 5. Studies reporting levels of vitamin D in children and adult patients with EoE.

Author, Year	Country	Study Design	Sample Size	Population	Outcomes
Mehta et al., 2018 [24].	U.S.A.	Prospective study	91 patients (GERD = 38, EoE = 53)	Children (0–7 years)	Enrolled children had adequate nutrient intakes, except for vitamin D levels that were low in both groups.
Slack et al., 2015 [54].	U.S.A.	Cross-sectional study	69 EoE patients	Children and adults	The median vitamin D level was 28.9 ng/mL. Patients with low vitamin D levels were older (25.5 years) and had a higher body mass index (25.2 kg/m^2). Vitamin D insufficiency was not associated with IgE and surrogate markers of severity (dilation in adults or hospitalization or emergency visits in children).

EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease.

Although there is emerging evidence of vitamin D in the development of the immune system and pathogenesis of allergic diseases, such as asthma, atopic dermatitis, and food allergy, no studies have evaluated its possible role in EGIDs development and remission [53].

Furthermore, based on the design of available studies (cross-sectional data analysis) no cause–effect relationship can be inferred. It is reasonable to argue that toddlers and young children with EoE could present with feeding difficulty and refusal, with subsequent nutrient deficiencies, thus malnutrition. Besides, food elimination diets, mostly milk-free diets, could increase the risk of vitamin D deficiency in EoE patients, as reported in children with cow's milk allergy [57,58].

5. Management of EGIDs Patients: From Traditional Tools and Treatments to Future Insights

Diagnoses of EGIDs are not always straightforward and require chronic GI symptoms, coupled with suggestive endoscopic findings, prevalent eosinophilic inflammation (≥15 eosinophils/high-power field (HPF) for EoE) in biopsy specimens, and the exclusion of other causes of GI eosinophilia [1,4,5]. Symptoms of EGID are generally heterogeneous and often overlap with other conditions and may occur concomitantly. In EoE, the eosinophilic inflammation leads to progressive esophageal dysfunction, mainly characterized by feeding refusal and vomiting in children, and dysphagia, heartburn, and food bolus impaction in adolescents and adult patients [3]. Patients do not always appear to have feeding or eating disorders; only 24% of younger patients showed a failure to thrive. As reported in this review, most patients were normal weight or even obese. A meticulous evaluation of the patient's symptoms should be recommended, and the clinician should ask the right questions to detect suspicious eating habits (Table 6) [59].

Table 6. Useful questions to ask patients with EoE (Adapted from Muir et al., 2019) [59].

Does the patient take longer than others to eat?
Does the patient have to be reminded to chew a lot?
Does the patient need to cut food, especially steak, into small pieces?
Does the patient always need to drink during the meals?
Does the patient eat steak or crusty bread?

Although several research efforts have produced fascinating progress in the diagnosis and management of EGIDs, especially EoE, the only currently available tool to confirm the clinical suspicion is GI endoscopy with a biopsy [4,5]. Nevertheless, surrogate measures for EoE activity and response to therapy, such as the esophageal String test, transnasal esophagoscopy, and Cytosponge, have emerged as effective, less invasive tools for obtaining esophageal tissue samples [60,61].

Since EoE was initially identified in the mid-1990s, multiple EoE treatment strategies have been developed. Dietary treatment represented the first-line therapeutical approach for EGIDs [1,4,5]. Elemental (exclusive amino acid-based formulas) and six-food (milk, wheat, egg, soy, fish and shellfish, nuts) elimination diet (SFED) are the two main nutritional methods for EGID management with high rates of remission [1,4,5]. Trials have reported that a significant proportion of EoE patients achieved histologic remission on less restrictive (two/four food elimination) diets. Thus, personalized dietary strategies might offer the greatest success, improving the nutritional status and quality of life of affected subjects [60]. Successful targeted removal of specific foods based on allergy tests have been reported as case reports. However, targeted food removal might not be effective and is not recommended, because response to therapy did not seem to correspond to food allergies identified by skin prick testing or measuring serum food-specific IgE concentrations [62].

Swallowed steroids are alternative EGID treatments to diet-based interventions. The two most common approaches include swallowed fluticasone and viscous budesonide [4,5]. Comparisons between elimination diets and swallowed steroids are difficult, due to the heterogeneity of available studies. Meta-regression analyses showed that both therapeutical approaches are generally equivalent at inducing histologic remission in EGIDs patients [63].

Unfortunately, a significant population of patients with EGIDs has persistent active disease. Therefore, several ongoing efforts identify promising biological therapies beyond diet or steroid strategies [60,64]. Future efforts should be targeted to particular EGID endotypes using traditional and biologic therapies to achieve a new and high disease control degree.

How to Manage Malnutrition in Children with EGIDs?

This study suggests that a multidisciplinary approach (allergist, gastroenterologist, nutritionist, psychologist) is a key winner of EGIDs management (Figure 2), especially in children with allergic and non-allergic phenotypes. Moreover, the nutritional status assessment may help recognize patients with an inadequate nutrient intake, especially if they require restrictive food elimination diets (Figure 3).

Figure 2. The multidisciplinary approach of children and adolescents with eosinophilic gastrointestinal disorders.

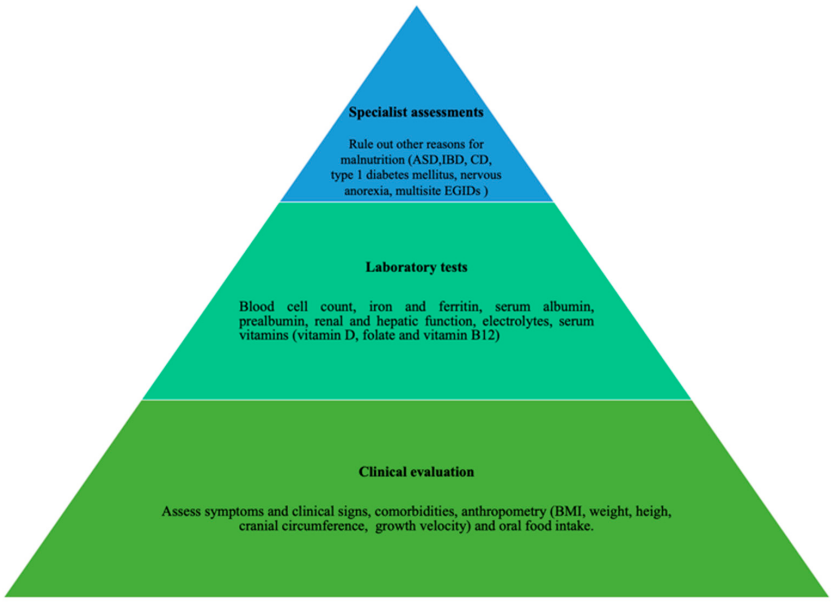

Figure 3. Nutritional status assessment of children and adolescents with eosinophilic gastrointestinal disorders.

This review summarized evidence on pediatric EGIDs malnutrition and underly conflicting findings. While some studies have reported normal or high BMI, especially in adults with coexisting GERD, FTT might mostly afflict young children. As reported for allergic diseases, EGIDs may also show vitamin D deficiency. However, no study has assessed how intestinal inflammation or EGIDs therapies may impact serum vitamin D and bone metabolism. Despite an inadequate investigation, EGID malnutrition is a relevant clinical field that requires further efforts to strengthen the efficacy of therapies and improve the patients' quality of life.

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SUPPLEMENT ARTICLE

WILEY

Nutritional status in eosinophilic gastrointestinal disorders: A pediatric case-control study

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Abstract

Eosinophilic gastrointestinal disorders (EGIDs) represent an emerging group of heterogeneous diseases associated with failure to thrive, weight loss, protein-losing enteropathy, and malnutrition. To date, no studies have assessed the nutritional status, vitamin D, and other vitamin levels in patients with non-esophageal EGIDs. We aim to evaluate the nutritional profile of a cohort of children and adolescents with EGIDs. We performed a case-control study, enrolling a total of 98 patients, 38 (39%) patients with EoE, 22 (22%) patients with non-esophageal EGIDs, and 38 (39%) patients with non-allergic controls. Children with EGIDs had both mean ferritin and mean hemoglobin levels, together with other values such as folates and vitamin B12, within normal range and therefore did not have anemia. Albumin and prealbumin levels were within normal limits. Patients with EGIDs have mean vitamin D values slightly higher than non-allergic controls. Although this study is retrospective and referred to only one pediatric center, we found that Italian children and adolescents with EGIDs are neither malnourished nor deficient in vitamin D compared with controls.

KEYWORDS
adolescents, children, eosinophilic esophagitis, Eosinophilic gastrointestinal disorders, nutritional status, vitamin D

1 | INTRODUCTION

Primary eosinophilic gastrointestinal disorders (EGIDs) are emerging inflammatory diseases of unknown etiology which may involve any part of the gastrointestinal (GI) tract and lead to a pathological eosinophilic mucosal infiltration.[1,2] Although their pathogenic mechanisms are mostly unknown, EGIDs seem to be commonly associated with atopy.[3] Based on the GI tract involved, EGIDs are classified in eosinophilic esophagitis (EoE) and non-esophageal EGIDs. EoE is currently considered one of the major causes of upper gastrointestinal morbidity, with a significant burden on patients, caregivers, and the healthcare system.[4] Children with non-esophageal EGIDs may present non-specific GI symptoms, mainly depending on depth (mucosal, muscular, and serosal forms) and the extension of the inflammatory process.[1] On the contrary, patients with EoE generally develop symptoms due to esophageal dysfunction and inflammation. Although the prevalence is still unknown, several studies reported that EGIDs may be associated with malnutrition, including undernutrition, inadequate intake of vitamins and/or minerals, and overweight/obesity.[4] Vitamin D deficiency has also been reported in

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children with EoE with conflicting results.[5] To date, no studies have assessed the vitamin D and other vitamin levels in patients with non-esophageal EGIDs.

This study aims to evaluate the nutritional status of a cohort of children and adolescents with EGIDs, comparing to non-allergic controls and primarily focusing on BMI values and vitamin D levels.

2 | MATERIAL AND METHODS

We performed a case-control study, enrolling patients with EGIDs followed at the Center for Pediatric Eosinophilic gastrointestinal Disorders (CPED) in Pavia. The diagnosis of EoE was made according to current guidelines.[6] As there are no consensus guidelines for the diagnosis of non-esophageal EGIDs, we reviewed pathology reports based on the pathological cutoffs proposed by Collins et al (stomach ≥30 eos/HPF, small intestine ≥50 eos/HPF; ≥54 eos/HPF at ileum, right colon ≥100 eos/HPF, transverse and left colon ≥84 eos/HPF, rectosigmoid colon ≥64 eos/HPF).[1] Controls were non-allergic children and adolescents diagnosed with functional GI disorders (irritable bowel syndrome, functional constipation/diarrhea/dyspepsia) made according to the Rome IV criteria.[7] Patients <19 years were enrolled. All patients with a secondary cause of pathological eosinophilic inflammation of the GI tract, inflammatory bowel diseases, or coeliac disease were excluded. Data collected from enrolled patients included demographics (age at diagnosis, gender, ethnicity) and nutritional profiles. For each enrolled individual, we evaluated serum 25-hydroxy-vitamin D levels and body mass index (BMI). We also investigated the nutritional status of patients with EGIDs determining serum levels of folates, vitamin B12, albumin, prealbumin, hemoglobin, and ferritin. All data were extracted from electronic medical records (Ormaweb™ and Fenix™, Software) and entered into a spreadsheet. We replaced every patient identifier (patient name) with a specific numeric code. Informed consent was obtained from all participants.

Continuous variables were expressed as means and standard deviation (SD), while categorical variables were reported as numbers and percentages. Frequencies were tabulated for categorical variables. Bivariate analysis of categorical variables was conducted with the chi-square test or Fisher's exact test. Student's t test and Kruskal-Wallis test were used to compare continuous variables. A p-value less than .05 was considered significant. All analyses were performed using GraphPad Prism 8 for Mac, version 8.4.3 (GraphPad Software, San Diego, CA, USA).

Key Messages

Vitamin D deficiency has been reported in children with eosinophilic gastrointestinal disorders (EGIDs) with conflicting results. To date, a few studies and no Italian articles assessed the vitamin D and other vitamin levels in patients with EGIDs.

Italian children and adolescents with EGIDs are neither malnourished nor deficient in vitamin D when compared to controls.

Further, more extensive and multicentric studies should be realized to investigate the nutritional status and vitamin profile of children with EGIDs.

3 | RESULTS

We enrolled a total of 98 patients, 38 (39%) with EoE, 22 (22%) patients with non-esophageal EGIDs, and 38 (39%) patients as non-allergic controls (Table 1). Male sex was prevalent in patients with EGIDs compared to controls. In children with EGIDs, there is no statistical difference in BMI values and prevalence of obese patients (p .52 and p .70, respectively) (Table 2). The mean vitamin D levels were a bit below the normal limit in children with non-esophageal EGIDs compared to those with EoE (27.1 ng/mL and 32.2 ng/mL, respectively). Children with EGIDs had both mean ferritin and mean hemoglobin levels, together with other values such as folates and vitamin B12, within normal range and therefore did not have anemia. Albumin and prealbumin levels were within normal limits.

The mean value of vitamin D was higher in patients with EGIDs (32.2 ng/ml in the EoE group and 27.1 ng/ml in the non-esophageal EGIDs group) than non-allergic controls (20.0 ng/ml), despite there was no statistically significant difference (p .05) (Table 3, Figure 1(A)). The BMI of children with EGIDs (19.0 kg/m^2 in the EoE and 18.1 kg/m^2 in the non-esophageal EGIDs group) is similar to that of the control group (19.4 kg/m^2), with no statistical difference (Figure 1(B)).

4 | DISCUSSION

To date, a few retrospective studies and no articles in Italy assessed the nutritional status of patients with EGIDs. Despite several limitations (Table 4), these preliminary data showed that Italian children

TABLE 1 Demographic features of enrolled patients

	EoE ($n = 38$)	Non-esophageal EGIDs ($n = 22$)	Controls ($n = 38$)
Age, *mean ± SD*	9.9 ± 5.1	9.0 ± 4.1	9.2 ± 4.4
Males, *n (%)*	29 (76.3)	15 (68.2)	18 (47.3)
Caucasians, *n (%)*	29 (76.3)	21 (95.5)	34 (89.5)

Abbreviations: EGIDs, eosinophilic gastrointestinal disorders; EoE, eosinophilic esophagitis; SD, standard deviation.

TABLE 2 Nutritional status of patients with EGIDs

Nutritional status	EoE	Non-esophageal EGIDs	p-value
BMI (kg/m^2), *mean ± SD*	18.9 ± 5.0	18.1 ± 3.6	.52
Obese patients, *n (%)*	4 (10.5)	3 (13.6)	.70
Vitamin D (ng/mL), *mean ± SD*	32.2 ± 20.0	27.1 ± 10.1	.50
Folates (ng/mL), *mean ± SD*	7.5 ± 3.7	10.2 ± 6.5	.17
Vitamin B12 (ρg/mL), *mean ± SD*	564.1 ± 332.5	598.0 ± 288.7	.80
Albumin (mg/dL), *mean ± SD*	4263.0 ± 330.4	4188.0 ± 413.4	.60
Prealbumin (mg/dL), *mean ± SD*	19.4 ± 4.6	20.7 ± 4.0	.50
Hemoglobin, *mean ± SD*	13.1 ± 1.1	13.5 ± 1.0	.13
Ferritin, *mean ± SD*	33.4 ± 19.7	29.7 ± 10.3	.5

Note: Normal values: albumin 3500–5200 mg/dL; folates 2–19.9 ng/mL; hemoglobin 12–17 g/dL; ferritin ng/mL (18–440) F (8–120); prealbumin 20–40 mg/dL; vitamin B12 243–894 ρg/mL; vitamin D 30–100 ng/mL.

Abbreviations: BMI, body mass index; EGIDs, eosinophilic gastrointestinal disorders; EoE, eosinophilic esophagitis; SD, standard deviation.

TABLE 3 BMI values and vitamin D levels of enrolled patients

	EoE	Non-esophageal EGIDs	Controls	p-value*
BMI (kg/m^2), *mean ± SD*	18.9 ± 5.0	18.1 ± 3.6	19.4 ± 5.0	.63
Vitamin D (ng/mL), *mean ± SD*	32.2 ± 20.0	27.1 ± 10.1	20.0 ± 6.0	.05

Abbreviations: BMI, body mass index; EGIDs, eosinophilic gastrointestinal disorders; EoE, eosinophilic esophagitis; SD, standard deviation.

**Kruskal-Wallis test.*

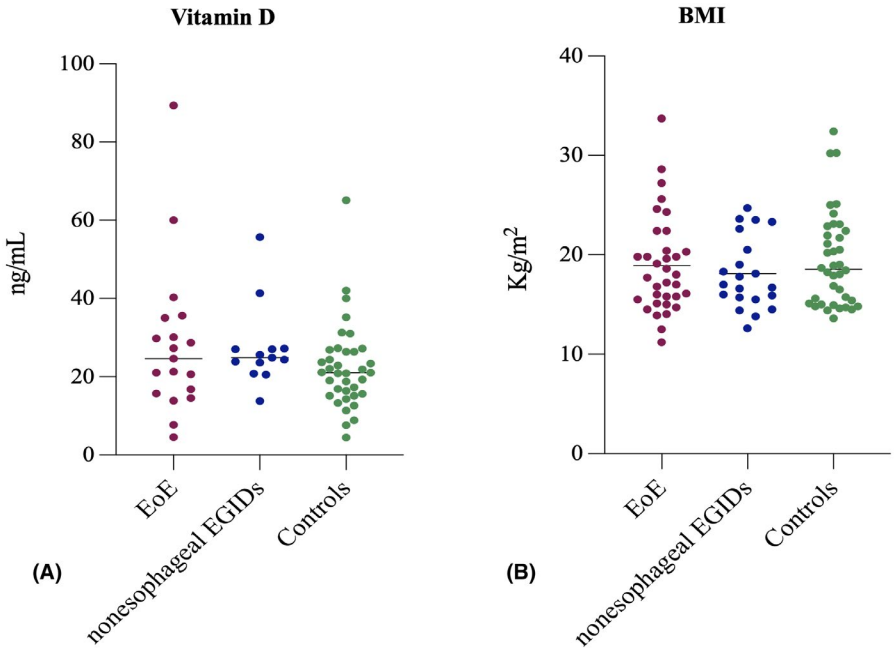

FIGURE 1 (A)Vitamin D levels of enrolled patients. (B) BMI values of enrolled patients

and adolescents with EGIDs are neither malnourished nor deficient in vitamin D, compared with non-allergic controls. Almost all values concerning the nutritional profile were within normal limits, and none of the children with EGIDs showed signs of anemia or protein-losing enteropathy. There is still limited published literature on vitamin deficiencies associated with EGIDs both pre-intervention

TABLE 4 Limitations and strengths of the study

Limitations	Strengths
• Retrospective and monocentric pediatric study with a small sample size. • Lack of consensus criteria for the diagnosis and therapy of non-esophageal EGIDs. • Vitamin D levels and BMI values were assessed at diagnosis. These values may be influenced by treatment, and the absence of follow-up data did not allow to evaluate their modification over time. • Controls are non-allergic children with functional gastrointestinal (GI) disorders. It is still unclear whether BMI and vitamin D may be related to the development or the worsening of functional GI diseases.	• First Italian pediatric study that assessed the nutritional status of children and adolescents with eosinophilic gastrointestinal disorders (EGIDs), mainly focusing on vitamin D. • Although retrospective, we realized a case-control study. • Italian children and adolescents with EGID are neither malnourished nor deficient in vitamin D compared with non-allergic controls. • EGIDs-related malnutrition is a clinical field that requires further effort to strengthen the efficacy of therapies and ensure a good patient's quality of life. • A multidisciplinary approach (allergist, gastroenterologist, nutritionist, psychologist) is a winner key of EGIDs management.

and post-intervention.[5]Statistically, there was no difference in BMI values and prevalence of obese patients. Obesity is a global health problem associated with many chronic diseases. The pediatric obesity epidemic and obesity-related inflammation could be responsible for the increased prevalence of allergic disorders, including EGIDs.[5] To date, no study has investigated the possible role of obesity in EGIDs development. New insights about obesity as a possible EoE risk factor that may impair esophageal inflammation and symptoms are uncovered, but a tangible link between obesity and other allergic disorders, including EGIDs, is yet to be established.[5]

The mean vitamin D levels of children with EGIDs were slightly higher than those found in healthy controls. However, when considering the standard deviation of the mean vitamin D level of children with EGIDs, it can be inferred that lower levels of vitamin D were present among them. Vitamin D deficiency is mainly due to the quality of diet and the lack of sun exposure. Vitamin D has been shown to have a direct influence on immune function, inhibiting human dendritic cells and inducing T regulatory cells. Moreover, there is growing evidence on the influence of vitamin D on the pathogenesis of allergic diseases, such as asthma, atopic dermatitis, and food allergies.[8,9] Possibly, vitamin D deficiency could be somehow related to the pathogenesis of EGIDs, giving the fact that the prevalence of EoE is higher in Western countries and cold climate zones.[5] Vitamin D appears to play a role in maintaining the intestinal mucosal barrier and altering gene expression in smooth muscle cells, affecting pathways for cell recruitment, growth, and survival, which could contribute to tissue remodeling.[8] Low levels of vitamin D were reported in 42% of adults and 50% of children with EoE, clinically characterized by symptoms of food impaction.[5] Such data on non-esophageal EGID are yet to be reported. In our study, we could not demonstrate a possible link between vitamin D deficiency and EGIDs, possibly because of the small sample size and the retrospective study design. More research is needed on the causal relationship of vitamin D when it comes to EGIDs and if supplementation would aid remission. Further, more extensive studies should be carried out to investigate whether vitamin D deficiency in children with EGIDs is just a circumstantial coincidence as a side effect of personal lifestyle or medical restriction of sources due to other comorbidities such as allergies.

CONFLICT OF INTEREST

The authors declare they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Martina Votto: Conceptualization (equal), methodology (equal), and writing—original draft (equal). **Giacomo Bonitatibus**: Writing—review & editing (equal). **Maria De Filippo**: Writing—review & editing (equal). **Serena Anjali Pitigalage Kurera**: Writing—review & editing (equal). **Ilaria Brambilla**: Methodology (equal) and writing—review & editing (equal). **Carmen Guarracino**: Methodology (equal) and writing—review & editing (equal). **Mara De Amici**: Methodology (equal). **Gian Luigi Marseglia**: Supervision (lead) and writing—review & editing (equal). **Amelia Licari**: Conceptualization (equal), supervision (lead), and Writing—review & editing (equal).

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REVIEW

NOVEL INSIGHTS INTO PEDIATRIC ALLERGY AND IMMUNOLOGY

Behavioral issues and quality of life in children with eosinophilic esophagitis

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ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic disease characterized by symptoms related to esophageal dysfunction and eosinophil-predominant inflammation (≥15 eosinophils/high power field). In the last ten years, several epidemiological studies showed a significant increase in the incidence and prevalence of EoE, especially in children in Western Countries. Although EoE often presents with gastrointestinal symptoms, adults and children may develop extraintestinal symptoms and behavioral issues. Also, the chronic nature of the disease, long-term therapies, and strict follow-up may impair the quality of life of patients and their family. This review summarizes current knowledge on the behavioral and psychosocial issues and quality of life of children and adolescents with EoE and their caregivers.

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KEY WORDS: Eosinophilic esophagitis; Child; Quality of life; Mood disorders.

Eosinophilic esophagitis (EoE) is a chronic, allergic esophageal disease characterized by symptoms related to esophageal dysfunction and eosinophil-predominant inflammation (≥15 eosinophils/high power field).[1] The main antigen triggers are foods.[1] EoE affects about 1/2000 patients in the USA, with a higher prevalence rate in adults (43.4/100,000) than in children (29.5/100,000), prevailing in Caucasian patients and male sex.[2] In the last ten years, several epidemiological studies showed a significant increase in the incidence and prevalence of EoE, especially in children in Western Countries.[3-5] Although EoE often presents with gastrointestinal (GI) symptoms (Table I), adults and children may develop extraintestinal symptoms and behavioral issues. Also, the chronic nature of the disease, long-term therapies, and strict follow-up may impair the quality of life (QoL) of patients and their family.

This study aims to realize an extensive review of the current knowledge on the behavioral and psychosocial issues of children and adolescents with EoE.

A scoping review of articles was performed via the online database PubMed, combining the terms "eosinophilic esophagitis" AND "children" AND "quality of life" and "eosinophilic esophagitis" AND "children" AND "anxiety." All studies that met the following criteria were included: 1) cross-sectional and cohort studies published in English in a peer-reviewed journal;

TABLE I.—*Symptoms and signs of EoE.*

Infants and children	Adolescent and adults
Feeding difficulties	Decreased appetite
Food aversion	Heartburn
Decreased appetite	Early satiety
Heartburn	Chest pain
Chest pain	Nausea
Abdominal pain	Regurgitation
Gagging	Uncommon sialorrhea
Nausea	Vomiting
Regurgitation	Dysphagia
Vomiting	Food impaction
Slow growth/failure to thrive/weight loss	
Cough after eating	
Dysphagia	
Food impaction	

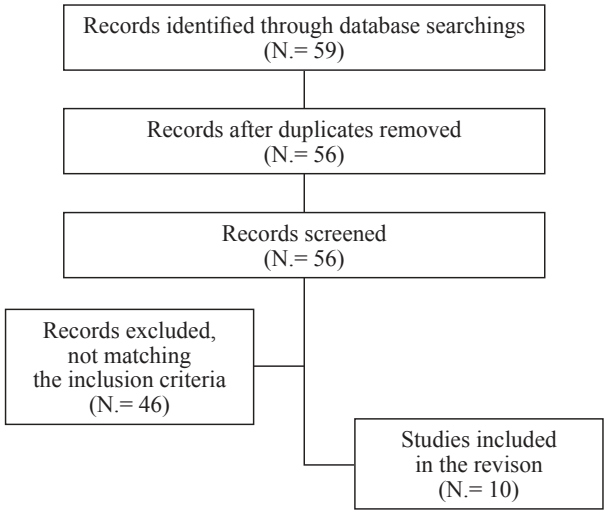

Figure 1.—Inclusion criteria and search strategy.

2) participants were children and adolescents with a diagnosis of EoE; and 3) anxiety, depression, and QoL were assessed using standardized tools. Potentially eligible publications were manually screened and reviewed, and nonrelevant publications were excluded (Figure 1).

Why and how can EoE impact the patient's behavior and mood?

The QoL and behavior of patients with EoE may be influenced by several clinical factors (Table II).

Firstly, symptoms of EoE typically depend on the patient's age and may often be underestimated, mostly in the pediatric age.[1, 6, 7] Patients generally appear in good health, and symptoms may manifest upon the ingestion of solid foods. Besides, symptoms may often overlap or occur concomitantly with other GI conditions, mainly the gastroesophageal reflux disease. These clinical features may often delay the diagnosis of EoE, especially in young children and toddlers. Infants and children might present a wide variety of nonspecific symptoms, including feeding difficulty, nausea, vomiting, heartburn, and failure to thrive. In contrast, teenagers and adults are more likely to present with dysphagia and episodes of food impaction. Nevertheless, patients of different age groups may develop compensatory changes in eating habits, such as eating slowly, chewing carefully, cutting food into small pieces, lubricating foods with sauces, drinking liquids to dilute foods, and avoiding pills and foods (meat and bread) likely to cause dysphagia.[1] Also, patients may be afraid to eat in public places and worried about eating difficulty.[1]

Secondly, the gold standard for the diagnosis of EoE is the esophageal biopsy, endoscopically obtained, demonstrating increased intraepithelial esophageal eosinophil counts, without concomitant eosinophilic infiltration in other GI tracts.[8] Upper endoscopy requires general anesthesia in children and conscious sedation in adults. Also, upper GI endoscopy is an invasive and expensive procedure that is currently the only diagnostic tool to assess the esophageal inflammation during the follow-up and in response to therapy.

Thirdly, once the diagnosis is established, EoE management often requires significant dietary

TABLE II.—*Main stressful factors that may induce behavioral and mood issues and impaired quality of life in children and adolescents with EoE.*

Clinical issues
Recurrent or chronic GI symptoms
Most GI symptoms are often non-specific and may overlap with other GI diseases, delaying the diagnosis of EoE.
Patients may develop compensatory changes in eating habits (eating slowly, chewing carefully, cutting food into small pieces, lubricating foods with sauces, drinking liquids to dilute foods, and avoiding pills and foods).
EoE may be associated with other disabling diseases: • allergic diseases (IgE-mediated food allergies, asthma, atopic dermatitis, allergic rhinitis); • autoimmune diseases (coeliac disease, inflammatory bowel diseases, thyroiditis; • chronic monogenic diseases (cystic fibrosis, collagen's disorders); • neuropsychiatric diseases (autism and ADHD).
Patients may develop clinical complications (failure to thrive, weight loss, asthenia, delayed puberty, need to enteral feeding).
Illness stigma, especially in patients with IgE mediated food allergy or other chronic diseases.
A negative experience of eating in public with other children.
Parents' anxiety.
Diagnostic issues
Currently, upper endoscopy is the only validated diagnostic tool to monitor the response to therapy and the esophageal inflammation.
Upper endoscopy requires general anesthesia in children and conscious sedation in adults.
Strict follow-up (with several upper endoscopies and constant medical evaluations).
Therapeutic issues
Long-term therapies.
Parents 'fear of potential side effects of long-term therapies (especially failure to thrive in children).
Restrictive diets and changes in eating habits.
Give up favorite foods and meals.
Failure to thrive and feeding difficulties may be treated with exclusive aminoacidic formula through nasal-gastric or G-tube.

ADHD: Attention Deficit Hyperactivity Disorder; EoE: eosinophilic esophagitis; GI: gastrointestinal; G-tube: gastrostomy tube.

restrictions, several follow-up endoscopies, and, in specific cases, the gastrostomy tube (G-tube) feeding, which may also affect childhood psychosocial development. There are three main therapeutic approaches: diet therapy, swallowing topical steroid, and esophageal dilatation. Choosing between these therapies is dependent on the patient's lifestyle and therapeutic compliance, QoL, and severity of esophageal inflammation. Also, since clinical symptoms of EoE do not always correlate with histologic findings, endoscopy with biopsies should be performed approximately 3-4 months after therapy is started or changed.

Arias *et al.* reported that the elemental diet with amino acid formula induced histologic remission in more than 90% of treated children.[9] In adults and teenagers, the compliance to elemental diet is reduced by taste, restricted meal variety, and lack of insurance coverage.[9] Also, several numbers of endoscopies are required to identify specific triggers during food reintroduction. Given the difficulties of the elemental diet, several studies have successfully proposed the empiric food-elimination diet.[9] The 6-food elimination diet (SFED) eliminates cow's milk, egg, soy, wheat, peanuts/tree nuts, and fish/shellfish, and showed a histologic remission in about 74% of affected children.[10-12] Both in adults both in pediatric populations, milk, wheat, egg, and soy have been identified as the most common food triggers for EoE, leading to investigation of the 4- and 2-food elimination diets.[13, 14] The dietary approach requires a long time and undergo multiple endoscopies before finding the allergen trigger.[15]

Fourthly, EoE might progresses to esophageal remodeling and stricture when left untreated or when patients are unresponsive to therapies.[16, 17] The prevention of esophageal fibrosis requires early diagnosis and treatment, strict follow-up, and high patient compliance. Schoepfer *et al.* demonstrated that the prevalence of esophageal strictures was correlated with the duration of untreated disease, suggesting that it is fundamental to minimize the diagnostic delay that mainly occurs in childhood.[18]

Finally, for children and adolescents with EoE, the QoL is further impacted by additional medical disorders. In the last years, several stud-

ies allowed to recognize different phenotypes of EoE, based on clinical features and the medical history of affected patients. Children with EoE may often present one or more allergic comorbidities (asthma, IgE mediated food allergy, atopic dermatitis, allergic rhinitis). On the other hand, a significant amount of EoE patients shows non-atopic comorbidities, mostly autoimmune disorders and monogenic diseases.[19] Chronic atopic and non-atopic diseases may further impair the QoL and the mental health of children and adolescent with EoE, increasing the number of therapies and specialist consultations.

EoE is a chronic inflammatory disease of the esophagus affecting people at any age. Symptoms are often recurrent and may compromise normal feeding and eating habits. Diagnosis is often delayed, and when achieved, affected patients are treated with long term therapies that required a strict endoscopic follow-up. Therapies are effective but characterized by poor compliance, due to expensive cost, diet limitations, nutritional changes, poor palatability of amino-acidic formula, and long-term administration. Taken together, chronic symptoms, feeding issues, long-term therapies, and a strict endoscopic follow-up may impair the behavioral health and QoL of patients and their families.

Behavioral issues and quality of life in children and adolescents with EoE

Children with chronic diseases are more likely to develop psychosocial and behavioral issues in comparison with healthy children.[20] Generally, a few studies and clinical reports described significant effects on behavioral and psychosocial aspects in patients with EoE, particularly in children (Table III).[21-27] Moreover, depression and mood issues were less investigated compared to anxiety.

A recent review by Taft *et al.* showed that children and adolescents with EoE had higher rates of anxiety and depression symptoms, which increased with age.[28] In a cross-sectional study of 705 patients, Chehade *et al.* reported symptoms of anxiety and depression in above 15% of enrolled children and adolescents, confirming the increased prevalence with age.[26] In a less recent study, Cortina *et al.* reported that about 43% of children and adolescents with eosinophilic GI diseases developed depressive symptoms, anhedonia, anxiety, and negative mood, mainly due to the fear of their chronic clinical condition and recurrent GI symptoms.[21] Similar results were showed by Harris *et al.*, who reported 41% of anxiety symptoms among children with EoE.[23] Klinnert *et al.* also confirmed higher rates of behavioral issues in children with G-tube for feeding difficulty or with multiple IgE-mediated food allergies.[29] Anxiety symptoms most likely seem to arise from worries of chronic symptoms, long-term therapies (dietary restrictions), G-tube, and recurrent endoscopies.[29]

Furthermore, in children and adolescents with EoE, depressive, and anxiety symptoms might appear with panic disorders and impaired adherence to therapy, sleep, and school attendance.[25, 30] A recent retrospective study by Reed *et al.*, evaluated the rate of EoE patients (adults and children with a mean age of 26.6 years) with psychiatric comorbidity, reporting that the 28% of participants had a mood issue (mainly anxiety or depression), treated pharmacologically.[27]

The term quality of life (QoL) denotes a comprehensive multidimensional concept that usually includes subjective considerations of both positive and negative aspects of life.[31] Health is considered the main domain that affects the overall QoL. Since the 1980s, the concept of health-related quality of life (HRQoL) has evolved to include those aspects of QoL that can affect the physical and mental health.[32-35] In clinical practice, the evaluation of HRQoL allows one to assess: 1) the mental and health impact of chronic disease; 2) the burden of preventable chronic disease and disabilities; and 3) the disease progress.[32] In children, chronic diseases are generally characterized by impaired HRQoL, according to recurrent or persistent disease-flares, long-term therapies, and strict clinical follow-up.[36] Although long-term therapies may induce a psychosocial issue, their positive impact on symptoms might subsequently improve the QoL of patients. Symptoms, diagnostic endoscopies, and standard treatments may negatively impact the QoL and mental health of children with eosinophilic GI diseases, including EoE.[21, 29, 37] Lynch

TABLE III.—*Summary of the main pediatric studies on behavioral and mood issues in children with EoE.*

Author and year	Study design	Sample size	Median age of participants (years)	Assessment of behavioral variables	Results
Cortina *et al.*, 2010[21]	Cross-sectional	108 children with EGIDs	8.5	BASC, CDI, MASC, PedsQL	A higher percentage of children and adolescents (45.3%) with eosinophilic GI disorders demonstrated levels of internalizing symptoms. Patient reported depressive symptoms, anhedonia, and negative mood compared to controls anhedonia. Also, they reported physical symptoms of anxiety and autonomic arousal than controls.
Hommel *et al.*, 2012[22]	Cross-sectional study	96 children and adolescents	8.3	BASC-2.	Maternal report of internalizing behavioral symptoms (anxiety and depression), particularly depression, is significantly associated with non-adherence in patients with EoE.
Harris *et al.*, 2013[23]	Retrospective study	64 children	7.1	Behavioral health clinicians' reports.	Sixty-nine percent of children experienced some form of psychosocial problems, including social difficulties (64%), anxiety (41%), sleep difficulties (33%), depression (28%), and school problems (26%). Older children experienced more adjustment difficulties than younger children. Sleep disturbances and feeding problems predominated in younger children, while anxious behavior and depressive feelings increased with age. Children with G-tubes had more social, school, and psychological problems than those without.
Case *et al.*, 2017[24]	Cross-sectional study	46 family of children with EoE	7.8	Three questionnaires: RCADS, SCARED, and PedsQL EoE, 3.0	50% of children reported a high frequency of worry, anger, and sadness due to restriction diets.
Jose *et al.*, 2017[25]	Cross-sectional study	20 children	13	SCARED	Parents of children with EoE reported more symptoms of anxiety, panic disorder, and school avoidance compared to healthy children.
Chehade *et al.*, 2018[26]	Cross-sectional study	705 children	11.2	Patients responded to their medical history. All data were collected in a multi-center registry.	Around 15% of subjects reported depression and anxiety, which increased in prevalence with age.
Reed *et al.*, 2020[27]	Retrospective study	883 children and adults	26.6	The database contains data extracted from electronic medical records.	Two thousand and forty-one patients (28%) had psychiatric comorbidity, treated pharmacologically. The most common diagnosis was anxiety (23%), followed by depression (17%). Cases with EoE with a psychiatric diagnosis were more likely to be women, white, and 18 years or older and to have more prolonged symptoms duration before diagnosis.

BASC (-2): Behavior Assessment System for Children, 2nd edition; CDI: Children's Depression Inventory; MASC: Multidimensional Anxiety Scale for Children; RCADS: Revised Child Anxiety and Depression Scale; SCARED: Screen for Child Anxiety Related Disorders; PedsQL EoE, 3.0: Pediatric Quality of Life Eosinophilic Esophagitis Module Version 3.0.

et al. reported that epigastric pain is the main predictor of poor physical and psychosocial HRQoL in enrolled children and their caregivers.[38] In a prospective and multicentric study, Klinnert *et al.* reported that children with EoE had a diminished HRQoL compared to healthy individuals, and the diminished QoL was associated with symptom severity. During the follow-up period, as symptom severity decreased according to prescribed therapy, HRQoL concomitantly improved.[39] Therapies for EoE plays a double and conflicting role in the psychosocial and mental health of affected children. On one side, steroid and diet therapies represent long term treatments burdened by side effects and food restriction; on the other side, in the vast majority of children, they concomitantly improve GI symptoms and QoL of children with EoE.

In children and adolescents with EoE, psychosocial issues and low QoL increase with age and severity of disease-flares; also, they often impair social activities and are mainly due to the chronic nature of symptoms, change of eating habits, therapies, and strict endoscopic follow-up (Table IV).[38-40]

How do families live with the disease of their children?

Pediatricians who take care of children and adolescents with chronic diseases may also consider the anxiety and psychosocial aspects of families. Chronic diseases may negatively impact the QoL of every family member. Parents of chronically ill children reported increased emotional stress and financial burdens, limiting the social life.[41]

In families of EoE children, the QoL of caregivers was significantly affected compared with that of healthy children.[37] A recent systematic review of Mukkada *et al.* confirmed that EoE has a significant impact on overall HRQoL of affected patients, resulting in restrictions on daily life for their caregivers and families.[42] Several issues re-

TABLE IV.—*Summary of the main pediatric studies on the quality of life of children with EoE and their families.*

Author and year	Study design	Sample size	Median age of participants (years)	Assessment of behavioral variables	Results
Klinnert *et al.*, 2014[39]	Prospective, longitudinal, multicentered study	97 children and their caregivers	7.7	HRQoL was measured with the PedsQL parent proxy-report, child self-report, and FIM.	Patients with EoE and their families had diminished QoL compared to healthy individuals. The diminished QoL was associated with increased symptom severity, and, on average, QoL improved over time.
Lynch *et al.*, 2018[38]	Cross-sectional study	91 children and their caregivers	8.7	Children and their caregivers completed questionnaires addressing HRQoL and EoE symptoms.	In children's reports, epigastric pain was found to be a significant predictor of poor physical and psychosocial HRQoL. In caregiver reports, epigastric pain resulted in being a significant predictor of poor physical HRQoL.
Hiremath *et al.*, 2019[40]	Case-control study	42 family of children and adolescents with EoE	11	Caregivers provided the assessment of the eating behavior of their child with CEBQ and FS-IS questionnaires.	Caregivers reported that their child's feeding or swallowing problems adversely impacted the quality of their life. Also, in FS-IS, caregivers indicated that they were worried about the way their child would breathe or if the child would choke while feeding, and reported that it was hard for them to feed their child as it took a long time to prepare liquids and foods the "right" way.

CEBQ: Child Eating Behavior Questionnaire; FIM: Family Impact Module; FS-IS: Feeding/Swallowing Impact on Children's Caregivers Questionnaire; HRQoL: Health-Related Quality of Life.

lated to the disease may affect the QoL of parents and family members of EoE patients.

Firstly, parental anxiety often arises from the clinical condition of their children and the difficulty of deciphering and monitoring GI symptoms, especially in infants and toddlers.[29] Weak growth, feeding difficulty, episodes of food impaction were the most common sources of worries and anxiety of parents.[29] Parents were often worried about the breath and chewing of their child during mealtime and were afflicted by the fear of administering foods wrongly.[40]Also, caregivers reported that feeding and swallowing problems of their child adversely impact the QoL.[40]

Secondly, the diagnosis and management of EoE may be accompanied by significant increases in parental burden, anxiety, and distress.[29] Therapies may involve different dietary restrictions, changing the entire nutritional lifestyle of an entire family, as described in families of children with food allergies. In children with EoE and IgE-mediated food allergy, parents also feel anxiety due to the possibility of accidental exposure to the allergen and subsequently life-threatening reaction. Restrictive diets represent a significant daily problem for a family of children with EoE, especially in patients with associated IgE-mediated food allergies and feeding dysfunction. Caregivers stress was associated with: 1) buying and preparing separate foods to fit the child's dietary requirements; 2) cost of alternative foods; and 3) disruption of the family structure at mealtimes.[42]

Thirdly, side effects therapies may represent another source of parental anxiety. Parents are often frustrated by the possible effects of oral steroids on child growth, mostly if their child manifests feeding difficulties, malnutrition, and failure to thrive. Therefore, the choice of the best treatment for a patient with EoE should be discussed with parents, explaining the risks and benefits of every therapy, and answering to their doubts and questions.

Finally, the strict follow-up with several endoscopies may also economically affect a family: parents are often absent from work, move from another city, and may encounter coverage insurance issues.

In synthesis, EoE may have a profound effect on the QoL and psychosocial adjustment of family members of an affected child. Much time and work are required to decipher and monitor symptoms, to meet dietary requirements, and to plan medical follow-up, resulting in tremendous emotional and financial stress. The emotional stress and resultant strain on family relationships are exacerbated by the limited information currently available about the natural history and treatment outcome of EoE in children and adolescents. Therefore, pediatricians should consider multidisciplinary management, also involving psychologists, social workers, and, if necessary, neuropsychiatrists.

Limitations of the study

This work presents several limitations. First of all, the limited number of pediatric studies did not allow a comprehensive assessment of the psychological burden of EoE in children. Also, none of the available studies were prospectively realized or compared to children's reports with parents' ones. Finally, the prescription of antidepressants was never investigated in children. On the other hand, this review shows strengths. This is a first review that summarizes the current studies evaluating psychosocial issues and QoL in children and adolescents with EoE. This review also underlines the importance of a multidisciplinary approach in the management of EoE patients, including psychological assessment.

Conclusions

EoE is an emerging inflammatory disease affecting children at any age. The chronic nature of eosinophilic inflammation, the association with atopic and non-atopic disabling diseases, as well as long-term restrictive therapies and strict endoscopy follow-up, are the main stressful factors for affected children and their families.

The field of mood issues and psychosocial dysfunctions in patients with EoE is still poorly investigated. Further prospective and extensive studies are needed, mainly to assess 1) the prevalence and the burden of neuropsychiatric disorders and their clinical manifestations (sleep disorders, school performance, family relation-

ships), 2) the early prescription and administration of antidepressants, and 3) psychological impact of families with an affected child.

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CORRESPONDENCE

Food-induced immediate response of the esophagus: A first report in the pediatric age

Eosinophilic esophagitis is an emerging allergic disease characterized by symptoms of esophageal dysfunction and the eosinophilic infiltration of the esophagus.[1] Eosinophilic esophagitis symptoms generally vary with age. Young children and toddlers usually experience vomiting, regurgitation, abdominal pain, and feeding refusal. On the contrary, dysphagia and food impaction are predominant in adolescents and adults and are generally related to advanced tissue remodeling.[2]

Recently, Biedermann et al. identified a group of symptoms referred to as "food-induced immediate response of the esophagus" (FIRE) in adults with EoE.[3] FIRE is a novel syndrome characterized by an intense, unpleasant, or even painful retrosternal sensation, occurring rapidly and reproducibly after esophageal contact with specific foods or liquids.[3,4] These symptoms are distinguished and unrelated to dysphagia and gastroesophageal reflux disease (GERD).[3,4] To date, FIRE has been described in adults, and no pediatric cases have been reported. This article reports the first pediatric case of FIRE.

In January 2021, a 9-year-old Caucasian boy was referred to our Pediatric Allergy-Immunology Unit with a history of vomiting, solid food dysphagia, and feeding refusal that had worsened in the last month. The patient also reported a self-resolved episode of food impaction with meat. His history was negative for food and respiratory allergies, autoimmune diseases, or connective tissue disorders.

TABLE 1 Patient's feature

Age at diagnosis, years	9
Sex, M/F	M
History of allergy, yes/no	No
EoE symptoms duration, months	Not clearly reported by the family
Episodes of food impaction, yes/no	Yes
Total EREFS score at diagnosis, 0–8	4
Peak of eosinophil count at diagnosis, eos/HPH	62
Total PEESS score at diagnosis, 0–80	38
Total EREFS score at follow-up[a], 0–8	6
Peak of eosinophil count at follow-up[a], eos/HPH	61
Total PEESS score at follow-up[a], 0–80	22
FIRE symptoms	Chest tightness, esophageal burn
Time to onset, min	10
Duration, min	10–20
Identified foods	Honey, pumpkin seed
SPT, mm	
Honey, mm	4
Pumpkin seed, mm	7
Total IgE, KU/L	72.3
Specific IgE, KU/L	
Honey, KU/L	0.38
Pumpkin seed, KU/L	0.43

Abbreviations: EoE, eosinophilic esophagitis; eos, eosinophils; EREFS, endoscopic reference score; FIRE, food-induced immediate response of the esophagus; HPF, high power field; IgE, immunoglobulin E; PEESS, pediatric eosinophilic esophagitis symptom score; SPT, skin prick test.

[a]Eight weeks after the beginning of PPI therapy.

A complete allergic evaluation was performed with no evidence of sensitization to common food and pollen antigens. The upper GI tract x-ray exam ruled out the leading causes of esophageal stenosis. Thus, the child underwent the esophagogastroduodenoscopy (EGD) that showed longitudinal furrows, mucosal edema, and white exudates (Table 1). The histology confirmed the eosinophil-predominant infiltration of the esophagus. A high-dosage proton pump inhibitor (PPI) therapy (40-mg daily) was started to improve his symptoms. After 1 month of PPI therapy, the child developed two episodes of chest tightness and esophageal burn after 10 min from the ingestion of pumpkin seeds mixed with yogurt and honey that he previously tolerated. The symptoms self-resolved after about 15 min and did not require any medication. The patient distinguished between these symptoms and the well-known swallowing difficulties and dysphagia that previously experienced. Skin prick tests with fresh foods and serum-specific IgEs were positive for honey and pumpkin seeds. The immunoCAP© assay was negative for inhalants and other food allergens. After 8 months of PPI therapy, the follow-up EGD with biopsies still showed signs of active disease (Table 1). Therapy was switched to swallowed corticosteroids (budesonide 1 mg daily). The child did not report other FIRE episodes and EoE symptoms since the swallowed budesonide was introduced.

We believe that this is a pediatric case of FIRE meeting several of FIRE patient characteristics recently reported.[4] FIRE appeared distinct from the patient's reported EoE symptoms (solid food dysphagia, vomiting, and food refusal), GERD (symptoms improve with PPI therapy), and pollen food allergy syndrome (PFAS), where symptoms are generally limited to the oral mucosa and due to fresh fruits and vegetables. Moreover, no sensitization to inhalant allergens was found as generally described in patients with PFAS. Finally, FIRE symptoms may immediately occur after a culprit food comes into direct contact with the esophagus and is confined to this portion of the gastrointestinal tract. Although the pathogenesis of FIRE is still undetermined, a putative local immunologic factor causing the immediate mucosal response has been postulated.[4] Furthermore, the inflamed esophageal epithelium may also play a part in the allergic sensitization as reported for the skin in atopic dermatitis.[5] Cases of FIRE syndrome in children may be underestimated because symptoms could be attributed to EoE, and patients are too young to distinguish between typical EoE, PFAS, and FIRE symptoms. The differential diagnosis between FIRE and PFAS might be challenging to discriminate also for gastroenterologists and allergists. An accurate history of FIRE symptoms should be considered in the routine management of EoE children. Further research is needed to understand the epidemiology and the underlying pathogenetic mechanisms of FIRE in adults and children.

KEYWORDS

children, eosinophilic esophagitis, food-induced immediate response of the esophagus, pediatrics

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Review

Eosinophilic Gastrointestinal Diseases in Inborn Errors of Immunity

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Abstract: Inborn errors of immunity (IEI) are disorders mostly caused by mutations in genes involved in host defense and immune regulation. Different degrees of gastrointestinal (GI) involvement have been described in IEI, and for some IEI the GI manifestations represent the main and characteristic clinical feature. IEI also carry an increased risk for atopic manifestations. Eosinophilic gastrointestinal diseases (EGIDs) are emerging disorders characterized by a chronic/remittent and prevalent eosinophilic inflammation affecting the GI tract from the esophagus to the anus in the absence of secondary causes of intestinal eosinophilia. Data from the U.S. Immunodeficiency Network (USIDNET) reported that EGIDs are more commonly found in patients with IEI. Considering this element, it is reasonable to highlight the importance of an accurate differential diagnosis in patients with IEI associated with mucosal eosinophilia to avoid potential misdiagnosis. For this reason, we provide a potential algorithm to suspect an EGID in patients with IEI or an IEI in individuals with a diagnosis of primary EGID. The early diagnosis and detection of suspicious symptoms of both conditions are fundamental to prevent clinically relevant complications.

Keywords: eosinophilic gastrointestinal disorders; eosinophilic esophagitis; inborn errors of immunity; immunodeficiency

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1. Inborn Errors of Immunity and Gastrointestinal Manifestations

Inborn errors of immunity (IEI) are disorders mostly caused by mutations in genes involved in immune host defense and regulation [1–3]. These conditions are characterized by various combinations of increased susceptibility to infections, autoimmunity, autoinflammatory manifestations, lymphoproliferation, allergy, bone marrow failure, and/or malignancy [1]. The recently updated IEI classification from the International Union of Immunological Societies (IUIS) Expert Committee has increased the number of known genetic defects identified as causing IEI to 485 [4]. According to the IUIS classification, IEI are categorized into ten groups based on the specific clinical and immunological phenotype: combined immunodeficiencies (I); combined immunodeficiencies with syndromic features (II); predominantly antibody deficiencies (III); diseases of immune dysregulation (IV); congenital defects of phagocytes (V); defects in intrinsic and innate immunity (VI); autoinflammatory diseases (VII); complement deficiencies (VIII); bone marrow failure (IX); and phenocopies of inborn errors of immunity (X) [5]. Although IEI present with a broad spectrum of clinical features, in about one-third of them, various degrees of gastrointestinal (GI) involvement have been described, and for some IEI, the GI manifestations represent the characteristic clinical feature [6,7]. In addition, there has been an increasing understanding of which IEI carry an increased risk for specific atopic manifestations, with most studies focusing on atopic dermatitis, allergic rhinitis, asthma, and immunoglobulin E (IgE)-mediated food allergy [8]. Although eosinophilic esophagitis (EoE) is thought to co-occur with these

atopic disorders following a common atopic pathophysiology, eosinophilic gastrointestinal diseases (EGIDs) and their association with IEI are relatively poorly understood.

2. Eosinophilic Gastrointestinal Diseases

EGIDs are emerging disorders characterized by chronic/remittent and prevalent eosinophilic inflammation affecting the GI tract from the esophagus to the anus in the absence of secondary causes of intestinal eosinophilia [9,10]. Based on the site of the inflammation, EGIDs have been recently classified into EoE and non-EoE EGIDs (Table 1). EoE affects approximately 1 in 1–2000 persons; however, it is currently considered one of the major causes of upper gastrointestinal morbidity [11]. EoE is found in 12–23% of patients with dysphagia and 50% in those with esophageal food impaction [12,13]. According to current guidelines, diagnosis of EoE requires (1) suggestive clinical symptoms; (2) an esophageal eosinophilic infiltrate greater than 15 eosinophils per high-powered field (HPF) (~60 eos/mm2) in endoscopically obtained biopsies; and (3) the exclusion of secondary causes of esophageal eosinophilia (gastroesophageal reflux disease [GERD], hypereosinophilic syndrome, inflammatory bowel diseases, autoimmune disorders, vasculitis, hyper-IgE syndrome, drug hypersensitivity, infections, pill esophagitis, and graft versus host disease). EoE symptoms are non-specific and vary with age. Feeding issues, failure to thrive, and recurrent vomiting generally prevail in infants and toddlers, whereas school-aged children present epigastric pain or GERD-like symptoms. Dysphagia and esophageal food impaction are typically prevalent symptoms in adolescents and adults.

Table 1. Clinical features of EGIDs.

	Symptoms	Diagnosis	Treatments
Eosinophilic esophagitis (EoE)	Symptoms mainly depend on the patient's age - Infants and toddlers: food refusal, feeding issues, recurrent vomiting, failure to thrive - Children: esophageal reflux not responding to conventional therapy, epigastric pain, vomiting - Adolescents and adults: dysphagia, esophageal food impaction. Change in eating behaviors	(1) Suggestive clinical symptoms (2) ≥15 eos/HPF in esophageal biopsies (3) Exclusion of secondary causes of intestinal eosinophilia	- Medical therapies ○ Topical steroids Slurry budesonide Oral fluticasone Budesonide tablets (EMA approved) ○ Biological therapy: dupilumab (anti-IL-4R, FDA approved) - Food elimination diets ○ Empirical food elimination diet ○ Elemental diet - Esophageal dilatation
Non-EoE EGIDs • Eosinophilic Gastritis (EoG) • Eosinophilic Enteritis (EoN) ○ Eosinophilic Duodenitis (EoD) ○ Eosinophilic Jejunitis (EoJ) ○ Eosinophilic Ileitis (EoI) • Eosinophilic Colitis (EoC)	Symptoms mainly depend on the site and the depth of intestinal inflammation - Mucosal form: abdominal pain, diarrhea, vomiting, weight loss, protein-losing enteropathy, GI bleeding - Muscle form: intestinal obstruction - Serosal form: eosinophilic ascites	Stomach ≥ 30 eos/HPF Small intestine ≥ 52 eos/HPF Right colon ≥ 100 eos/HPF Transverse and descending colon ≥ 84 eos/HPF Rectosigmoid ≥ 64 eos/HPF	- Medical therapies ○ Systemic steroids (oral budesonide or prednisolone; IV corticosteroids) ○ Immunosuppressants ○ Biological therapies: infliximab, adalimumab (anti-TNF), mepolizumab, reslizumab and benralizumab (anti-IL-5 and anti-IL5R), dupilumab (anti-IL-4R) - Food elimination diets ○ Empirical food elimination diet ○ Elemental diet - Surgery

HPF: high power field; IV: intravenous.

In contrast, non-EoE EGIDs are still less understood disorders. Epidemiology of non-EoE EGIDs is limited to a few observational studies; however, in the general population, prevalence is estimated at 3–8/100,000 cases, although it was approximately 2% in patients with gastrointestinal symptoms [14]. Symptoms of non-EoE EGIDs depend on the site (stomach, intestine, or colon) and the depth (mucosal, muscular, or serosal layer) of the eosinophilic inflammation and are generally represented by abdominal pain, nausea,

vomiting, and diarrhea [10]. In rare cases, patients with non-EoE EGIDs may develop GI complications, such as intestinal obstruction or eosinophilic ascites. However, they may commonly experience malnutrition or weight loss [15]. Diagnosis of the non-EoE EGIDs is challenging and often requires more endoscopies with potential misdiagnosis and diagnostic delays. The diagnostic cut-offs of tissue eosinophils vary according to the specific site of the GI tract (Table 1).

Allergic comorbidities are prevalent in patients with EGIDs. However, several non-allergic diseases have also been associated with EoE, including autism spectrum disorders, coeliac disease, esophageal malformation, and inflammatory bowel disorders [16–18]. EoE is now considered a type 2-mediated disease, developing from a genetic predisposition and impaired esophageal barrier functioning [19]. In this context, the esophageal exposure to allergens (mostly foods) elicits the local production of alarmins (interleukin [IL]-25, IL-33, and thymic stromal lymphopoietin) and the typical type 2 (Th2)-driven eosinophilic inflammation [20]. IL-4 has been characterized as one of the critical drivers of inflammation in EoE since it is upregulated in the esophageal mucosa and blood of affected patients [21]. While eosinophilic gastritis and enteritis show the same pathogenetic mechanisms of EoE, the pathogenesis of eosinophilic colitis is different from that of other non-EoE EGIDs and is mainly related to apoptosis gene expression, reduced epithelial cell proliferation, and minimal evidence of Th2 inflammation.

EGIDs are clinically heterogeneous diseases with symptoms depending on the age at onset, the site of inflammation, response to treatments, and related comorbidities (allergic and not allergic), thus, defining a spectrum of different diseases [22]. Recently, data from the USIDNET reported that EGIDs are more commonly found in patients with different IEI, such as common variable immunodeficiency (CVID) (43.2%), chronic granulomatous disease (CGD) (8.1%), hyper-IgE syndrome (6.8%), and autoimmune lymphoproliferative syndrome (6.8%) [23]. Nevertheless, more research is needed to confirm these findings and understand if patients with EGIDs and IEI may have distinct clinical features, responses to therapies, and disease endotype. Therefore, this study aims to analyze the potential relationship between these two entities, reviewing current evidence and proposing a potential diagnostic algorithm to help clinicians suspect IEI in EGID patients and vice-versa.

3. Material and Methods

The literature review was performed in November 2022, including all publication years. All studies that met the following criteria were included: (i) articles published in English in peer-reviewed journals, and (ii) participants were children and adult IEI patients diagnosed with EGIDs. Potentially eligible publications were manually screened and reviewed, and non-relevant publications were excluded.

The literature search was performed via the online database PubMed, combining the terms “eosinophilic gastrointestinal diseases AND primary immunodeficiency”, “eosinophilic gastrointestinal diseases AND inborn errors of immunity”, “eosinophilic esophagitis AND inborn errors of immunity”, “eosinophilic esophagitis AND primary immunodeficiency”, and “eosinophilic esophagitis AND immunodeficiency”.

4. Results

The database search found 58 articles. Based on the title and abstract, fifteen articles met the inclusion criteria. After removing duplicates, seven articles were analysed for the review (Figure 1).

In 2016, Yamazaki et al. reported the case of a 30-year-old man with a diagnosis of X-linked agammaglobulinemia, who suffered from chronic diarrhea and persistent low serum IgG, despite the intravenous immunoglobulin replacement (Table 2) [24]. He underwent a colonoscopy with biopsies that detected eosinophilic infiltrate >20 eos/HPF, supporting the diagnosis of eosinophilic gastroenteritis. Treatment with prednisolone was started and led to a significant improvement in diarrhea.

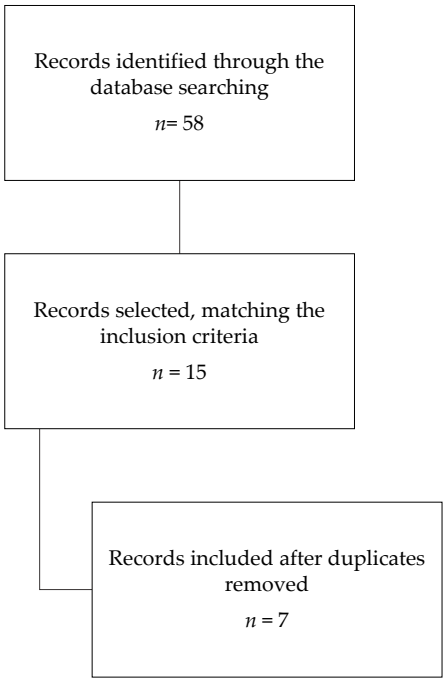

Figure 1. Search strategy.

Table 2. Summary of reviewed articles.

Author, Year [Ref]	Type of Study	IEI	EGID	Age at EGID Diagnosis	Family History	EGID Symptoms	Other Comorbidities	EGID Diagnosis	Complications	EGID Treatment
Yamakazi et al., 2016 [24]	Case report	XLA	EoC	27 years	n.a.	Chronic diarrhea, emaciation	Recurrent infections	>20 eos/HPF	n.a.	Prednisolone
Chen et al., 2016 [25]	Case report	CVID	EoE	28 years	n.a.	Dysphagia, recurrent episodes of esophageal food impaction	Recurrent sinopulmonary infections	n.a.	Esophageal stenosis	Esophageal dilatation, PPI, FED, Oral fluticasone
Hannouch et al., 2016 [26]	Case report	CVID	EoE	n.a.	n.a.	Weight loss, food impaction	Burkitt's lymphoma	n.a.	n.a.	Oral inhaled corticos-teroids
Dixit et al., 2021 [27]	Case report	STAT3-HIES	EoE	n.a.	n.a.	Abdominal pain, dysphagia	Eczema, recurrent respiratory tract infections, cutaneous and retropharyngeal abscesses, and mycosis.	n.a.	n.a.	Dupilumab
Scott et al., 2022 [28]	Case report	STAT1-GOF	EoE	Late adolescence	Mother with choking episodes and CMCC; a daughter with CMCC and recurrent AOM.	Choking episodes, solid and liquid dysphagia	Vaginal candidiasis, scalp fungal infection, Candida esophagitis	22 eos/HPF	Esophageal stenosis	Balloon dilatation FED Montelukast PPI Slurry budesonide
Tang et al., 2020 [29]	Case report	XIAP-deficiency	EoC	Infancy	Mother and sister had the mutation	Abdominal distension, perianal abscess.	Anemia, respiratory tract infections, impaired growth	n.a.	n.a.	n.a.
Tran et al., 2022 [23]	Retrospective cohort study	CVID (43.2%), combined im-munodeficiencies (21.6%), CGD (8.1%), HIES (6.8%), and ALPS (6.8%).	61/74 (82,5%) patients with EoE and 13/74 (17.5%) with EoG, EoN, and EoC.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

ALPS: autoimmune lymphoproliferative syndrome; AOM: acute otitis media; CGD: chronic granulomatous disease; CMCC: chronic mucocutaneous candidiasis; CVID: common variable immunodeficiency; EGID: eosinophilic gastrointestinal disease; EoC: eosinophilic colitis; EoE: eosinophilic esophagitis; EoG: eosinophilic gastritis; EoN: eosinophilic enteritis; FED: food elimination diet; GOF: gain of function; HIES: hyper-IgE syndromes; HPF: high power field; IEI: inborn error of immunity; N.A: not available; PPI: proton pump inhibitor; XIAP: X-linked inhibitor of apoptosis; XLA: X-linked agammaglobulinemia.

A few cases reported the association between common variable immunodeficiency (CVID) and EoE [25,26]. Chen et al. described a 34-year-old woman affected by CVID who was referred to a gastroenterologist for dysphagia, recurrent mild esophageal food impactions, and hard-textured foods that worsened in the previous 5–6 years [25]. She underwent an upper GI endoscopy that showed macro- and microscopic findings compatible with EoE. The patient partially achieved control of their symptoms with oral fluticasone. Hannouch et al. described the case of Burkitt's lymphoma development in a patient affected by CVID and EoE [26].

STAT3-hyper-IgE syndrome (HIES) has been primarily associated with GI manifestations, including gastroesophageal reflux disease, dysphagia, and abdominal pain. A recent cohort study enrolling STAT3-HIES patients investigated the GI manifestations unexpectedly observing that EoE occurred in 65% (11/17) of patients who underwent esophagogastroduodenoscopy [30]. Dixit et al. published the case of a 14-year-old boy affected by STAT3-HIES with severe atopic dermatitis and EoE, clinically characterized by dysphagia and abdominal pain. The patient was treated with dupilumab, effectively controlling skin manifestations and resolving EoE symptoms [27].

Scott et al. reported the case of a 39-year-old woman with EoE refractory on a six-food elimination diet, fluticasone, montelukast, and proton pump inhibitor, but responsive to subsequent therapy with slurry budesonide [28]. She probably developed the first GI symptoms in late adolescence, but she was not formally investigated until she was 31. The patient's family history revealed that her 70-year-old mother suffered from chronic mucocutaneous candidiasis (CMCC) and had a 50-year history of dysphagia and choking episodes, endoscopically evaluated at the age of 66 with biopsies demonstrating extensive tissue fibrosis and rare eosinophils. Even her daughter had a history compatible with CMCC but no symptoms suggestive of EoE. All three underwent a genetic evaluation, demonstrating a novel heterozygous missense variant in the N-terminal domain of STAT1 (c.194A > C; p.D65A). Through immunoblotting studies, a gain of function STAT1 phenotype was demonstrated in all family members investigated. This report first described a STAT1 gain of function mutation characterized by severe and refractory EoE as presenting clinical manifestation.

In 2020, Tang et al. reported the case of a 22-month-old boy with abdominal distension, anemia, and recurrent respiratory tract infections diagnosed with an X-linked inhibitor of apoptosis (XIAP) deficiency. He underwent a GI endoscopy that showed chronic active enteritis with different degrees of eosinophil infiltration compatible with eosinophilic colitis. XIAP deficiency is associated with inflammatory bowel diseases (IBD); however, this case report may extend the spectrum of chronic GI diseases associated with this immunodeficiency [29].

5. Discussion

Recently, Tran et al. reviewed the U.S. immunodeficiency Network (USIDNET), finding that 74 IEI patients had a concomitant diagnosis of EGID [23]. In this study, 61 patients were affected by EoE, and 27 (44.2%) had CVID. In 34.4% of patients, a specific immunodeficiency was identified, including HIES and chronic granulomatous disease (CGD). Thirteen (17.5%) patients were affected by non-EoE EGIDs (eosinophilic gastritis, enteritis, and colitis). A total of 38.4% had CVID, 46% had a combined immunodeficiency, 15.3% had CGD, and one patient had FOXP3-deficient immune dysregulation, polyendocrinopathy, and enteropathy X-linked (IPEX) syndrome. These data suggest that EGIDs may be coexisting comorbidities of patients with specific IEI and seem more common than expected. According to these results, CVID is the IEI most likely complicated by an EGID.

The potential link between IEI and EGIDs has not been elucidated yet. IEI are caused by monogenic germline mutations associated with immune function. These diseases are rare, but the prevalence is likely to be at least 1/1000–5000 [4]. Different IEI can manifest with elevated serum IgE or eosinophilia and increased Th-2 cytokine production, such as IL-5, which is an essential promoter of eosinophil differentiation, maturation, and survival [4,10].

Eosinophils are multifunctional leukocytes that play an essential role against helminth infections and are considered pro-inflammatory cells because they release pleiotropic cytokines, chemokines, lipid mediators, and cytoplasmic granule constituents [31]. Eosinophils are considered the key effector cells in EoE, since, in the absence of eosinophils, disease features (tissue remodeling, collagen accumulation, and gastric motility) are attenuated in animal models [32]. Eosinophils are also involved in the pathogenesis of allergic disorders and are implicated in EGIDs and IBD pathogenesis. Intestinal eosinophilia is not the hallmark of EGIDs, because it has been described even in IBD and celiac disease [33]. Eosinophils are also implicated in IBD pathogenesis, probably playing a significant role in the chronic inflammatory process. In recent years, a growing number of IEI manifesting with IBD have been described [7]. XIAP deficiency is considered one of the mendelian causes of inherited IBD in infancy [34]. When a XIAP deficiency patient shows recurrent and severe abdominal pain, failure to thrive, GI bleeding, and diarrhea, it is reasonable to suspect an IBD and perform a GI endoscopy. Despite this robust evidence, Tang et al. reported the case of a patient with XIAP deficiency and eosinophilic colitis, thus extending the spectrum of GI manifestations potentially related to this immunodeficiency [29]. However, the authors did not report data on long-term follow-up or the diagnostic cut-off used for EoC diagnosis [29]. Standardized international guidelines for EGID diagnosis are still lacking. Most experts agreed that a definitive diagnosis requires recurrent/chronic GI symptoms and increased intestinal eosinophilia, excluding secondary causes of EGIDs (Table 1) [10]. Considering this element, it is reasonable to highlight the importance of an accurate differential diagnosis in patients with IEI associated with mucosal eosinophilia to avoid potential misdiagnosis. We provide a potential algorithm to suspect an EGID in patients with IEI or an IEI in individuals with a diagnosis of primary EGID (Figure 2). The early diagnosis and detection of suspicious symptoms of both conditions are fundamental to prevent clinically relevant complications (severe or fatal infections, esophageal stenosis, intestinal obstruction). Of note, it is still unclear if IEI patients experience a more severe EGID phenotype than those without immunodeficiency.

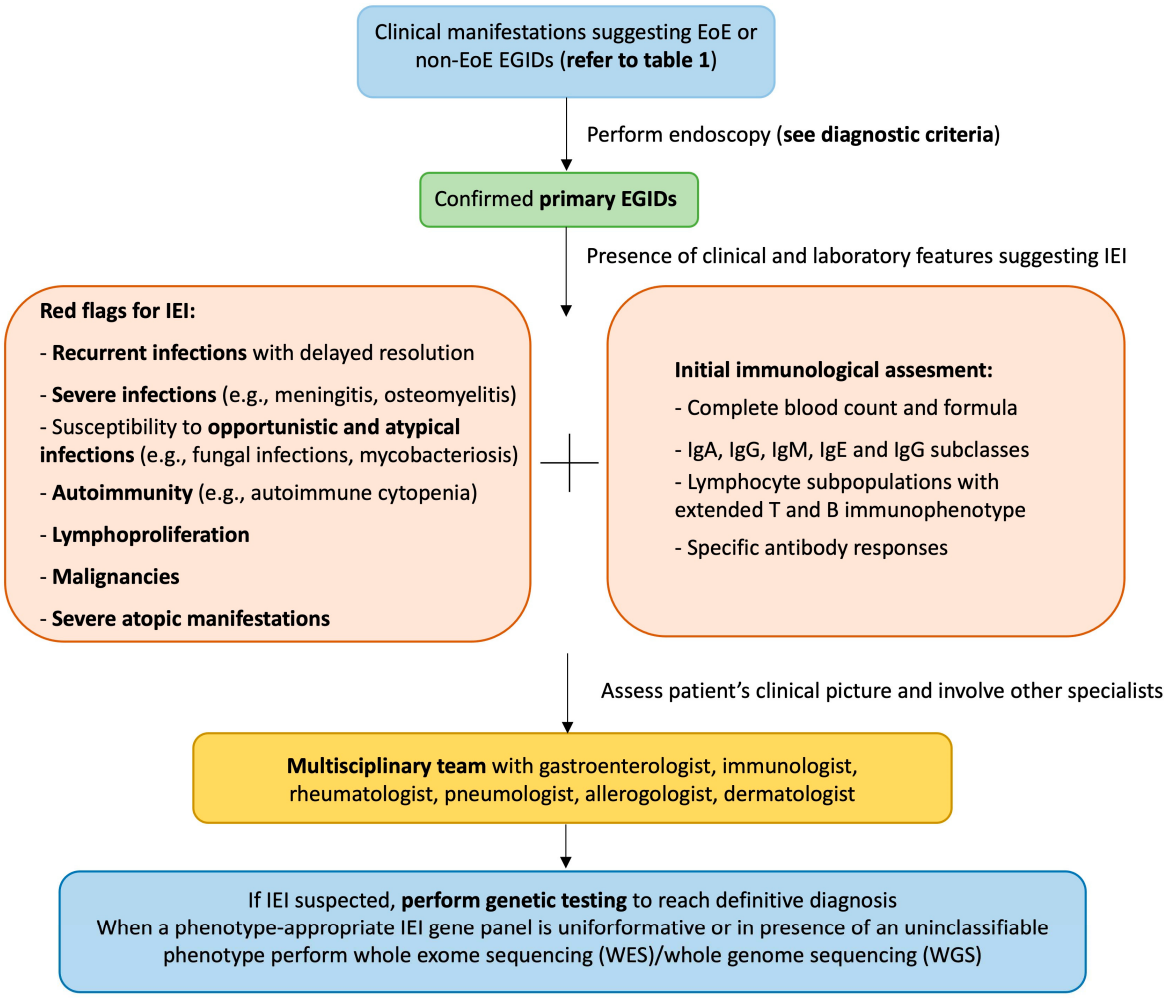

Figure 2. Proposed diagnostic algorithm. The figure can be read from the top to the bottom and vice versa. EGID: eosinophilic gastrointestinal disease; EoE: eosinophilic esophagitis; IEI: inborn errors of immunity.

6. Conclusions

This review first analyzed current evidence of a potential relationship between EGIDs and IEI. According to recent data, EGIDs seem more common in IEI patients than was already reported in the literature. It is reasonable to speculate that EGID can worsen the course of IEI, and vice versa. For this reason, early diagnosis is crucial to prevent complications and define the best personalized treatment. In this context, several unmet needs are still to be clarified. The literature data are still limited, and more research is needed to understand the pathogenetic relationship between these two chronic and invalidating clinical entities. Multicentric prospective studies should be performed to establish the real epidemiology of EGID in IEI patients, the disease-course phenotype, and the response to available treatments.

Author Contributions: Conceptualization, M.V. and R.C.; methodology, M.V. and R.C.; writing—original draft preparation, M.V. and M.N.; writing—review and editing, M.V., M.N., I.B. and R.C.; supervision, I.B., M.D.F., S.C., A.L., G.L.M. and R.C. All authors have read and agreed to the published version of the manuscript.

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WILEY

LETTER TO THE EDITOR

Cluster analysis of clinical data reveals three pediatric eosinophilic gastrointestinal disorder phenotypes

To the Editor,

Primary eosinophilic gastrointestinal disorders (EGIDs) are a spectrum of emerging inflammatory diseases, which may involve any part of the gastrointestinal (GI) tract and lead to a pathological eosinophilic mucosal infiltration.[1,2] Based on the anatomical site of the eosinophil inflammation, EGIDs are classified into eosinophilic esophagitis (EoE) and nonesophageal EGIDs. There is increasing interest in EGIDs heterogeneity related to clinical presentation, comorbidities, natural history, and response to therapies. To date, no studies stratifying pediatric patients with EGIDs into clinical phenotypes with a data-driven approach have been published.

This study aimed to characterize EGIDs heterogeneity by performing cluster analysis on a cohort of children and adolescents followed at the Pediatric Center for Eosinophilic Gastrointestinal Disorders (CPED) in Pavia, Italy, using an extensive pediatric primary care database from our University Hospital.

Diagnosis of EoE was based on the finding of ≥15 eosinophils/high-power field (HPF) in at least one esophageal biopsy.[3] As there are no consensus guidelines for the diagnosis of nonesophageal EGIDs, pathology reports were reviewed based on the pathological cut-offs proposed by Collins et al.[4] All patients with a secondary cause of pathological eosinophilic inflammation (ie, inflammatory bowel diseases, parasite infections, intestinal vasculitis, and malignancies) of the GI tract were excluded. Data collected from enrolled EGIDs patients included demographics (date of birth, age at diagnosis, gender, and ethnicity), early life history (gestational age, birth weight, delivery mode, neonatal intensive care unit [NICU] admission, exclusive breastfeeding for the first three months of life, and bronchiolitis), early environmental tobacco smoke (ETS) exposure, medical history of coexisting atopic (allergic rhinitis, asthma, atopic dermatitis, and food allergy), and nonatopic diseases (congenital and genetic diseases, autoimmune diseases, connective tissue disorders, neuropsychiatric disorders, and recurrent respiratory infections), and symptoms at the time of diagnosis. All patients underwent skin prick tests for foods (milk, egg, soy, rice, codfish, shrimp, almond, hazelnut, walnut, peanut, tomato, kiwi, and peach) and inhalant allergens (dust mites, grass, birch, hazel, molds, cat, dog, mugwort, and ragweed). Laboratory data included serum total immunoglobulin E (IgE) and peripheral blood eosinophil count. According to the current validated reference score (EREFS), endoscopic findings were reported, and esophageal mucosa was considered pathological when the EREFS total score was ≥2. For nonesophageal EGIDs, endoscopic findings were deemed abnormal when macroscopic alterations (mucosal hyperemia, edema, erosions, or nodular lymphoid hyperplasia) were reported. Data about treatments initiated at the time of diagnosis were also collected, including medications (corticosteroids and proton-pump inhibitors [PPIs]) and food elimination diets. All data were extracted from electronic medical records (Ormaweb™ and Fenix™, Software). Every patient identifier (name and surname) was replaced with a specific numeric code. The Ethics Committee approved this study (protocol number 2021.3-11/457, GOLDEN study, identifier: NCT05219903).

A total of 31 variables were used as input for the clustering algorithm. Gower's general dissimilarity coefficient was used to compute the distance matrix since the input variables were of mixed types (numerical and categorical).[5] Then, we applied the "partitioning around medoids" algorithm, increasing the number of candidate clusters from one to five.[6] The Silhouette statistic was used to determine the optimal number of clusters (the larger, the better).[7] For each input variable, we used the Fisher's exact test (categorical variables) or the Kruskal-Wallis test (numerical variables) to perform pairwise comparisons between the clusters. Holm's method was used to adjust the p-values for multiple comparisons. The statistical analyses were performed through R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

The study population comprised 60 patients (73% males); 38 (63%) subjects had EoE and 22 (37%) had nonesophageal EGIDs (Table S1). According to the Silhouette statistics, the best data partition comprised three clusters. Pairwise association tests identified 13 distinctive features (Table 1, Figure 1). Cluster 1 (38%): EoE diagnosis with pathological endoscopic findings (EREFS > 2), common allergic rhinitis and allergic sensitization, especially to dust mites, grass and hazel tree, and peanut (Table S2), epigastric/abdominal pain without diarrhea, topical corticosteroid therapy and PPIs use, and infrequent NICU admission. Cluster 2 (27%): nonesophageal EGIDs diagnosis with normal endoscopic findings, diarrhea, rare gastroesophageal reflux disease (GERD), and infrequent PPIs use. Cluster 3 (35%): EoE diagnosis with pathological endoscopic findings (EREFS > 2), GERD, ETS exposure, NICU admission, PPIs use, infrequent allergic sensitization, infrequent abdominal pain and diarrhea, infrequent corticosteroid use.

Martina Votto and Salvatore Fasola equally contributing co-first authors.

TABLE 1 Distribution of distinctive features by cluster and cluster separation

	Cluster 1 $n = 23$ (38%)	Cluster 2 $n = 16$ (27%)	Cluster 3 $n = 21$ (35%)	*p*-Value 1 vs. 2	*p*-Value 1 vs. 3	*p*-Value 2 vs. 3	Cluster separation§
EoE	18 (78)	2 (12)	18 (86)	**<0.001**	0.701	**<0.001**	{2}{13}
Pathological endoscopic finding	14 (61)	3 (19)	14 (67)	**0.040**	0.761	**0.021**	{2}{13}
Allergic rhinitis	19 (83)	5 (31)	4 (19)	**0.004**	**<0.001**	0.458	{32}{1}
Allergic sensitization	22 (96)	8 (50)	5 (24)	**0.003**	**<0.001**	0.165	{32}{1}
Blood eosinophils, cell/mm^3	663.0 (388.1)	422.5 (348.4)	381.3 (300.3)	**0.044**	**0.023**	0.645	{32}{1}
Serum IgE, kU/L	1000.5 (979.2)	324.5 (368.9)	212.3 (331.0)	**0.032**	**0.002**	0.276	{32}{1}
Epigastric/abdominal pain	17 (74)	8 (50)	4 (19)	0.179	**0.001**	0.154	{32}{21}
Diarrhea	0 (0)	13 (81)	1 (5)	**<0.001**	0.477	**<0.001**	{13}{2}
GERD	7 (30)	1 (6)	12 (57)	0.218	0.218	**0.005**	{21}{13}
Early ETS exposure	7 (30)	6 (38)	15 (71)	0.736	**0.044**	0.103	{12}{23}
NICU admission*	1 (4)	2 (12)	10 (48)	0.557	**0.004**	0.070	{12}{23}
Corticosteroids	18 (78)	7 (44)	2 (10)	**0.048**	**<0.001**	**0.048**	{3}{2}{1}
PPIs	15 (65)	3 (19)	17 (81)	**0.016**	0.318	**0.001**	{2}{13}

Note: Data are presented as absolute (%) frequency or mean (standard deviation). *p*-Values are from the Fisher's exact (categorical variables) or the Kruskal-Wallis test (numerical variables). Values in bold indicate significant differences.

Abbreviations: EoE, eosinophilic esophagitis; ETS, environmental tobacco smoke; GERD, gastroesophageal reflux disease; NICU, neonatal intensive care unit; PPIs, proton-pump inhibitors.

§Cluster separation: cluster numbers are reported in increasing order of mean/percentage for each variable. Significant separation occurs between clusters included within different pairs of brackets. For instance, {21}{13} indicates similarity between pairs 2-1 and 1-3, and a statistically significant difference between Cluster 2 and Cluster 3.

*For preterm birth, neonatal respiratory distress, or congenital malformations.

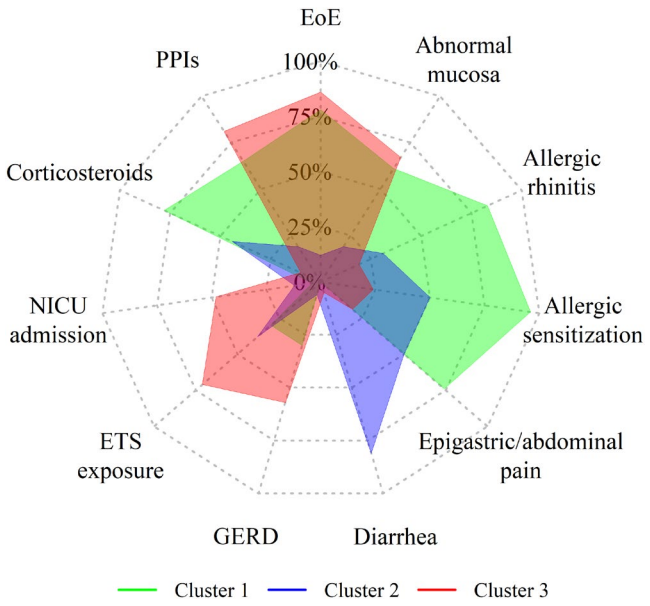

FIGURE 1 Percentage distribution of distinctive categorical features across the clusters. EoE; eosinophilic esophagitis; GERD; gastroesophageal reflux disease; ETS; environmental tobacco smoke; NICU; neonatal intensive care unit; PPIs; proton-pump inhibitors

This study is the first that explores the clinical heterogeneity of pediatric EGIDs using a cluster analysis approach. This multidimensional analysis identified two clinical phenotypes of EoE. Cluster 1 was mainly composed of EoE patients with an atopic phenotype, marked by high levels of total serum IgE and blood peripheral eosinophils (Figure 2). This result highlights that EoE affects allergic patients, especially those with respiratory allergic diseases, as already described in previous observational and longitudinal studies.[8] Conversely, Cluster 3 consisted of a nonatopic EoE phenotype, mainly characterized by nonallergic children with a history of early ETS exposure and NICU admission. Although ETS is a risk factor for allergic disease development throughout life, data on the effect of early ETS exposure on EoE are limited and contradictory and require further investigations.[9] In Cluster 3, most patients had a history of NICU admission, which may be related to a higher (although not statistically significant) frequency of congenital malformations (such as esophageal atresia) than in other clusters (Table S1). Several studies reported the close association between EoE and congenital esophageal malformations, such as esophageal atresia.[9] Different pathogenetic mechanisms have been assumed, such as early life exposures (mother's diet and lifestyle, C-section, prematurity, early antibiotic and PPIs prescription, and formula feeding), dysregulated genes, and risk factors affecting the esophageal mucosal barrier and motility.[10] This finding highlights that the impaired esophageal barrier (for congenital or genetic reasons) may be the *primum movens* of the eosinophilic inflammation, and atopic predisposition could not be the only EoE risk factor.[10] Cluster 2 included subjects with nonesophageal EGIDs who mainly presented diarrhea and normal endoscopic findings. Indeed, according to a recent systematic review with meta-analysis, abdominal pain and diarrhea are the main symptoms

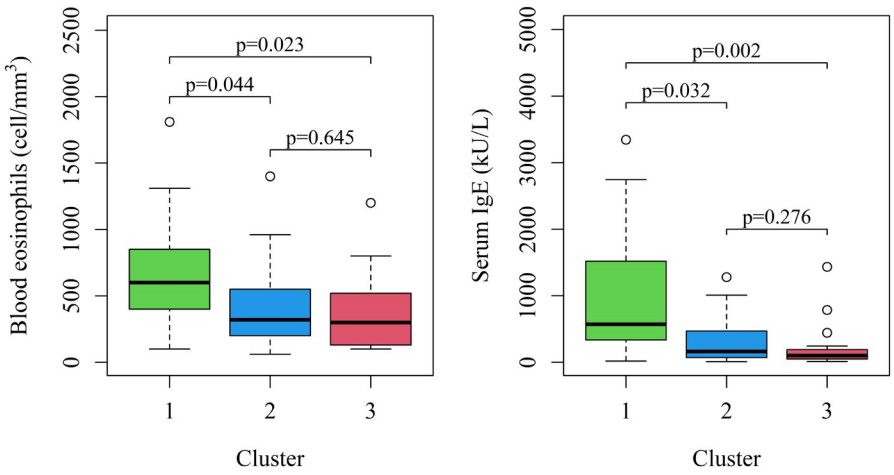

FIGURE 2 Boxplots of distinctive numerical features across the clusters. *p*-Values are from the Kruskal-Wallis test

in children and adults with nonesophageal EGIDs, and a normal mucosa is the prevalent endoscopic finding in these patients.[2] Notably, in Cluster 2, the coexistence of allergic diseases was less prevalent than in the other clusters, confirming what we clinically observed in a recent single-center study.[11]

In summary, we identified for the first time three potential phenotypes of pediatric EGIDs using a cluster analysis approach. Notably, we confirmed and characterized two subgroups of EoE patients, an atopic and nonatopic phenotype, with a relevant impact on clinical practice and potential significance in prognosis and response to therapy. Some of the limitations within this analysis need to be highlighted. Firstly, this is a single-center study with a small number of patients enrolled and confined to a small geographical area; thus, pooling data across several centers may be helpful to reinforce our results. Moreover, the possibility that other variables may be of greater significance in developing meaningful phenotypes cannot be excluded. Therefore, this is the first step towards more extensive studies to confirm the results and verify cluster stability over time.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Martina Votto: Conceptualization (equal); Methodology (equal); Writing – original draft (equal). **Salvatore Fasola:** Conceptualization (equal); Data curation (lead); Formal analysis (lead); Methodology (equal); Writing – original draft (equal). **Giovanna Cilluffo:** Formal analysis (equal); Methodology (equal). **Giuliana Ferrante:** Conceptualization (equal); Methodology (equal). **Stefania La Grutta:** Conceptualization (equal); Methodology (equal); Supervision (lead); Writing – review & editing (supporting). **Gian Luigi Marseglia:** Supervision (lead); Writing – review & editing (supporting). **Amelia Licari:** Conceptualization (equal); Methodology (equal); Supervision (lead); Writing – review & editing (supporting).

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Chapter 4

DIAGNOSIS OF EGIDs

Italian Journal of Pediatrics

LETTER TO THE EDITOR

Open Access

Evaluation of diagnostic time in pediatric patients with eosinophilic gastrointestinal disorders according to their clinical features

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Abstract

Eosinophilic gastrointestinal disorders (EGIDs) are chronic/remittent inflammatory diseases associated with a substantial diagnostic delay, often attributable to misdiagnosis and variable clinical presentation in adults. In the pediatric population, few studies have been conducted worldwide reporting EGID diagnostic delay and its consequences on patients. This study aims to analyze and identify potential clinical factors and complications associated with a longer diagnostic time. We performed a retrospective analysis of pediatric patients with EGIDs followed at the Center for Pediatric EGIDs in Pavia, Italy. A total of 60 patients with EGIDs were enrolled. Thirty-nine (65%) patients had EoE, and 21 (35%) non-esophageal EGIDs. EGID diagnosis was achieved about 2 years after the symptom onset, and the median diagnostic time was 12 months (IQR 12–24 months). Diagnostic time was 12 months (IQR 12–69) in non-esophageal EGIDs and 12 months (IQR 4–24 months) in EoE patients. EoE patients presenting with FTT and feeding issues experienced a longer diagnostic time ($p = 0.02$ and $p = 0.05$, respectively) than children without growth and feeding impairments.

In this study, symptoms appeared about 2 years before the definitive EGID diagnosis was reached, and this diagnostic time was shorter than the delay observed in other published studies. Especially in EoE children, the diagnostic time is significantly associated with impaired child growth, highlighting the importance of an early diagnosis to prevent esophageal stenosis and failure to thrive.

Keywords Adolescents, Children, Diagnostic time, Eosinophilic esophagitis, Failure to thrive, Growth, Non-esophageal eosinophilic gastrointestinal disorders

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To the Editor,

Eosinophilic gastrointestinal disorders (EGIDs) are clinically heterogeneous chronic diseases with non-specific symptoms that vary with age and the site of pathological eosinophilic gastrointestinal (GI) inflammation [1]. As a consequence, EGIDs are associated with a substantial diagnostic delay, often attributable to misdiagnosis and variable clinical presentation in adults [2]. Instead, in the pediatric population, only a few studies have been conducted worldwide reporting EGID diagnostic delay, its risk factors, and its consequences on patients [3, 4]. Therefore, this study aims to analyze the time from symptom onset to EGID diagnosis and identify potential clinical factors or predictable complications associated with a longer diagnostic delay.

We performed a retrospective analysis (from June 2021 to July 2022) of pediatric patients followed at the Center for Pediatric Eosinophilic GI Disorders (CPED) in Pavia, Italy. Patients enrolled were younger than 19 years at the time of the EGID diagnosis. EGIDs have been categorized into eosinophilic esophagitis (EoE) and non-esophageal EGIDs. Diagnosis of EoE was defined as ≥ 15 eosinophils/high power field identified in at least one esophageal biopsy [5]. There are no universal guidelines for the diagnosis of non-esophageal EGIDs; therefore, pathology reports were reviewed according to the cut-offs proposed by Collins et al. [6] All children with other causes of intestinal eosinophilic inflammation (i.e., inflammatory bowel diseases, parasite infections, intestinal vasculitis, malignancies) were excluded. Data collected from enrolled patients included demographics (date of birth, age at diagnosis and symptoms onset, gender, ethnicity), medical history of coexisting atopic diseases (allergic rhinitis, asthma, atopic dermatitis, and food allergy), and symptoms at the time of diagnosis. In EoE patients, endoscopic findings have been reported according to the validated EoE endoscopic reference score (EREFS) [7]. Diagnostic time was estimated as the time-lapse (months) between the onset of symptoms and the final diagnosis of EGIDs. All data were extracted from electronic medical records and semi-anonymized. The Ethical Committee approved this study (protocol number 0003241/22, GOLDEN study, NCT05219903). All patients provided written informed consent, according to the Declaration of Helsinki and more recent amendments [8, 9]. Continuous data were described with median and interquartile range (IQR; i.e., 25th–75th percentiles), whereas categorical data as counts and percentages. Comparative analysis was performed using the Mann Whitey U and Fisher exact tests. The Kruskal Wallis test was used to compare the diagnostic time through different age ranges (≤ 1 year, 1–5, 6–11, and ≥ 12 years). Statistical significance was set at $p \leq 0.05$. The statistical analyses were performed through Stata v17 (StataCorp USA 2020).

A total of 60 patients with EGIDs were enrolled. Thirty-nine (65%) patients had EoE, and 21 (35%) non-esophageal EGIDs (Table 1). Most enrolled EGID patients were males (70%) and Caucasians (88%). Overall, 63% of the enrolled patients showed other coexisting allergic diseases that were more evident in the EoE patients (70%) compared to non-esophageal EGID forms (52%). Food impaction, dysphagia, and feeding issues were only reported in patients with EoE (21%, 23%, and 18%, respectively); on the other hand, diarrhea with weight loss specifically depicted the non-esophageal EGID forms (38% and 14%, respectively). Failure to thrive (FTT) was found in 20% of all EGID patients (26% of EoE and 10% of non-esophageal EGID patients, respectively). About 76% of all patients received an EGID diagnosis during school age and adolescence; in particular, EoE and non-esophageal EGIDs were diagnosed in 35.9 and 52.4% of patients 6–11 years old, respectively (Table 1). EGID symptoms appeared at a median age of 8 years (IQR 3–11 years). EGID diagnosis was achieved about 2 years after the symptom onset, and the median diagnostic time was 12 months (IQR 12–24 months) (Table 2). Diagnostic time was 12 months (IQR 12–69) in non-esophageal EGIDs and 12 months (IQR 4–24 months) in EoE patients. In the EGID cohort, the longest diagnostic time was registered among school-aged children (24 [IQR 8–54] months) and adolescents (12 [12–30] months) compared to other age ranges. No significant differences in diagnostic time were found according to sex and allergic comorbidities in EoE and non-esophageal EGID patients. EoE patients presenting with FTT and feeding issues experienced a longer diagnostic time ($p = 0.02$ and $p = 0.05$, respectively) than children without growth and feeding impairments (Fig. 1). Suggestive symptoms of EoE, such as food impaction and dysphagia, were not significantly associated with a shorter diagnostic time ($p = 0.21$ and $p = 0.61$, respectively). Similarly, the diagnostic time in non-esophageal EGID patients with FTT was longer than that found in children without FTT, although this difference was not statistically significant ($p = 0.53$) (Fig. 1). In non-esophageal EGID patients, neither diarrhea nor abdominal pain was related to a shorter diagnostic time ($p = 0.92$ and $p = 0.82$, respectively). In the EoE cohort, the finding of a fibro-stenotic phenotype (esophageal fixed rings and structures) was not associated with a longer diagnostic time compared to patients with an inflammatory endoscopic pattern (mucosal edema, furrows, white exudates).

In this study, symptoms appeared about 2 years before the definitive EGID diagnosis was reached, and this

Table 1 Demographic and clinical features of enrolled EGID patients

	Overall	EoE	Non-esophageal EGIDs
EGID patients, *n (%)*	60 (100)	39 (65)	21 (35)
Male, *n (%)*	42 (70)	29 (74)	14 (67)
Caucasian, *n (%)*	53 (88)	33 (85)	20 (95)
Age at diagnosis			
≤ 1 year, *n (%)*	4 (6.7)	3 (7.8)	1 (4.8)
1–5 years, *n (%)*	10 (16.7)	9 (23)	1 (4.8)
6–11 years, *n (%)*	25 (41.6)	14 (35.9)	11 (52.4)
≥ 12 years, *n (%)*	21 (35)	13 (33.3)	8 (38.0)
Coexisting allergic diseases, *n (%)*	38 (63)	27 (70)	11 (52)
Allergic rhinitis, *n (%)*	30 (50)	19 (49)	11 (52)
Asthma, *n (%)*	12 (20)	10 (26)	2 (10)
Atopic dermatitis, *n (%)*	11 (18)	9 (23)	2 (10)
Food allergy, *n (%)*	15 (25)	13 (33)	2 (10)
Symptoms			
Abdominal pain, *n (%)*	32 (53)	14 (36)	18 (86)
Diarrhea, *n (%)*	8 (13)	0 (0)	8 (38)
Dysphagia, *n (%)*	9 (23)	9 (23)	0 (0)
Failure to thrive, *n (%)*	12 (20)	10 (26)	2 (10)
Food impaction, *n (%)*	8 (13)	8 (21)	0 (0)
GERD-like symptoms, *n (%)*	20 (33)	20 (51)	0 (0)
Nausea and vomiting, *n (%)*	15 (25)	12 (31)	3 (14)
Reduced appetite and feeding issues, *n (%)*	7 (12)	7 (18)	0 (0)
Weight loss, *n (%)*	3 (5)	0 (0)	3 (14)
Endoscopic findings			
Edema, *n (%)*	19 (32)	19 (49)	0 (0)
Rings, *n (%)*	9 (15)	9 (23)	0 (0)
Exudates, *n (%)*	6 (10)	6 (15)	0 (0)
Furrows, *n (%)*	7 (12)	7 (18)	0 (0)
Stricture, *n (%)*	2 (3)	2 (5)	0 (0)
Normal mucosa, *n (%)*	11 (18)	0 (0)	11 (52)
Nodular lymphoid hyperplasia, *n (%)*	5 (8)	0 (0)	5 (24)
Mucosal inflammation, *n (%)*	5 (8)	0 (0)	5 (24)

EGIDs eosinophilic gastrointestinal disorders, *EoE* eosinophilic esophagitis

diagnostic time was shorter than the delay observed in other published studies. Nevertheless, studies assessing the diagnostic delay in EGID patients are limited and have been mainly realized in adults [2–4]. Schoepfer et al. observed a median diagnostic delay of 6 years that was longer in the first two decades of life [3]. Conversely, a registry of 705 EoE patients highlighted that the diagnostic delay was higher in adults than in pediatric patients [10]. Only one study assessed the diagnostic delay in non-esophageal EGID patients, reporting a mean delay of 3.6 years that was longer in adults than children [4]. Lenti et al. identified an overall diagnostic delay of 36 months and found at least one previous misdiagnosis in 41.8% of adults with EoE [2]. Similarly, Chehade et al. found that 44.3% of patients with eosinophilic gastritis/duodenitis received a documented diagnosis of another gastrointestinal condition before the definitive diagnosis [4]. These data, together with the finding of a shorter diagnostic time in infancy in our cohort, suggest that toddlers and young children are less likely to receive an alternative diagnosis and the spectrum of differential diagnoses for pediatric patients is not as broad as for adult patients or adolescents. Initially, all enrolled patients, especially adolescents, were treated as functional GI disorders or gastroesophageal reflux disease, prolonging the diagnostic time; however, the non-response to conservative

Table 2 Diagnostic time according to clinical features of EGID patients

Overall EGID patients	**Diagnostic time (months) *median (IQR)*[a]**	***p*-value**
Age at symptoms onset, *years*	8 (3 – 11)	-
≤ 1 year	4.5 (1.5 – 10)	***0.04*** (1 year vs. 12 years)
1 – 5 years	12 (1 – 15)	
6 – 11 years	24 (8 – 54)	
≥ 12 years	12 (12 – 30)	
Age at diagnosis,*years*	10 (6 – 13)	-
Diagnostic time, *months*	12 (12 –24)	-
Eosinophilic esophagitis	**Diagnostic time (months) *median (IQR)*[a]**	***p*-value**
Sex		
Male	12 (4.5 – 24)	0.57
Female	12 (3 – 22)	
Age at symptoms onset, *years*	8 (3 - 12)	-
≤ 1 year	3 (1 – 6)	n.s.
1 – 5 years	12 (1 – 17.5)	
6 – 11 years	12 (3.3 – 30)	
≥ 12 years	12 (12 – 30)	
Age at diagnosis, *years*	10 (4 – 14)	-
Diagnostic time, *months*	12 (4 – 24)	-
Comorbidities		
Allergic diseases		
Yes	12 (4 – 24)	0.97
No	17 (1.5 – 26)	
Symptoms		
Dysphagia		
Yes	12 (8 – 30)	0.61
No	12 (3 – 24)	
Food impaction		
Yes	18 (12 – 33)	0.21
No	12 (3 – 23)	
Feeding issues and reduced appetite		
Yes	24 (12 – 27)	0.05
No	12 (3 – 23)	
Failure to thrive		
Yes	25.5 (12 – 48)	***0.02***
No	12 (3.5 – 23.5)	
GERD-like symptoms		
Yes	12 (4.5 – 24)	0.80
No	12 (3 – 24)	
Nausea and vomiting		
Yes	8 (1 – 21)	0.10
No	12 (12 – 24)	
Abdominal pain		
Yes	12 (4 – 39)	0.42
No	12 (2 – 23)	
Endoscopic pattern		
Fibro-stenotic pattern[b]		
Yes	12 (4 – 27)	0.90
No	12 (4 – 24)	

Table 2 (continued)

Non-esophageal EGIDs	Diagnostic time (months) *median (IQR)*[a]	*p*-value
Sex		
Male	18 (12 – 82.5)	0.31
Female	12 (11 – 60)	
Age at symptoms onset, *years*	7 (3 – 11)	-
≤ 1 year	11 (11 – 11)	n.s.
1 – 5 years	12 (12 – 12)	
6 – 11 years	24 (12 – 78)	
≥ 12 years	12 (12 – 69)	
Age at diagnosis, *years*	11 (6.5 – 12)	-
Diagnostic time, *months*	12 (12 – 69)	-
Comorbidities		
Allergic diseases		
Yes	18 (12 – 69)	0.87
No	12 (12 – 69)	
Symptoms		
Failure to thrive		
Yes	90 (12 – 168)	0.53
No	12 (12 – 60)	
Weight loss		
Yes	12 (11 – 96)	0.67
No	18 (12 – 64.5)	
Nausea and vomiting		
Yes	24 (12 – 60)	0.82
No	12 (12 – 79.5)	
Abdominal pain		
Yes	12 (0 – 79.5)	0.82
No	24 (12 – 60)	
Diarrhea		
Yes	18 (12 – 51)	0.92
No	12 (12 – 90)	

EGIDs eosinophilic gastrointestinal disorders, *EoE* eosinophilic esophagitis, *IQR* interquartile range, *SD* standard deviation

[a] 25^{th}-75^{th} percentiles

[b] Esophageal rings and stricture

treatments allowed us to perform GI endoscopy. Esophageal strictures generally correlate with the duration of untreated disease and a longer diagnostic delay period [3]. In the Swiss study, Schoepfer et al. found that the diagnostic delay was the only risk factor for esophageal stenosis at the time of EoE diagnosis [3]. This correlation was not confirmed by our results; however, this discrepancy may be explained by the small pediatric population enrolled and a shorter diagnostic time than that reported in the Swiss study. Finally, the shorter diagnostic time observed in our cohort may be further related to the fact that patients are followed in a third-level Hospital with a multidisciplinary pediatric team and specialized pediatric endoscopists.

Notably, we observed a high diagnostic time in children with non-esophageal EGIDs whose symptoms are heterogeneous, non-specific, and often misdiagnosed with other more common GI disorders, such as functional GI disorders [1]. The clinical heterogeneity of EGIDs and the absence of specific non-invasive biomarkers are probably the main limitations to a prompt diagnosis and a shorter diagnostic process, especially in non-esophageal EGID cases.

This study first identified that the diagnostic time is significantly associated with impaired child growth in children with EGIDs, probably due to the prolonged intestinal inflammation (that worsens feeding issues and nutritional status) and more differential diagnoses of

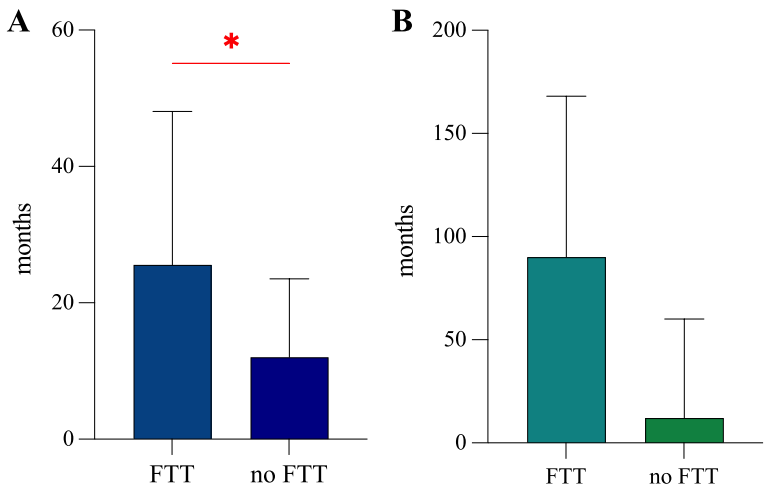

Fig. 1 Box plots displaying the median and interquartile range of diagnostic time in EoE **(A)** and non-esophageal EGID patients **(B)**. Diagnostic time (months, y-axis) is higher in EGID children and adolescents with failure to thrive (FTT, x-axis) compared to those without ($p=0.02$ and $p=0.53$ in EoE [A] and non-esophageal EGIDs [B], respectively)

FTT in comparison to other more suggestive GI symptoms like dysphagia or food impaction [11]. Common GI inflammatory disorders, such as celiac disease, are often associated with FTT, weight loss, and delayed puberty. FTT is a clinical complication often reported in toddlers and young children with severe active EoE that might require child hospitalization and the restoration of nutritional needs with large volumes of the aminoacid-based formula [12].

This study highlighted that it is fundamental to identify all delay points, starting with raising awareness among family pediatricians on EGIDs and promptly referring suspicious cases to specialized pediatric centers with a multidisciplinary team. On the other hand, allergists and gastroenterologists should promptly consider GI endoscopy with correct biopsy sampling in all those children with refractory GI symptoms, especially if complicated by atopy, peripheral eosinophilia, FTT, or feeding issues. Multidisciplinary pediatric evaluation and close collaboration with endoscopists and pathologists are pivotal in early identifying suspected cases, monitoring confirmed cases of EGIDs, and preventing potential growth complications.

Although this study first demonstrated the adverse effects of diagnostic time on growth in children with EGIDs, some limitations should be mentioned. This is a retrospective single-center study with a relatively small sample size. Moreover, these results may be influenced by the recent COVID-19 pandemic, distance from our Pediatric Hospital, or pediatric visits performed before the CPED evaluation, which we did not assess in this study. Collecting data across other pediatric centers may help reinforce these results. Further research is needed to improve EGID knowledge among pediatricians and identify non-invasive diagnostic tools and guidelines for non-esophageal forms for achieving an early diagnosis and avoiding potential complications (esophageal stenosis) and adverse effects on growth.

Abbreviations

CPED	Center for pediatric eosinophilic gastrointestinal disorders
EGIDs	Eosinophilic gastrointestinal disorders
FTT	Failure to thrive
GI	Gastrointestinal

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Authors' contributions

MV realized the entire manuscript with the support of MDF, FB, and AR. MVL revised the entire manuscript providing valuable suggestions and improvements. ADS and CK analyzed the data. MB, SC, EC, ADS, GR, GLM, AL, and IB supervised the entire study from conceptualization to manuscript editing and revision. All authors approved the final version of the manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this article.

Declarations

Ethics approval and consent to participate

The Ethical Committee of Pavia, Italy, approved this study (protocol number 0003241/22, GOLDEN study, NCT05219903). All patients provided written informed consent. All methods were performed according to the ethical standards, the Declaration of Helsinki, and its later amendments or comparable ethical standards.

Consent for publication

not applicable.

Competing interests
The authors declare that they have no competing interests.

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Review

Non-invasive biomarkers of eosinophilic esophagitis

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Abstract. Eosinophilic esophagitis (EoE) is an emerging allergen-mediated disease characterized by symptoms of esophageal dysfunction and eosinophilic inflammation. EoE diagnosis requires 15 eosinophils per high power field (eos/HPF) in tissue biopsies endoscopically obtained. The need for several endoscopies to monitoring the disease and the absence of validated non-invasive biomarkers or tools are the main reasons for the significant burden on affected patients and the healthcare system. There is a critical need for non-invasive or minimally invasive biomarkers. In the last years, several efforts have been made to identify potential biomarkers for diagnosing and monitoring the disease that we summarized in this review. The future of EoE is exciting from both a diagnostic and therapeutic standpoint. Further research is required to confirm phenotypes and histological or serological biomarkers to provide a novel endotype classification based on different cytokine or genetic signatures relevant to precision medicine. (www.actabiomedica.it)

Keywords: eosinophilic esophagitis, biomarkers, cytokines, genes, atopy.

Introduction

Eosinophilic gastrointestinal disorders (EGIDs) are emerging inflammatory diseases which may involve any part of the gastrointestinal (GI) tract and lead to the eosinophilic mucosal infiltration in the absence of secondary causes of intestinal eosinophilia (1, 2). Based on the site of the eosinophil inflammations, EGIDs are classified into eosinophilic esophagitis (EoE) and nonesophageal EGIDs, distinct in eosinophilic gastritis (EoG), gastroenteritis (EoGE), and colitis (EoC) (1). While nonesophageal EGIDs still represent a clinical enigma for clinicians, EoE is considered the prototype of EGIDs with standardized guidelines (1, 3). EoE is a chronic/remittent, allergen-mediated disease characterized by esophageal dysfunction and eosinophilic infiltration, affecting both children and adults, with a male-female ratio of 3:1 (4). The prevalence of EoE is significantly increased in the last decade. It is currently considered one of the most common causes of upper gastrointestinal morbidity, detected in 12% - 23% of patients undergoing endoscopy for dysphagia and about 50% of subjects with food impaction (4, 5). EoE diagnosis requires 15 eosinophils per high power field (eos/HPF) in tissue biopsies endoscopically obtained, without concomitant eosinophilic infiltration in other GI tracts (3). The need for several endoscopies to monitoring the disease and the absence of validated non-invasive biomarkers or tools are the main reasons for a significant burden on affected patients and the healthcare system (6). In the last years, several efforts have been made to identify

Table 1. Biomarker classification and definition.

Biomarker classification	Definition
Diagnostic Biomarker (DB)	A DB detects or confirms the presence of a disease or identifies an individual with a disease subtype.
Monitoring Biomarker (MB)	An MB assesses the status of a disease or detects the clinical (efficacy and safety) and pharmacodynamic effects of treatment (i.e., biological therapy).
Predictive Biomarkers (PreB)	A PreB assesses if the exposure to therapy or environmental agent induces favorable or unfavorable effects in a patient or group of individuals.
Prognostic Biomarkers (ProB)	A ProB can identify the likelihood of a clinical event, disease recurrence, or progression in affected patients.
Risk Biomarker (RB)	An RB indicates the potential for developing a disease in a healthy individual.

potential non-invasive biomarkers for diagnosing and monitoring the disease. Biomarkers may provide new insight into the understanding of EoE pathogenesis and defining potential endotypes with relevant impact on precision medicine.

Biomarkers are measures of biological status. According to the Food and Drug Administration (FDA) - National Institutes of Health (NIH) definition, a biomarker is a "defined characteristic measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention" (7). This definition is broad and encompasses therapeutic interventions and molecular, histologic, radiographic, or physiologic characteristics. According to their putative applications, several categories of biomarkers have been identified, and often, they may overlap each other (Table 1) (8). Notably, an ideal biomarker should present different features, such as reasonable costs and a significant impact on clinical management (Table 2). This review aimed to summarize current evidence on non-invasive biomarkers for EoE diagnosis and monitoring, highlighting promising tools and future potential candidates. We performed a non-systematic review of articles via the online database PubMed, combining the terms "eosinophilic esophagitis" AND "biomarkers." The literature review was performed in May 2021. All studies that met the following criteria were included: 1) case series, cross-sectional and cohort studies, published in English in peer-reviewed journals in the last ten years, 2) participants were children and adult patients diagnosed with EoE, according to current guidelines (3). Articles were also required to assess non-invasive biomarkers. Potentially eligible publications were manually screened and reviewed, and non-relevant publications were excluded (Figure 1).

Serological and biochemical markers

Blood eosinophils, eosinophil granule, and cell-surface proteins

Considering the allergic pathogenesis, most studies have focused on the rationale that EoE patients

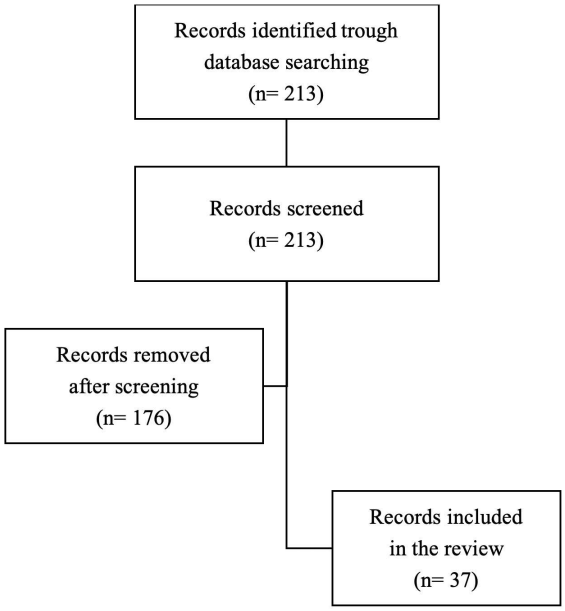

Figure 1. Methods and search strategy.

Table 2. Features of an ideal biomarker for the diagnosis and monitoring of EoE.

Features of an ideal biomarker
Correlate with the EoE state
Connect with EoE severity
Non-invasive and easy to collect or perform
Standardized
Have high sensitivity
Carry high specificity
Cost-effective
Low biological variation

may have elevated peripheral eosinophils compared to healthy controls or subjects with gastroesophageal reflux disease (GERD) (Table 3) (9-11). Many of these studies showed that peripheral eosinophil levels might increase during active disease, but whether this marker alone reflected mucosal inflammation is still unclear. Recently, Wechsler et al. have demonstrated that absolute eosinophil count (AEC), together with a panel of plasma biomarkers, such as galectin-10 (GAL-10), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), eotaxin-3 (EOT3), and major basic protein 1 (MBP-1) were useful to identify EoE subjects and predicted esophageal eosinophilia (10). Another study showed that AEC, ECP, EDN, and interleukin-(IL)-5 had statistically significant correlations with esophageal eosinophilia (11). Less recently, Rodriguez-Sanchez et al. assessed the potential usefulness of eosinophil activity markers (peripheral eosinophils, total serum IgE, ECP) as a predictor of diet response. Authors demonstrated that peripheral blood eosinophils decreased significantly in responders but not in non-responders patients (9).

Other studies have evaluated blood eosinophil progenitors (EoP) and eosinophil-surface markers with promising results (12-14). Johansson et al. recently reported that platelet activation and platelet-eosinophil association pathways might be involved in EoE pathogenesis, showing that CD41 (aIIb-integrin subunit) expressed on eosinophils surface was a potential non-invasive biomarker for esophageal eosinophilic inflammation (14). Another study examined whether phenotypic analysis of eosinophil surface markers could

Table 3. Serum biomarkers of EoE.

Author, year	Population	Study	Biomarkers	Outcome
Rodriguez-Sanchez et al, 2013 (9)	30 Adults	Cross-sectional	ECP, total IgE, peripheral blood eosinophils, and the maximum peak of eosinophils/hpf	Serum total IgE and ECP do not act as markers for EoE activity
Wechsler et al, 2021(10)	71 Children and adolescents	Prospective case-control study	Blood AEC. Plasma EDN, ECP, MBP-1, GAL-10, EOT2, EOT3. Urine OPN and MMP-9	Plasma (GAL-10, ECP, EDN, Eotaxin-3, MBP-1), and urine (OPN) biomarkers were increased in EoE compared to control. Therefore, GAL-10 is a potential biomarker for EoE screening
Min et al, 2017 (11)	115 Children and adults	Prospective case-control study	Serum analysis of AEC, EOT3, EDN, ECP, and IL-5	AEC, ECP, and EDN were higher in EoE subjects compared to controls and correlated with the degree of esophageal eosinophilia
Nguyen et al, 2011 (12)	77 Children and adolescents	Case-control study	CD66b, phospho-STAT1, and phospho-STAT6	Measurements of CD66b and phospho-STAT levels in peripheral eosinophils may be beneficial for identifying EoE
Morris et al, 2017 (13)	31 Children and adolescents	Case-control study	Peripheral blood EoP.	EoP levels were increased in patients with active EoE and significantly correlated with esophageal eosinophilia
Johansson et al, 2020 (14)	25 Adults	Prospective study	IIb-integrin (CD41)	CD41 associated with circulating eosinophils is a potential non-invasive biomarker for esophageal eosinophilic inflammation
Schwartz et al, 2019 (15)	31 Children and adolescents	Retrospective study	Peripheral blood EoP	Blood EoP correlates with tissue pathology during active EoE

Table 3. Serum biomarkers of EoE.

Author, year	Population	Study	Biomarkers	Outcome
Henderson et al, 2020 (16)	34 Children and adolescents	Prospective study	Circulating eosinophil progenitors	Blood EoP levels may be used as a biomarker to detect active EoE disease
Subbarao et al, 2011 (17)	80 Children and adolescents	Case-control study	Serum IL-5 and EDN	Serum EDN levels were significantly higher in subjects with EoE than controls
Schlag et al, 2013 (18)	15 Adults	Prospective observational study	ECP and TRP	ECP but not TRP could be a promising non-invasive biomarker to assess response to topical corticosteroid therapy
Doménech Witek et al, 2017 (18)	19 Adults	Retrospective study	Serum ECP	The serial determination of ECP was proper to monitor patients with EoE
Cengiz, 2019 (20)	29 Adults	Case-control study	Serum ECP	Serum ECP level was significantly higher in patients with EoE than in controls. In addition, ECP is strongly correlated with EREFS and the symptom of food impaction
Wright et al, 2018 (21)	39 Adults	Prospective case-control study	Serum EPX	EoE subjects had significantly lower median EPX levels
Lu et al, 2018 (23)	31 Children and adolescents	Case-control study	Serum 15-HETE	15(S)-HETE may aid in the diagnosis of EoE
Dellon et al, 2016 (24) Dellon et al, 2015 (25)	61 Adults	Case-control study	Serum periostin. Serum IL-4, IL-5, IL-6, IL-9, IL-13, TGF-α, TGF-β, TNF-α, EOT-1, -2, and -3, TSLP, MBP, and EDN	Serum periostin and cytokines levels were similar in cases and controls, and there were no changes post-treatment
Dellon et al, 2017 (27)	48 Adults	Case-control study	Autoantibodies (IgG1 and IgG4) to DSG1, DSG3, and to collagen XVII (NC16A)	Anti-NC16A and anti-DSG3 IgG4 autoantibodies were strongly associated with EoE. Anti-NC16A levels decreased significantly in EoE cases with a histologic response after topical corticosteroid treatment

AEC, absolute eosinophil count; CD, cluster of differentiation; DSG, desmoglein; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EoPs, eosinophil progenitors; EOT, eotaxin; EPX, eosinophil peroxidase; GAL-10, galectin-10; HETE, hydroxyeicosatetraenoic acid; Ig, immunoglobulin; IL, interleukin; MBP-1, major basic protein-1; MMP, matrix metalloproteinase; OPN, osteopontin; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TLSP, thymic stromal lymphopoietin; TNF, tumor necrosis factor; TRP, tryptase.

distinguish treated from untreated disease. In 2011, Nguyen et al. found elevated surface CD66 intracellular phospho-STAT1 and phospho-STAT6, which differentiated children with active EoE from treated and healthy controls (12, 15, 16). Three studies recently assessed the levels of blood EoP as potential biomarkers of active EoE, esophageal inflammation, and response to treatments both in children both adults (13, 15, 16).

Eosinophil granule proteins have been investigated as other potential markers of disease, showing inconsistent and conflicting results (17-21). Subbarao et al. determined that EDN levels provided a sustained decrease following treatment in 66 children with EoE (17). More recently, a small prospective study of 15 adults showed that serum ECP, but not tryptase (TRP), significantly correlated with tissue eosinophils

after swallowed steroid therapy (18). Moreover, ECP was high in adults with EoE, and its serial determination was also helpful in monitoring the disease (19-20).

Recent evidence suggested a pathogenetic role for arachidonate 15-lipooxygenase (ALOX15) in EoE. ALOX15 is upregulated and overexpressed in mucosal biopsies of EoE patients (22). 15(S)-hydroxyeicosatetraenoic acid (15(S)-HETE), a metabolite of ALOX15, detectable in peripheral blood, was found elevated in the EoE compared to the non-EoE group, suggesting its potential role as a disease indicator (23).

Type 2 (T2) cytokines

With an advanced understanding of EoE pathogenesis, several studies sought to assess whether T2 cytokines, including interleukin (IL)-4, IL-5, IL-6, IL-9, IL-13, TGF-α, transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, EOT-1, -2, -3, thymic stromal lymphopoietin (TSLP) and periostin were increased in the peripheral circulation of affected patients (24, 25). Therefore, peripheral cytokine measurements did not consistently characterize the esophageal inflammation or disease activity. In addition, the results of these studies are limited by the confounding influence of other concomitant allergic diseases.

Autoantibodies

EoE has been associated with a range of autoimmune conditions, such as inflammatory bowel diseases, coeliac disease, vasculitis, or type 1 diabetes mellitus (26). Moreover, esophageal epithelial barrier dysfunction is essential in EoE pathogenesis. Antibodies against epithelial adhesion molecules are founded in several autoimmune skin conditions. Therefore, EoE may even be associated with these specific autoantibodies. Dellon et al. recently demonstrated that anti-collagen XVII (NC16A) and anti-desmoglein 3 (DSG3) IgG4 autoantibodies were strongly associated with EoE. Moreover, anti-NC16A levels decreased significantly in EoE patients after topical corticosteroid treatment (27).

Histopathological biomarkers

Immunohistochemical markers

Diagnosis of EoE requires more than 15 eos/HPF in the esophageal tracts. Therefore, other diagnostic histological findings, including a thickened mucosa with basal layer hyperplasia and papillary lengthening, eosinophil surface layering, and eosinophilic microabscesses, have been proposed (28). Several studies assessing histological biomarkers have been reported. Extracellular deposition of eosinophil granule proteins, such as eosinophil peroxidase (EPX), is present in the esophagus of patients with EoE and positively correlates with the peak of tissue eosinophils (Table 4) (29, 30). Moreover, EPX levels decreased in treatment responders (29). On the contrary, Schroeder et al. demonstrated that the less invasive assessment of pharyngeal EPX did not correlate with the esophageal eosinophil count in children with EoE compared to healthy controls (31).

Other eosinophil granule proteins, such as MBP-1, TRP, EDN, and EOT-3, have been evaluated as potential histological biomarkers of EoE and response to therapy, with conflicting results. (32-36). Notably, EDN in brushing samples obtained with the nasogastric endoscopy was significantly higher in children and young adults with active EoE than patients in remission, healthy controls, and GERD. (37).

Other tissue markers

ALOX15 plays an essential role in the metabolism of fatty acids and the production of various cytokines and chemokines. ALOX15 is expressed in blood eosinophils and respiratory epithelium. ALOX15 is also upregulated in the esophageal epithelium from patients with active EoE in contrast to esophageal fragments from patients in remission, subjects with GERD, or healthy controls (38). Thus, ALOX15 immunohistochemistry may be helpful in the diagnosis of cases with clinical features of EoE but that do not meet the histological criteria (39).

IgG4

The role of immunoglobulin G4 (IgG4) in EoE pathogenesis has not been precisely defined, and

Table 4. Immunohistochemical biomarkers.

Author, year	Population	Study	Biomarkers	Outcome
Wright et al, 2021(29)	87 Adults	Case-control study	EPX	EPX was strongly correlated with tissue eosinophils accurately identified subjects with EoE and decreases in treatment responders
Saffari et al, 2017 (30)	36 Adults	Case-control study	EPX	EPX levels from esophageal mucosal samples correlated with eosinophilic inflammation
Schroeder et al, 2017 (31)	21 Children and adolescents	Case-control study	Pharyngeal and nasal EPX	EPX levels from the throat swabs do not correlate with esophageal eosinophil counts
Peterson et al, 2019 (32)	34 Adults	Retrospective study	MBP1	MBP1 is increased in esophageal biopsy specimens from symptomatic patients with EoE and may be a marker of disease activity
Kim et al, 2019 (33)	72 Adults	Retrospective study	TRP, EDN, and EOT3	TRP, EDN, and EOT3 could be promising biomarkers for disease activity, symptoms, and endoscopic response
Dellon et al, 2020 (34)	110 Adults	Retrospective study	MBP, EOT3, and TRP	Pretreatment MBP, EOT3, and TRP levels were not strongly associated with response to topical steroids. In contrast, elevated TRP levels may be associated with nonresponse compared with complete response
Dellon et al, 2014 (35)	196 Adults	Case-control study	MBP, EOT3, and TRP	Esophageal tissues from patients with EoE have substantially higher MBP, EOT3, and tryptase than controls
Dellon et al, 2012 (36)	105 Children and adults	Case-control study	MBP and EOT3	Patients with EoE had substantially higher levels of MBP and EOT3 staining than GERD patients
Smadi et al, 2018 (37)	94 Children and adults	Prospective cross-sectional study	EDN	EDN in brushing samples is significantly higher in patients having active EoE compared to healthy controls, GERD, and EoE in remission
Hui et al, 2017 (39)	21 Children and adolescents	Retrospective case-control study	ALOX15	ALOX15 immunohistochemistry helped support the diagnosis of EoE in situations with strong clinical suspicion
Clayton et al, 2014 (40)	30 Adults	Retrospective case-control study	IgG4	The level of IgG4-positive plasma cells was increased in the lamina propria and granular extracellular IgG4 deposits
Zukerberg et al, 2016 (41)	46 Adults	Case-control study	IgG4 deposits	76% of EoE cases showed int extracellular IgG4 deposits, whereas all GERD cases were negative
Rosenberg et al, 2018 (42)	36 Children and adolescents	Case-control study	IgG4	Tissue IgG4 levels correlated with esophageal eosinophil counts, histologic grade, stage scores, IL-4, IL-10, IL-13 expression, and had strong associations with a subset of the EoE transcriptome

ALOX, arachidonate lipoxygenase; EDN, eosinophil-derived neurotoxin; EPX, eosinophil peroxidase; GERD, gastroesophageal reflux disease; Ig, immunoglobulin; IL, interleukin; MBP-1, major basic protein-1; TRP, tryptase.

available studies reported conflicting data. One of the first studies showed an increased level of IgG4-positive plasma cells (IgG4-PC) in the lamina propria and granular extracellular IgG4 deposits (40). Zuckeberg et al. reported IgG4 deposits between the squamous cells in biopsies from patients with EoE. Additionally, IgG4-PC in submucosa were identified in 58% of EoE patients, but without significant difference compared to patients with GERD (41). A more recent study has demonstrated a significant relationship between IgG4 and EoE in adults and the pediatric population (42). Rosenberg et al. detected

increased IgG4 levels in children with EoE compared to healthy controls.

Moreover, IgG4 in the esophagus showed a positive correlation with concurrent peak tissue eosinophilia, histological grade, and stage according to the EoE histology scoring system (EoEHSS) (42). However, the high amount of IgG4 in esophageal mucosa still represents a conundrum. Thus, current data do not conclusively determine if high tissue IgG4 titers could be good predictors of diet response in EoE patients.

Microribonucleic acids (miRNAs) and DNA methylation

MiRNAs are single-stranded RNA molecules of 19-25 nucleotides involved in the post-transcriptional gene silencing. Several studies reported that EoE patients had a marked change in tissue-specific gene expression (Table 5). Lu et al. investigated esophageal miRNA expression profile in patients with active disease and responsive to steroids, finding that the expression levels of the most upregulated miRNAs (miR-21 and miR-223) and the most downregulated miRNA (miR-375) strongly correlated with esophageal eosinophil levels (43). More recently, Bhardwaj et al. found that the expression of salivary miR-4668 is higher in EoE compared to non-EoE subjects, suggesting its potential role as a non-invasive biomarker (44).

Other epigenetic mechanisms, different from miRNA and involved in EoE pathogenesis or response to therapies, have been recently assessed. For example, pediatric patients with EoE showed differences in mucosal DNA methylation profiles compared to controls (45). Moreover, DNA methylation differences have also been found in responder and non-responder patients (46).

Other non-invasive biomarkers

Exhaled nitric oxide

Fractional exhaled nitric oxide (FeNO) is a biomarker of eosinophilic asthma (47). However, considering the common atopic etiology, FeNO was also measured in a prospective study of 11 non-asthmatic subjects with active esophagitis before and after treatment, without any supporting role in the management of EoE (Table 6) (48). Moreover, FeNO did not help distinguish EoE from GERD (48). Therefore, no studies have shown a potential role of FeNO in EoE diagnosis and monitoring (49).

Metabolomics

Only one study assessed the metabolomic profile in patients with EoE. However, Moye et al. showed that plasma urea cycle metabolites (dimethylarginine, putrescine, and N-acetylputrescine) are elevated in children with EoE, and their levels are modified by proton pump inhibitor treatment (50).

Table 5. Epigenetic biomarkers.

Author, year	Population	Study	Biomarkers	Outcome
Lu et al, 2012 (43)	29 Children and adolescents	Case-control study	miRNAs	The expression levels of the most upregulated miRNAs (miR-21 and miR-223) and the most downregulated miRNA (miR-375) were strongly correlated with esophageal inflammation
Bhardwaj et al, 2020 (44)	44 Adults	Case-control study	Salivary miR-4668-5p	The expression of miR-4668 is higher in EoE vs. non-EoE subjects, suggesting its potential role as a non-invasive biomarker
Strisciuglio et al, 2021 (45)	20 Children and adolescents	Case-control study	Mucosal DNA methylation profile	Analyses revealed striking disease-associated differences in mucosal DNA methylation profiles in children diagnosed with EoE compared to controls
Jensen et al, 2020 (46)	36 Children and adults	Case-control study	DNA methylation profile	EoE patients that respond versus do not respond to treatment have differences in their methylation profile

DNA, deoxyribonucleic acid; RNA, ribonucleic acid.

Table 6. Other non-invasive biomarkers				
Author, year	Population	Study	Biomarkers	Outcome
Leung et al, 2013 (48)	11 Children and adults	Prospective study	FeNO	No supporting role for FeNO determination in the management of EoE
Lanz et al, 2012 (49)	55 Children and adolescents	Case-control study	FeNO	Measurement of FeNO does not help identify EoE from GERD
Moye et al, 2019 (50)	24 Children and adolescents	Prospective case-control study	Plasma metabolomics profile	Notable candidate biomarkers include dimethylarginine, putrescine, and N-acetylputrescine
Cunnion et al, 2016 (51)	75 Children and adults	Case-control study	Urinary 3-BT	Median normalized 3-BT levels were increased 93-fold in patients with EoE compared to controls
BT, bromotyrosine; FeNO, Fractionated exhaled nitric oxide; GERD, gastroesophageal reflux disease.				

3-Bromotyrosine (3-BT) is a chemical marker of eosinophil activation and is high in patients with asthma. Cunnion et al. found that 3-BT levels were increased 93-fold in patients with EoE compared to controls, providing proof of concept testing urine by a mass spectrometry method (Eosinophil Quantitated Urine Kinetic, EoQUIK) can provide a non-invasive tool to evaluate eosinophil degranulation in EoE (51).

Genetic risk loci

Eosinophilic esophagitis is a multifactorial disease. Although recent evidence suggested a fundamental pathogenetic role of the environmental factors, several studies have also reported that genetic predisposition is a significant risk factor in the development of EoE (52). Different studies, including candidate-gene identification and genome-wide association studies (GWAS), have identified gene *loci* that have been associated explicitly with EoE (53). These gene *loci* are categorized into four major groups: 1) genes involved in Type 2 (T2) inflammation, 2) epithelial barrier dysfunction, 3) enhanced fibrosis, and 4) altered immune response (54). The main genes are TSLP, calpain 14 (CAPN14), CCL26, EMSY, LRRC32, STAT6, and ANKRD27 (Table 7). Additional studies founded mutations within the filaggrin gene and the promoter region of TGFB1 (55, 56). TSLP is released by activated epithelial cells and plays a fundamental role in promoting T2 differentiation (57). Levels of TLSP are increased in patients with atopic diseases, including EoE (58). CAPN14 is a cysteine protease and plays a fundamental role in the integrity of the esophageal epithelial barrier. Furthermore, its expression is only limited to the esophageal mucosa (59). However, CAPN14 expression was almost 4-fold increased in EoE patients compared to controls. Higher levels of CAPN14 expression are associated with the downregulation of DSG-1, filaggrin, and zonulin, which are pivotal proteins of the epithelial barrier (59). CCL26 gene, which encodes for EOT3, is the most highly overexpressed esophageal transcript in patients with EoE and is critical in disease pathogenesis (60). STAT6 is essential for T2 development and is a signaling intermediate for IL-4 and IL-13 post-IL-4 receptor alpha (IL-4Ra) engagement (53). LRRC32 is a TGF-beta binding protein, and EMSY is involved in transcriptional regulation (53). In this context, the Cincinnati Children's Hospital researchers developed a specific diagnostic panel comprising a 96-gene quantitative PCR array to identify patients with EoE, monitor the disease and response to therapy, and improve the diagnosis and treatment (61).

Conclusion

EoE is an emerging disease affecting patients at any age and is currently considered one of the upper GI tract disorders with a relevant burden on patients and the healthcare systems (6). To date, the GI endoscopy is the gold standard for the diagnosis and follow-up of patients with EoE. Therefore, there is a critical need for non-invasive biomarkers to replace such invasive monitoring. Although this review showed promising non-invasive biomarkers, none of these has

been incorporated into guideline recommendations. Despite several signs of progress in understanding EoE pathogenesis, we have more to learn as we strive to improve diagnostic modalities, discover more effective and patient-targeted therapeutic strategies, and develop more accurate disease monitoring systems. We are hopeful that the growing number of genetic, molecular expression, and immunologic analyses, in conjunction with increased differentiation of clinical phenotypes and biomarker supported endotypes, will help us explain differing therapeutic responses, predict clinical response, guide individual therapies, and improve patient outcomes. The future of EoE is exciting from both a diagnostic and therapeutic standpoint. Therefore, further research is required to confirm phenotypes and histological or serological biomarkers to provide a novel endotype classification based on different cytokine or genetic signatures.

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IL-17, GAL-10, and TGF-β are promising noninvasive biomarkers of pediatric eosinophilic esophagitis.

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Main text

To the Editor,

Eosinophilic esophagitis (EoE) is a chronic/remittent allergic disorder that significantly impacts the quality of life (QoL) of affected children, primarily because of the need to periodically monitor treatment response with esophagogastroduodenoscopy (EGD).[1] It was widely demonstrated that EoE symptoms often persist despite the resolution of esophageal eosinophilia, suggesting that other inflammatory mechanisms or cell mediators may contribute to EoE pathogenesis.[1] Several studies identified potential biomarkers that could be useful in EoE management. Still, they were limited by a non-randomized study design, a small sample size, outdated diagnostic criteria, and incomplete disease activity assessment that does not consider symptoms, endoscopic, and histologic findings.[1] Therefore, no potential noninvasive biomarkers have been validated and integrated into guidelines and routine clinical practice. Despite several attempts and progress, there is a clinical need for validated noninvasive or minimally invasive biomarkers to be used as surrogates of tissue eosinophils. This study aimed to identify potential noninvasive biomarkers for EoE diagnosis and monitoring, assessing disease activity with the new proposed set of outcome measures (Pediatric Eosinophilic Esophagitis Symptom Scores [PEESS® v.2.0], Endoscopic Reference Score [EREFS]), and the peak of eosinophils [PEC]) for improving the data quality of trials and observational studies (COREOS).[2] Materials and methods are reported in the online repository.

Twenty-one healthy controls and 21 EoE patients (14 [67%] males) were enrolled. Patient and control characteristics were reported in Table E1 (online repository). At enrollment and follow-up, most of the inflammatory, tissue, vascular, and eosinophil biomarkers were not significantly related to disease activity (Table 1 and Table E2). At enrollment, interleukin (IL)-10 was slightly correlated with EoE symptom severity in univariate (coefficient 0.40, 95% CI -0.1 to 0.9; p=0.02) and multivariate (coefficient 0.49, 95% CI 0.08 to 0.89; p=0.02) analysis. IL-10 values were also related to histologically active disease (HR 0.93, 95% CI 0.87 to 1.00; p=0.04). IL-17 values were strongly and significantly predictive of high disease activity (clinically and endoscopically expressed) both in

the univariate [(coefficient 303.10, 95% CI 15.9 to 590.2; p=0.04), (coefficient 303.34, 95% CI 66.57 to 594.11; p=0.01), (HR 5.91 x10^{10}, 95% CI 0.22 to1.58 x10^{20}; p=0.07)] and multivariate [(coefficient 347.01, 95% CI 93.45 to 600.58; p=0.01), (coefficient 428.86, 95% CI 198.77 to 658.95; p=0.0001), (HR 5.91x10^{10}, 95% CI 0.22 to 1.58 x10^{20}; p=0.07)] analysis. Moreover, high IL-17 values were correlated with histologically active disease in the univariate analysis (HR 4.17 x10^{9}, 95% CI 0.16 to 1.11 x10^{20}; p=0.07) (Table 1 and Table E2).

To address whether a noninvasive biomarker could screen for EoE, we assessed serum biomarker differences between EoE and control patients. Mean values of galectin (GAL)-10 (1.17 ± 0.44 *vs*. 0.91 ± 0.35) and transforming growth factor (TGF)-β (56,176.61 ± 26,251.29 *vs*. 25,997.67 ± 6,611.68) were significantly increased in EoE patients compared to healthy controls (p=0.02 and p=0.0001, respectively) (Figure 1A). For the other biomarkers, we did not find any statistically significant differences (Table E3). ROC curves were constructed to investigate the utility of GAL-10 and TGF-β for EoE diagnosis. The AUC for TGF-β values was 0.92 (sensitivity 0.84 and specificity 1.0), whereas less exciting results were obtained for GAL-10 (AUC 0.67, sensitivity 0.75, and specificity 0.57) (Figure 1B).

In this prospective and explorative study, we substantially identified three promising noninvasive biomarkers for EoE diagnosis and surveillance using a panel of inflammatory, tissue, vascular, and eosinophil-derived markers. IL-17 values predicted clinically, endoscopically, and histologically active disease. IL-17 is a pro-inflammatory cytokine involved in several autoimmune diseases and allergic disorders, including asthma. IL-17 acts by recruiting neutrophils (but not eosinophils), activating innate immune cells, promoting B-cell functions, and facilitating the production of other pro-inflammatory cytokines (IL-1, IL-6, TNF-α, TGF-β), chemokines, and prostaglandins.[3] The role of IL-17 and Th-17 cells in EoE is still unknown. Sindher et al. demonstrated that Th-17 cells are involved in EoE pathogenesis. The expression of IL-17 is age-related, with higher levels in adults with active EoE compared to children with the same condition.[4] Lianto et al. also postulated a potential mechanism in which the dysfunctional regulation of Th-17

cells triggers the unregulated inflammatory response and recruitment of innate immune cells into the esophagus.[4] In the asthma pathogenetic model, increased IL-17 production is associated with a "Th2-low" endotype and a more severe disease.[3] Similar to asthma, IL-17 might play a role in tissue remodeling, myofibroblast differentiation, esophageal dysmotility, and mechanisms of steroid resistance. Therefore, this finding may suggest the existence of a novel endotype of EoE and the presence of complex underlying pathogenetic mechanisms.

In the case-control comparison, GAL-10 and TGF-β values were significantly increased in EoE patients compared to healthy controls. GAL-10 is a lectin family member and is the main component of the Charcot–Leyden crystals localized in the eosinophil cytoplasm. Recently, GAL-10 was identified as a surrogate biomarker for several allergic diseases, alone or in combination with other biomarkers.[5] Luminal concentrations of several eosinophil biomarkers, including GAL-10, have been evaluated using the esophageal string test and significantly correlated with esophageal inflammation and distensibility.[6-8] Lingblom et al. found that peripheral eosinophils from children with EoE had higher levels of GAL-10 mRNA than adults, highlighting that eosinophil molecular patterns differ between children and adults.[9] In this context, GAL-10 might be a promising diagnostic biomarker for the pediatric age, although more extensive studies should be performed to confirm its specificity and sensitivity.

TGF-β is a multifunctional cytokine and is considered the primary mediator of fibrosis.[10] In EoE, TGF-β stimulates myofibroblast differentiation, promotes the synthesis of extracellular matrix proteins, and induces epithelial-mesenchymal transition, leading to esophageal subepithelial fibrosis.[8] TGF-β is also implied in epithelial barrier dysfunction and impaired esophageal smooth muscle cell contraction.[10] In a recent Poland study, statistically significantly higher concentrations of TGF-β were demonstrated in adults with EoE compared to controls and correlated with treatment response.[10] In our study, TGF- β levels are significantly elevated in EoE cases compared to controls and showed a high specificity and sensitivity, suggesting that tissue remodeling phenomena are probably active in affected patients regardless of disease activity.

The strengths of this study are the prospective design and the application to a cohort of children and adolescents who are the patient categories most afflicted by the disease burden and the need for several EGDs.[1] We applied - for the first time – a validated set of measures to analyze clinical, histological, and endoscopic findings that were correlated to serum biomarkers. Therefore, this study shows the scientific standards recently approved and required to standardize the results of observational studies in EoE. We also realized an AUR-ROC analysis that helped us identify the specificity and sensitivity of diagnostic biomarkers, demonstrating that TGF-β is a reliable potential diagnostic biomarker. Finally, we decided to evaluate serum biomarkers with a procedure (blood sample) that is less invasive, easier to collect, not expensive, and more rapid than other methods, including string testing or tissue cytokine expression. Some limitations need to be highlighted. Firstly, this is a pilot single-center study with a small number of patients enrolled; thus, pooling data across other pediatric centers may be helpful to confirm and reinforce our results. The panel of serum biomarkers assessed is limited to some - but not all - inflammatory, tissue-remodeling, and vascular mediators and eosinophil proteins. Healthy patients represented the control group; therefore, to confirm the application of GAL-10 and TGF-β as diagnostic markers, we are prospective enrolling children and adolescents who underwent EGD for gastrointestinal symptoms and received a definitive diagnosis of gastroesophageal reflux disease or non-EoE esophagitis as a control group.

The results of this explorative study are promising and open new future scenarios in EoE diagnosis and surveillance. IL-17 might be considered a new marker of EoE activity, severity, and poor treatment response. Besides, as reported in the asthma model, high expression of IL-17 might define a novel “Th-2 low" endotype, which might correspond to a severe and difficult-to-treat EoE phenotype. More extensive studies are needed to investigate the pathogenetic role of IL-17 and confirm its utility as a noninvasive biomarker of disease activity. The case-control comparison found that GAL-10 and TGF- β values were significantly higher in children with EoE than controls. They might help identify patients with EoE, thus improving the diagnosis of this chronic condition, which is still burdened by clinically relevant diagnostic delay and low QoL.[1] Notably, TGF- β values showed

105 excellent and interesting specificity and sensitivity in identifying patients with EoE. However, this
106 study is the first step towards more extensive studies to confirm the results and attempt the
107 identification of noninvasive biomarkers, which are an urgent need in pediatric EoE diagnosing and
108 management.
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Ethical Approval: This study was conducted according to the Helsinki Declaration. All patients provided written informed consent. The Ethical Committee of Fondazione IRCCS Policlinico San Matteo approved this study (protocol number 3241/22).

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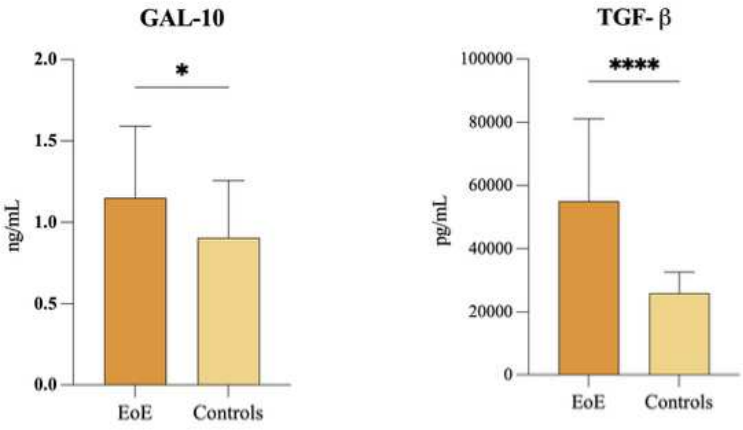
Table

Table 1 Results of the multivariate analysis.

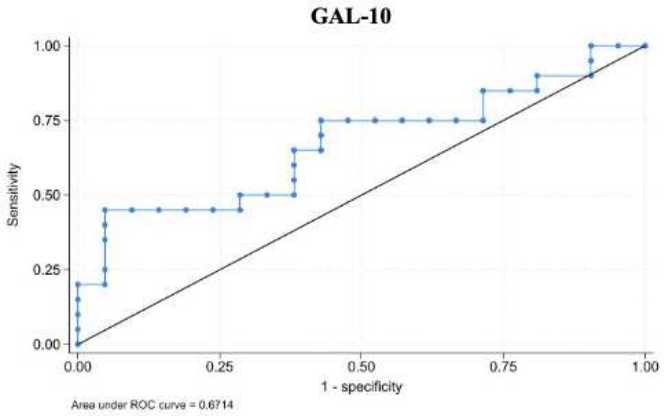
PEESS v2.0						
Biomarker	**Enrollment**			**Follow-up**		
	coefficient	**95% CI**	***p*-value**	**coefficient**	**95% CI**	***p*-value**
Eosinophils, %	-	-	-	-14.45	-43.64; 14.74	0.25
IL-17, *pg/ml*	347.01	93.45; 600.58	0.01	428.86	198.77; 658.95	0.0001
IL-10, *pg/ml*	0.49	0.08; 0.89	0.02	-	-	-
EREFS						
Biomarker	**Enrollment**			**Follow-up**		
	OR	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
IL-17, *pg/ml*	-	-	-	7.99×10^{12}	$2.42; 2.64 \times 10^{25}$	0.04
IL-10, *pg/ml*	-	-	-	0.96	0.91; 1.01	0.10
IgG4, *mg/L*	0.98	0.96; 1.01	0.26	-	-	-
Tryptase, μU/L	9.77	0.11; 10807.69	0.22	-	-	-
PEC						
Biomarker	**Enrollment**			**Follow-up**		
	OR	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Tryptase, μU/L	-	-	-	0.50	0.16; 1.55	0.23
PAI-1, *pg/ml*	-	-	-	1.00	1; 1.01	0.22

EREFS: endoscopic reference score; HR: hazard ratio; IgG4: immunoglobulins G4; IL: Interleukin; OR: odds ratio; PAI: plasminogen activator inhibitor; PEC: peak of eosinophils; PEESS: pediatric eosinophilic esophagitis symptom scores.

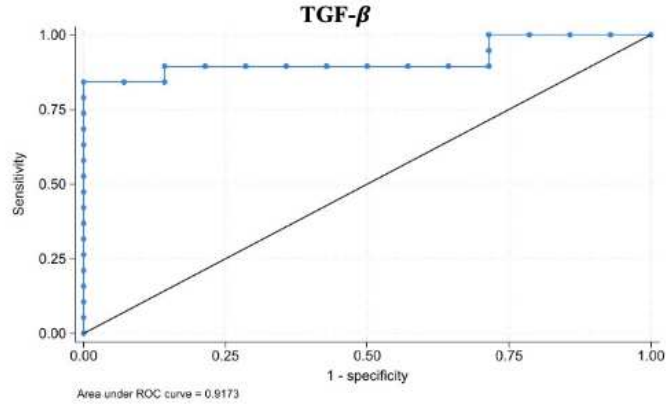
1A



1B



Empirical cutpoint estimation	
Method:	Nearest to (0,1)
Reference variable:	pat (0=neg, 1=pos)
Classification variable:	GAL10ngml
Empirical optimal cutpoint:	.98
Sensitivity at cutpoint:	0.75
Specificity at cutpoint:	0.57



Empirical cutpoint estimation	
Method:	Nearest to (0,1)
Reference variable:	pat (0=neg, 1=pos)
Classification variable:	TGFbpgml
Empirical optimal cutpoint:	37096.451
Sensitivity at cutpoint:	0.84
Specificity at cutpoint:	1.00

Figure 1A. Mean values of GAL-10 and TGF-β are significantly higher in EoE patients than in healthy controls.

Figure 1B. ROC curves for GAL-10 and TGF-β show their effectiveness as markers predicting the diagnosis of EoE.

AUC: area under the curve; GAL: galectin; ROC: receiver-operating characteristic; TGF: transforming growth factor.

Online Repository

Material and methods

For the first aim, we prospectively enrolled children and adolescents (≤ 18 years) with EoE, followed at the Pediatric Center for Eosinophilic Gastrointestinal Disorders (CPED) in Pavia, Italy. For the second aim, we also enrolled healthy controls, who were children and adolescents (≤ 18 years) without a history of atopy, allergic, or other chronic inflammatory conditions, including inflammatory bowel diseases, and evaluated at our Pediatric Clinic in Pavia. Subjects were recruited from January 2021 to May 2023.

Diagnosis of eosinophilic esophagitis (EoE) was based on the finding of ≥15 eosinophils/high power field (eos/HPF) in at least one esophageal biopsy in patients with suggestive symptoms and without secondary causes of esophageal eosinophilia, according to current international guidelines.[1] At enrollment and follow-up visits, we collected clinical (Pediatric Eosinophilic Esophagitis Symptom Scores [PEESS® 2.0]), endoscopic (Endoscopic Reference Score [EREFS 0-9]), and histologic (peak of eosinophils [PEC]) data, according to the new proposed set of outcome measures (COREOS)[2] The pediatric endoscopist calculated the EREFS at the time of endoscopy. EREFS assesses the presence and severity of esophageal edema, rings, exudates, furrows, and strictures, and the total score ranges from 0 to 9. Histology slides of mucosal biopsy samples were assessed for the peak of eos/HPF (surface area 0.26 mm^2). Endoscopic and histologic remission was defined by the EREFS score < 2 and PEC < 15 eos/HPF, respectively.[3] On the contrary, disease activity was established based on EREFS ≥ 2 and PEC ≥ 15 eos/HPF in clinically symptomatic patients.[3] Symptoms were assessed using the PEESS® v2.0, which is the only available instrument for assessing symptoms in pediatric patients with EoE. PEESS® v2.0 score ranges from 0 to 100, with a higher score indicative of more frequent and/or severe symptoms.[4]

We assessed blood eosinophil count (percent and absolute number), serum pro-inflammatory cytokines (interleukin [IL]-1, IL-2, IL-4, IL-5, IL-6, IL-17, tumor necrosis factor [TNF]-α), tissue (transforming growth factor [TGF]-β, IL-10, plasminogen activator inhibitor [PAI]-1) and vascular

(vascular endothelial growth factor [VEGF], vascular cell adhesion molecule [VCAM], angiopoietin [Ang]-2) remodeling markers, eosinophil proteins (eosinophilic cationic protein [ECP] and galectin [GAL]-10), tryptase, immunoglobulins G4 (IgG4). A blood sample was obtained from all subjects (patients and controls) at baseline and each follow-up visit from EoE patients. Samples were analyzed at the Immunology Laboratory of Fondazione IRCCS Policlinico San Matteo, Pavia. ECP and tryptase were measured by fluoroimmunoassay using Phadia^{TM} 1000 (Thermo Fisher Scientific) and expressed in μg/l. Ranges of ECP and tryptase were 15-20 μg/l and < 11.4 μg/l, respectively. To detect and quantify inflammatory cytokines, including TNF-α and TGF-β, we employed a commercial enzyme-linked immunosorbent assay kit (Immunoassay, R&D Systems, Inc. Bio-Techne Corporation Brands). The concentrations were expressed as pg/ml. GAL-10, the protein forming Charcot-Leyden crystals, was evaluated by enzyme-linked immunosorbent assay (Novus Biologicals, Bio-Techne Corporation Brands), and the results were expressed as ng/ml.

Given the observational and explorative nature of the study, the sample size was not calculated *a priori*. Continuous data were described with mean and standard deviation (SD), whereas categorical variables were used as counts and percent. The comparison of continuous variables between patients and controls was made using the Student's t-test. A 2-sided p-value < 0.05 was considered statistically significant. Cut-off levels were determined by receiver operating characteristic (ROC) curve analysis to maximize the sensitivity and specificity of those biomarkers that differentiate EoE from healthy controls. The correlation between each biomarker and disease activity at baseline and during the follow-up was analyzed by Spearman rank correlation. Linear and logistic regression analysis was used to identify independent predictors of disease activity and treatment response. Simple linear regression was applied to determine the association between serum biomarkers and continuous variables of clinical activity (PEESS® v2.0). Logistic regression was used to analyze the relationship between categorical disease activity variables (EREFS ≥ 2 and PEC $\geq$ 15 eos/HPF) with the noninvasive markers. Noncollinear variables (all measured serum biomarkers) with a p-value < 0.2 at the univariable analysis were included in a multivariable model. Results are reported as coefficient

(for PEESS® v2.0), odds ratio (OR), and hazard ratio (HR) with 95% confidence interval (CI). The software Stata 18.0 (StataCorp, College Station, TX, USA) was used for all computations.

All data were extracted from electronic medical records (Fenix™, Software). Every patient identifier (name and surname) was replaced with a specific numeric code. All patients provided written informed consent. The Ethical Committee of Fondazione IRCCS Policlinico San Matteo approved this study (protocol number 3241/22).

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Table E1 Clinical features of enrolled EoE patients and healthy controls.

Clinical features	EoE (n= 21)	Controls (n= 21)
Age at enrollement, *mean ± SD (years)*	9.1 (± 4.5)	10.8 (± 3.0)
Male, *n (%)*	14 (67%)	9 (43%)
Ethnicity, *n (%)*		
Caucasian	18 (85%)	19 (90%)
North African	2 (10%)	1 (5%)
Asian	1 (5%)	1 (5%)
Other coexistent allergic diseases, *n (%)*	17 (81%)	0 (0%)
Allergic rhinitis, *n (%)*	11 (65%)	-
Food allergy, *n (%)*	9 (53%)	-
Asthma, *n (%)*	4 (24%)	-
Atopic dermatitis, *n (%)*	4 (24%)	-
Anaphylaxis, *n (%)*	4 (24%)	-

SD: standard deviation.

Table E2 Results of the univariate analysis.

PEESS v2.0						
Biomarker	**Enrollment**			**Follow-up**		
	coefficient	**95% CI**	***p*-value**	**coefficient**	**95% CI**	***p*-value**
Eosinophils, *mm³*	12.58	-14.6; 39.8	0.34	-0.04	-5.28; 5.19	0.99
Eosinophils, *%*	0.87	-0.2; 3.8	0.53	1.92	0.34; 3.50	0.02
ECP, μU/L	-0.005	-0.4; 0.4	0.98	0.12	-0.14; 0.38	0.37
Tryptase, μU/L	0.19	-6.2; 5.8	0.95	-0.62	-4.13; 2.90	0.73
Gal-10, *ng/ml*	-9.67	-25.5; 6.2	0.22	2.13	-9.18; 13.46	0.71
IL-1, *pg/ml*	0.34	-0.1; 0.1	0.49	0.05	-0.034; 0.14	0.24
IL-2, *pg/ml*	-0.25	-0.6; 0.1	0.16	-0.03	-0.11; 0.50	0.44
IL-4, *pg/ml**	-	-	-	-0.68	-3.01; 1.64	0.57
IL-5, *pg/ml*	1.70	-15.4; 18.9	0.83	2.78	-8.79; 14.35	0.64
IL-6, *pg/ml*	0.06	-0.2; 0.3	0.55	0.1	-0.064; 0.26	0.23
IL-10, *pg/ml*	0.40	-0.1; 0.9	0.09	-0.12	-0.48; 0.24	0.50
IL-17, *pg/ml*	303.10	15.9; 590.2	0.04	330.34	66.57; 594.11	0.01
TNF-α, *pg/ml*	0.11	-0.5; 0.3	0.17	0.21	-0.166; 0.56	0.28
TGF-β, *pg/ml*	-0.0001	-0.0004; 0.0002	0.61	0.00003	-0.00011; 0.0002	0.61
VEGF-A, *pg/ml*	0.002	-0.05; 0.06	0.92	0.003	-0.07; 0.07	0.94
VCAM-1, *pg/ml*	-6.2×10^{6}	-0.00003; 0.00002	0.57	-6.91×10^{-6}	-0.00002; 0.0001	0.53
Ang-2, *pg/ml*	-0.04	-0.1; 0.005	0.39	0.004	-0.014; 0.006	0.41
PAI-1, *pg/ml*	-5.41×10^{-6}	$-0.0002; 6.6 \times 10^{-6}$	0.37	-9.4×10^{-6}	-0.00007; 0.00005	0.77
IgG4, *mg/L*	-0.01	-0.03; 0.006	0.18	0.002	-0.02; 0.03	0.84
EREFS						
Biomarker	**Enrollment**			**Follow-up**		
	OR	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Eosinophils, *mm³*	0.36	0.01; 12.00	0.57	1.30	0.22; 7.71	0.77
Eosinophils, *%*	0.78	0.52; 1.16	0.21	0.95	0.81; 1.11	0.52
ECP, μU/L	1.01	0.96; 1.07	0.69	0.98	0.94; 1.01	0.21
Tryptase, μU/L	5.40	0.82; 35.54	0.08	0.82	0.56; 1.21	0.33
Gal-10, *ng/ml*	1.82	0.19; 17.16	0.60	2.28	0.79; 6.63	0.13
IL-1, *pg/ml*	0.72	0.23; 2.25	0.57	1.00	0.97; 1.03	0.79
IL-2, *pg/ml*	0.97	0.92, 1.02	0.27	0.99	0.96; 1.02	0.36
IL-4, *pg/ml**	-	-	-	-	-	-
IL-5, *pg/ml*	0.76	0.09; 6.75	0.81	0.64	0.18; 2.24	0.49
IL-6, *pg/ml*	0.97	0.91; 1.03	0.41	0.93	0.86; 1.02	0.13
IL-10, *pg/ml*	1.08	0.94; 1.25	0.28	0.95	0.91; 1.00	0.05
IL-17, *pg/ml*	1	-	-	5.91×10^{10}	$0.22; 1.58 \times 10^{20}$	0.07
TNF-α, *pg/ml*	1	-	-	0.99	0.98; 1.00	0.28
TGF-β, *pg/ml*	1.00	0.99; 1.00	0.23	1.00	1; 1.00002	0.47
VEGF-A, *pg/ml*	1.00	0.99; 1.00	0.53	1.00	1; 1.01	0.73
VCAM-1, *pg/ml*	1.00	0.99; 1.00	0.20	1.00	1; 1.000001	0.52
Ang-2, *pg/ml*	1.00	0.99; 1.00	0.13	1.00	1; 1.0003	0.18

PAI-1, *pg/ml*	1.00	0.99; 1.00	0.67	1.00	1; 1000003	0.67
IgG4, *mg/L*	0.99	0.99; 1.00	0.09	1.00	1; 1.001	0.22
PEC						
Biomarker	**Enrollment**			**Follow-up**		
	OR	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Eosinophils	0.015	8.5×10^{-6}; 27.31	0.27	0.42	0.02; 10.92	0.61
Eosinophils, *%*	0.75	0.46; 1.23	0.26	0.98	0.74; 1.28	0.86
ECP, μU/L	0.97	0.90; 1.05	0.47	0.93	0.87; 1.00	0.05
Tryptase, μU/L	0.76	0.29; 2.02	0.58	0.64	0.40; 1.05	0.08
Gal-10, *ng/ml*	4.28	0.39; 46.89	0.23	1.38	0.37; 5.20	0.64
IL-1, *pg/ml*	1	-	-	0.97	0.71; 1.31	0.83
IL-2, *pg/ml*	0.99	0.93; 1.04	0.65	0.99	0.96; 1.02	0.54
IL-4, *pg/ml**	-	-	-	-	-	-
IL-5, *pg/ml*	1	-	-	0.45	0.09; 2.24	0.33
IL-6, *pg/ml*	0.95	0.81; 1.11	0.52	0.93	0.83; 1.05	0.23
IL-10, *pg/ml*	0.91	0.26; 7.34	0.70	0.93	0.87; 1.00	0.04
IL-17, *pg/ml*	1	-	-	4.17×10^{9}	0.16; 1.11×10^{20}	0.07
TNF-α, *pg/ml*	0.99	0.94; 1.04	0.60	0.98	0.94; 1.02	0.39
TGF-β, *pg/ml*	1.00	0.48; 1.35	0.42	1.00	1.00; 1.00002	0.99
VEGF-A, *pg/ml*	1.00	0.99; 1.01	0.14	1.003	1.00; 1.01	0.22
VCAM-1, *pg/ml*	1.00	0.99; 1.00	0.53	1.00	1; 1.000002	0.67
Ang-2, *pg/ml*	0.99	0.99; 1.00	0.42	1.00	1; 1.001	0.30
PAI-1, *pg/ml*	1.00	0.99; 1.00	0.07	1.00	1; 1.000002	0.09
IgG4, *mg/L*	1.00	0.99; 1.00	0.45	1.00	1.00; 1.002	0.50

*Omitted because of collinearity

Ang: angiopoietin; ECP: eosinophilic cationic protein; EREFS: endoscopic reference score; GAL: galectin; HR: hazard ratio; IgG4: immunoglobulins G4; IL: Interleukin; OR: odds ratio; PAI: plasminogen activator inhibitor; PEC: peak of eosinophils; PEESS: pediatric eosinophilic esophagitis symptom scores; TGF: transforming growth factor; TNF: tumor necrosis factor; VCAM: vascular cell adhesion molecule; VEGF: vascular endothelial growth factor.

Table E3 Case-control comparisons.

	Healthy controls		EoE patients		
Biomarker	**Mean, ± SD**	**95% CI**	**Mean, ± SD**	**95% CI**	***p*-value**
Eosinophils	0.24 ± 0.21	(0.14; 0.34)	0.31 ± 0.28	(0.17; 0.45)	0.19
Eosinophils%	3.48 ± 2.64	(2.25; 4.72)	4.26 ± 2.76	(2.89; 5.63)	0.19
ECP, μU/L	25.70 ± 20.88	(14.58; 36.83)	18.35 ± 19.80	(8.81; 27.90)	0.15
Tryptase, μU/L	2.82 ± 1.11	(2.22; 3.40)	3.30 ± 1.43	(2.57; 4.04)	0.14
Gal-10, *ng/ml*	0.91 ± 0.35	(0.75;1.07)	1.17 ± 0.44	(0.96;1.38)	0.02
IL-1, *pg/ml*	14.32 ± 41.62	(-15.46; 44.07)	15.75 ± 68.76	(-16.43;47.93)	0.48
IL-2, *pg/ml*	8.72 ± 15.91	(-0.46; 17.91)	13.85 ± 19.21	(4.86; 22.84)	0.21
IL-4, *pg/ml*	0.1 ± 0	(0.1; 0.1)	0.1 ± 0	(0.1; 0.1)	-
IL-5, *pg/ml*	0.19 ± 0.28	(-0.01; 0.39)	0.24 ± 0.43	(0.04; 0.44)	0.37
IL-6, *pg/ml*	36.45 ± 56.78	(6.19; 66.70)	13.67 ± 36.69	(-4.02; 31.35)	0.08
IL-10, *pg/ml*	13.06 ± 7.73	(8.60; 17.53)	12.52 ± 14.07	(5.93; 19.10)	0.45
IL-17, *pg/ml*	0.10 ± 0	(0.1; 1.0)	0.11 ± 0.022	(0.09; 0.12)	0.24
TNF-α, *pg/ml*	13.40 ± 24.63	(-0.81; 27.62)	10.60 ± 44.12	(-10.05; 31.24)	0.41
TGF-β, *pg/ml*	25,997.67 ± 6,611.68	(22,180.2; 29,815.15)	56,176.61 ± 26,251.29	(43,523.89; 68,829.33)	0.0001
VEGF-A, *pg/ml*	284.01 ± 176.18	(196.40; 371.61)	205.99 ± 151.74	(127.98; 284.01)	0.09
VCAM-1, *pg/ml*	558,282.7 ± 224,952	(446,416.7; 67,0148.7)	682,058.6 ± 358636.80	(497,664.6; 866,452.7)	0.11
Ang-2, *pg/ml*	1,304.56 ± 556.48	(1,027.83; 1,581.29)	1,398.88 ± 796.27	(989.48; 1,808.29)	0.34
PAI-1, *pg/ml*	190,321.8 ± 88,563.43	(146,280.3; 234,363.4)	355,181.8 ± 625,089.60	(33,790.33; 676,573.20)	0.14

Ang: angiopoietin; ECP: eosinophilic cationic protein; EREFS: endoscopic reference score; GAL: galectin; HR: hazard ratio; IgG4: immunoglobulins G4; IL: Interleukin; OR: odds ratio; PAI: plasminogen activator inhibitor; PEC: peak of eosinophils; PEESS: pediatric eosinophilic esophagitis symptom scores; TGF: transforming growth factor; TNF: tumor necrosis factor; VCAM: vascular cell adhesion molecule; VEGF: vascular endothelial growth factor.

Chapter 5

TREATMENTS OF EGIDs

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REVIEW ARTICLE

Eosinophilic Gastrointestinal Diseases in Children: A Practical Review

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Abstract: Primary eosinophilic gastrointestinal diseases (EGIDs) represent a heterogeneous group of disorders characterized by eosinophilic inflammation in the absence of known causes for eosinophilia, selectively affecting different segments of the gastrointestinal tract. While pediatric eosinophilic esophagitis (EoE) is a well-defined disease with established guidelines, Eosinophilic Gastritis (EoG), Eosinophilic Gastroenteritis (EoGE) and Eosinophilic Colitis (EoC) remain a clinical enigma with evidence based on limited anecdotal case reports. Large cross-sectional studies in the US defined a prevalence of EoG and EoGE ranging from 1,5 to 6,4/100.000 and from 2,7 to 8,3/100.000 subjects respectively, while the prevalence of EoC ranges from 1,7 to 3,5/100.000 subjects. Regarding the pathogenesis, it is hypothesized that EGIDs result from the interplay between genetic predisposition, intestinal dysbiosis and environmental triggers. Clinically, EGIDs might present with different and nonspecific gastrointestinal symptoms depending on the involved intestinal tract and the extension of eosinophilic inflammatory infiltrate. The diagnosis of EGIDs requires: 1. recurrent gastrointestinal symptoms, 2. increased eosinophils for high power field in biopsy specimens, 3. absence of secondary causes of gastrointestinal eosinophilia. No validated guidelines are available on the clinical management of patients with EGIDs. Evidence from case reports and small uncontrolled case series suggests the use of dietary and corticosteroids as the first-line treatments. Considering the clinical follow-up of EGIDs, three different patterns of disease course are identified: single flare, recurring course-disease and chronic course-disease. This review will focus on pediatric EGIDs distal to esophagus, including Eosinophilic Gastritis (EoG), Eosinophilic Gastroenteritis (EoGE) and Eosinophilic Colitis (EoC).

Keywords: Eosinophils, eosinophilic gastrointestinal diseases, eosinophilic gastroenteritis, eosinophilic colitis, food allergy, endoscopy, diet, corticosteroids.

1. INTRODUCTION

Primary eosinophilic gastrointestinal diseases (EGIDs), represent a heterogeneous group of disorders that selectively affects the different segments of the gastrointestinal tract, from the esophagus to the rectum, and are characterized by eosinophilic inflammation in the absence of known causes for eosinophilia [1]. EGIDs might present in adults and in children with different and nonspecific gastrointestinal symptoms depending on the involved intestinal tract and the extension of eosinophilic inflammation, including mucosal, muscular and serosal pattern [2]. While pediatric eosinophilic esophagitis (EoE) is a well-defined disease with established guidelines [3], EGIDs distal to esophagus, including Eosinophilic Gastritis (EoG), Eosinophilic Gastroenteritis (EoGE) and Eosinophilic Colitis (EoC) remain a clinical enigma with evidence limited to a small number of reported cases. For this review, the term EGIDs refers to EoG, EoGE, and EoC, unless otherwise specified.

2. EPIDEMIOLOGY

The exact incidence of EGIDs is still unclear. Since the first description of eosinophilic gastroenteritis in 1937 [4], about 400 cases have been reported and most of them are described in case reports, case series or retrospective studies [2, 5]. Large cross-sectional studies in the US defined a prevalence of EoG and EoGE ranging from 1,5 to 6,4/100.000 and from 2,7 to 8,3/100.000 subjects respectively, while the prevalence of EoC ranges from 1,7 to 3,5/100.000 subjects [6, 7]. In a recent review of a population-based database in the US of more than 35 million people, Mansoor *et al*. reported that the prevalence of EoGE in children (5,3/100.000) was slightly higher than in adults (5,1/100.000); the opposite pattern was observed for EoC (1,6/100.000 in children and 2,3/100.000 in adults) [8]. Furthermore, EGIDs resulted to be more prevalent in Cauca-

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sians (77,5% of all EoGE and 81,80% of all EoC) than African-Americans and Asians and in females than in males (57,7% *vs.* 42,3% for EoGE and 66,2% *vs.* 33,8% for EoC) [8]. The age at onset of EGIDs varies widely, and a relevant number of cases have been described in children (10,7/100.000 children in US) [7]; in adults the disease typically arises between the third and fifth decade of life [9]. In a large US survey on EGIDs, Spergel *et al*. reported a higher prevalence of EGIDs in the northern rather than in the southern states, and in urban/suburban rather than rural areas (7,2 patients/year *vs.* 5,2 patients/year respectively) [10].

3. PATHOGENESIS

The pathogenesis of EGIDs is only partially understood. Eosinophils are normally present in the lamina propria of the mucosa of healthy gastrointestinal (GI) tract, with the only exception for the esophagus. It is demonstrated that intestinal eosinophils are involved in the GI mucosal immune system, playing a main role in host defense, in particular against parasitic infection and food allergens, and their number increases during intestinal inflammation [11]. Several signals are responsible for the activation of intestinal eosinophils, including non-specific tissue damage, parasitic and bacterial infections and allergens. The activation of eosinophils in the gastrointestinal tract induces tissue damage and is responsible for the symptoms observed in patients with EGIDs [9]. Histopathologic findings in EGIDs patients revealed an excessive number of activated eosinophils with signs of degranulation [12]. The activated eosinophils produce highly bioactive inflammatory mediators, that could trigger degranulation of mast cells and release of chemokines, cytokines, lipid mediators and neuro-mediators (Table **1**), inducing the Th2-type immune response and bowel inflammation [13]. Recent studies showed that Th2 cytokines (IL-4, IL-5 and IL-13) and eotaxin-3 are upregulated in patient with EGIDs, playing a possible role in the pathogenesis of these diseases. Therefore, recent knowledge in eosinophil pathophysiology clearly demonstrates that the eosinophil is a multifunctional leucocyte expressing a wide pattern of surface markers and is able to interact with other immune cells at the frontier between innate and adaptive immunity [9, 14].

Food allergens are known as possible triggers of inflammation, especially in EoE [15, 16]. The elimination or elemental diets are one of the first-line therapy in patients with EoE, showing an improvement of symptoms and histological resolution in more than 70% of affected patients [15]. The association of allergy and atopy is also described in about 64% of patients with EGIDs, suggesting that other triggers might induce eosinophilic inflammation of the intestinal tract distal to the esophagus [17].

It is also reported that patients with EGIDs might present autoimmunity without atopy and intestinal eosinophilia might be explained by more complex immune or autoimmune pathways [18]. Other possible triggers that might play part in the pathophysiology of EGIDs include gastrointestinal dysbiosis [19] and anatomical malformations [20]. In combination, genetic predisposition, dysbiosis, and environmental triggers (ingested or inhaled allergens) might induce eosinophilic inflammation in EGIDs patients [21].

4. CLINICAL MANIFESTATIONS

EGIDs symptoms are heterogeneous and depend on the localization and the layer of the GI wall involved (Klein's classification) (Table **2**). At diagnosis, the mucosal form was reported from 44% to 57,5%, the muscular form from 12% to 30%, and the serosal form from 12,5% to 49% of the EGIDs patients [22, 23]. Generally, in EoGE and EoC patients, the most frequent symptoms of mucosal involvement are abdominal pain, diarrhea, bloating, nausea and vomiting [5, 24]. Severe EoGE might present with protein losing enteropathy, hypoalbuminemia, anemia, malabsorption and weight loss. Compared to adults, children and adolescents may develop growth retardation, failure to thrive, delayed puberty and amenorrhea (Table **3**). Moreover, the coexistence of EoE in children with EoGE has been reported [25]. Patients with muscular involvement - often affecting stomach and duodenum - might develop intestinal obstruction or sub-obstruction, as a consequence of mechanical and functional blockage due to the eosinophilic inflammation of the muscular layer [26]. The serosal form is characterized by the eosinophilic infiltrate of all layers of the bowel wall and it might present with eosinophilic-rich ascites, bloating and abdominal pain [1, 27].

EGIDs might associate with different complications. Acute pancreatitis secondary to the inflammatory obstruction of the pancreatic duct was described in an adult patient with eosinophilic duodenitis [27]. It is reported that adults with muscular EoGE underwent unnecessary laparoscopy for acute bowel obstruction [26]. Other studies showed adult patients presenting with duodenal ulcer or intestinal perforation [28, 29].

Table 1. Key-mediators involved in eosinophilic gastrointestinal inflammation.

Inflammatory Mediators	Chemokines	Cytokines	Lipid Mediators	Neuromediators
Eosinophil cationic protein (ECP) Eosinophil-derived neurotoxin Eosinophil peroxidase Major basic protein (MBP)	Eotaxin-3 (CCL26) Regulation upon Activation Normal T-cell Expressed and Secreted (RANTES)	IL-1 IL-3 IL-4 IL-5 IL-13 Transforming growth factors (TGF)	Leukotrienes Platelet activating factor (PAF)	Substance P Vasoactive intestinal polypeptide (VIP)

Table 2. Gastrointestinal manifestations of eosinophilic gastrointestinal diseases.

Mucosal Pattern	Muscular Pattern	Serosal Pattern
• Abdominal pain, • Nausea, • Vomiting, • Diarrhea, • Rectal Bleeding, • Anemia, • Protein-losing enteropathy, • Malabsorption, • Weight lose	• Bowel thickening, • Intestinal obstruction	• Eosinophilic ascites

Table 3. Childhood symptoms.

• Growth retardation
• Failure to thrive
• Delayed puberty
• Amenorrhea

It is widely described that EGIDs are associated with allergic diseases [7]. Patients often present with food and drug allergies, rhinitis, asthma, sinusitis, eczema or urticaria. Prevalent allergy comorbidities are food allergy, asthma and allergic rhinitis [8].

5. DIAGNOSIS

EGIDs diagnosis is difficult and often missed, mainly because the previously described presenting symptoms are non-specific and heterogeneous. Generally, the correct diagnosis occurs years after the onset of first symptoms [9].

EGIDs distal to the esophagus are characterized by the abnormal eosinophilic infiltration of different segments of the stomach, small intestine and colon. Although standard guidelines for EGIDs are still lacking, it is agreed that a definitive diagnosis requires [30]:

1. Recurrent gastrointestinal symptoms,
2. Increased eosinophils for high power field in biopsy specimens,
3. Absence of secondary causes of gastrointestinal eosinophilia.

5.1. Laboratory Tests

There are no diagnostic and prognostic biomarkers for EGIDs. Peripheral eosinophilia is often found in EoGE and EoC patients, but it is not required for the diagnosis. More than 70% of patients with EoGE have transient peripheral blood eosinophilia (eosinophils > 500/mm^3) [9]. Severe eosinophilia (> 1.500/ mm^3) could be observed in patients with predominantly serosal form of EoGE; in these cases, hypereosinophilic syndrome (HES) should be ruled out [9, 17, 31]. Many other clinical conditions might present with peripheral eosinophilia. In fact, mild-moderate peripheral eosinophilia is commonly detected in patients with allergies and parasitic infections, that should be excluded especially in children with recurrent abdominal pain [17]. Furthermore, peripheral eosinophilia is not an index of disease activity and response to therapy in EGIDs [32].

Allergy tests are not specific markers for EGIDs; positive skin prick tests, elevated serum total IgE levels and increased IgEs specific to inhaled and ingested allergens have been detected only in few patients with EGIDs [33]. Few studies reported higher levels of fecal and serum eosinophil cationic protein (ECP) and serum eosinophil-derived neurotoxin in EGIDs compared to inflammatory bowel diseases (Crohn diseases and ulcerative colitis) [34] and elevated levels of serum α2-macroglobulin have been found in EGIDs patients [35].

5.2. Endoscopy and Radiological Tests

In patients with EoGE and EoC, endoscopic findings might appear to be normal or non-specific. However, erythema, edema, white specks, focal erosions, ulcerations, fold thickening, polyps, nodules, and friability have all been described in EoGE [5, 30]. In EoC, colonoscopy can reveal non-specific mucosal alterations, such as patchy areas of edema or erythema, whitish lesions, and aphthous ulceration [36]. Although endoscopy is fundamental to demonstrate the mucosal disease, it is inadequate to detect the involvement of deeper GI layers. In fact, the diagnosis of EoGE in patient with symptoms of muscle and serosal involvement requires surgery or laparoscopy and it is not always ethically feasible, especially in pediatric patients.

The role of radiological tests is described in a few case reports. In patients with EGIDs, computer tomography (CT) scanning showed non-specific radiological findings; wall thickening, polyps, ulcers, strictures, ascites, omental thickening, and lymphadenopathy are described in patient with EoGE [36, 37] while wall thickening, isolated haustral thickening, and circumferential thickening in EoC patients [38]. The differential diagnosis of these radiological findings with the ones observed in the most common inflammatory bowel diseases, such as Crohn's disease, is difficult and requires specialized radiological competence.

5.3. Histology

Histology is the gold standard for the diagnosis of EGIDs. Eosinophils are common GI cells; they are present in all intestinal segments with the only exception of the esophagus. The eosinophil count in the lamina propria increases from the duodenum to caecum and then decreases from the right colon to the rectum [9, 39]. Currently, there is no consensus on the cut-off value of intestinal eosinophils to be considered pathological [9, 24, 30, 31]. Few studies evaluated the threshold of intestinal eosinophils in pediatric patients with inflammatory intestinal diseases compared to healthy children [39-43]. De Brosse *et al* showed a gradient of the eosinophil distribution in gastrointestinal tract of healthy pediatric patients: a maximum of 26 eosinophils per high-powered field (eos/hpf) in the duodenum, 50 eos/hpf in

the ascending colon, 30 eos/hpf distally [40]. Different pathological cut-off of eosinophilic inflammation has been used in various studies, ranging from 20 to more than 100 eos/hpf (Table **4**) [44-47]. The mucosal histopathology of EoGE and EoC is similar and characterized by the presence of a large amount of eosinophil clusters in the lamina propria with degranulation. The epithelium might show degenerative and regenerative alterations and foveolar and crypt hyperplasia [45]. Immunohistochemistry is useful to detect the deposition of major basic protein granules, that is specific of eosinophil degranulation and more common in patients with EGIDs than in healthy controls [12]. Analyses of ascites fluid or surgical specimens have an important role in demonstrating the abnormal presence of eosinophils in serosal and muscular EoGE [9].

Table 4. Pathological cut-off of intestinal eosinophils per higher power field.

Intestinal Tract	Eos/hpf
Stomach [44]	>30
Small intestine [44]	>52
Colon [44, 46, 47]	
Right	>100
Transverse and descending	>84
Rectosigmoid	>64

6. DIFFERENTIAL DIAGNOSIS

EGIDs are diagnosed after the exclusion of other causes of intestinal eosinophilia (Table **5**). Intestinal infections are the most frequent cause of secondary eosinophilic gastrointestinal inflammation. Especially in children with recurrent abdominal pain, parasitic infections must be considered if peripheral eosinophilia is observed. Higher levels of intestinal eosinophils are also described in patients with colonic spirochaetosis [47] and before and after the eradication treatment of Helicobacter pylori infection [48]. In children presenting with rectal bleeding and diarrhea allergic proctocolitis must be ruled out; in these cases, the diagnosis is usually clinic and symptoms resolve after the elimination of cow's milk proteins. In patients with food allergy, colonic eosinophils are increased and show signs of degranulation [49]. Mild eosinophilic infiltration of duodenum was described in patients with active coeliac disease and with severe mucosal atresia, suggesting that these cells might play part in mucosal inflammation [50]. Eosinophils are also present in gastrointestinal biopsies of patients with inflammatory bowel diseases [51], rheumatoid arthritis, systemic sclerosis, and vasculitis (in particular eosinophilic granulomatosis with polyangiitis) [52]. Interestingly, Talley *et al* described duodenal eosinophilia in patient with functional dyspepsia, particularly in those with early satiety, implicating duodenal eosinophils in the pathogenesis of functional gastrointestinal symptoms [53]. In patients with severe peripheral eosinophilia for more than 6 months, and signs and symptoms of organ involvement, HES must be ruled out and bone marrow aspiration, lymphocyte phenotyping, and testing for a FIP1L1-PDGFRA fusion transcript must be performed [54].

Table 5. Differential diagnosis.

Food and drug allergy
Parasite infections (ascariasis, toxocariasis, trichinosis, schistosomiasis, teniasis, ankylostomiasis, trichuriasis, strongyloidiasis)
Malignancies (leukemia, lymphoma)
Inflammatory bowel diseases (Crohn disease, ulcerative colitis)
Chronic graft-versus-host disease
Autoimmune disease (eosinophilic granulomatosis with polyangiitis or Churg-Strauss syndrome)
Hypereosinophilic Syndrome (HES)

7. TREATMENT

No validated guidelines are available on the clinical management of patients with EGIDs distal to the esophagus. Although reported in case reports and small uncontrolled case series, several therapeutic options are described. The first-line treatments are dietary and corticosteroids therapies (Table **6**).

7.1. Dietary Therapy

Robust evidence shows that elimination and elemental diets improve clinical symptoms and reduce mucosal eosinophils in children and adults with EoE [55, 56]. Dietary therapy is considered as a first-line treatment for EGIDs [30]. Recently, Lucendo *et al*. reported that the elemental diet is efficacious to induce clinical remission in about 75% of children with eosinophilic gastroenteritis and colitis, but low patient compliance limits its usefulness especially in adolescents and adults [57]. Chehade *et al*. also demonstrated that the elemental diet is more effective than elimination diet in children with severe EoGE and protein-losing enteropathy [58]. However, there are no large studies on long-term efficacy and safety of elemental diet and evidence is limited to a few case reports and small case series that do not evaluate the histological remission. Empiric elimination of allergy-associated foods is the most commonly and efficaciously used option with about 82% of clinical response rate [30]. It is reported that response to food-elimination diet does not correspond to food allergies identified by skin prick testing or serum specific IgE levels. Furthermore, many patients with EGIDs present specific serum IgE levels, without any history of food reaction [57].

7.2. Corticosteroids

Corticosteroids are the mainstay of therapy, if dietary treatment fails or is impractical and in case of severe or complicated eosinophilic gastroenteritis and colitis [30, 59]. Steroids are able to inhibit eosinophilic growth factors, such as IL-3, IL-5, and GM-CSF [33]. Most case series have reported clinical remission in 50 to 90% of patients with EGIDs treated with corticosteroids [9, 17]. The lack of an

Table 6. Therapeutic options of eosinophilic gastrointestinal diseases.

Therapy	Treatment Indication	Dose
Diet (six-food-elimination diet, elemental diet)	First line treatment	
Prednisone	First line treatment for induction of remission	20 - 40 mg/day or 0,5 - 1 mg/kg/day for 2 weeks, then tapering in 6-8 weeks
	Maintenance for steroid-depend EGID	5 - 10 mg/day
Budesonide	First line treatment for induction of remission	9 mg/day
	Maintenance for steroid-depend EGID	6mg/day then 3mg/day
Montelukast	Steroid sparing agent	5 - 10 mg/day
Sodium cromoglicate	Steroid sparing agent	100-300 mg every 6 hour daily in adults
Ketotifen	Steroid sparing agent	2 - 4 mg/day
Azathioprine	Steroid sparing agent	2 - 2,5 mg/day
Mepolizumab	In refractory EGID	-
Omalizumab	In refractory EGID	-
Infliximab/Adalimumab	In refractory EGID	-

initial response should lead to a reevaluation of the diagnosis [60]. Various treatment strategies have been reported. At diagnosis, therapy with oral prednisone at dose of 20-40 mg/day [61] or at higher doses (0,5–1 mg/kg per day) for 2 weeks is recommended [30]. Once clinical remission is achieved, dose of prednisone is tapered over the next 6-8 weeks until it is stopped [62]. About 20% of patients with EoGE develop corticosteroid dependency [9]. Maintenance treatment with a low dose of prednisone (5–10 mg per day, or the minimum required dose to guarantee the clinical response) might be necessary for patients with disease relapse during or after drug tapering [30, 62]. Use of systemic corticosteroids is limited by their undesirable long-term side-effects (in particular, growth retardation, bone abnormalities, and adrenal axis suppression). An alternative to prednisone is budesonide, a synthetic steroid with high topical glucocorticoid activity and low systemic bioavailability due to its first-pass hepatic metabolism, thus minimizing systemic side effects [24, 63]. Although the use of budesonide is described in a few case reports, it might be considered an efficacious and safe option. The recommended dose of budesonide is 9 mg/day, then it can be tapered to 6 mg/day and finally 3 mg/day for maintenance therapy [9, 64, 65].

7.3. Steroid-sparing Agents

Despite their efficacy, the long-term use of corticosteroids is not desirable because of their known side effects. Several steroid-sparing agents result in clinical experience with the treatment of inflammatory bowel disease (IBD) (immunosuppressant and anti-TNF- α therapies) or asthma (sodium cromoglycate, ketotifen, montelukast, anti-IL-5 and anti-IgE therapies) [24, 30]. There are no clinical trials nor large studies on their efficacy in maintenance therapy or when corticosteroid therapy fails. Our current knowledge is limited to case reports and small case series.

7.3.1. Mast Cell Inhibitors and Leukotriene Receptor Antagonists

Few studies reported clinical improvements with mast cell inhibitors, such as sodium cromoglycate and ketotifen [30, 66]. Sodium cromoglycate has been used with some success in adult patients with mucosal and subserosal EoGE, alone or in combination with steroids [67]. The recommended oral dose varies from 100 to 300 mg per dose four times daily in adult patients [24]. Ketotifen is a mast-cell inhibitor with antihistaminic effect, administered in dosages of 2-4 mg/day [24]. Melamed *et al*. showed an improvement in symptoms, a reduction of intestinal eosinophils, and a decrease in IgE levels in six treated patients with EoGE [68].

7.3.2. Montelukast

Montelukast is a selective leukotriene (LTD4) inhibitor that blocks leukotriene-induced vascular permeability, smooth muscle contraction and chemotaxis of eosinophils and basophils [69]. Montelukast is efficaciously used in patients with asthma. The efficacy of Montelukast in EGIDs remains controversial. Some studies suggested that treatment with Montelukast (5-10 mg/day) induces clinical improvement in adults and children with steroid-resistant and recurrent EoGE and duodenal eosinophilia [70, 71]. However, Daikn *et al*. reported that Montelukast had no effect on tissue eosinophils or symptoms in a patient with severe and stricturing EoGE [72].

7.3.3. Anti-interleukin 5 and Anti-IgE Agents

Mepolizumab and reslizumab are two humanized anti-interleukin 5 (anti-IL-5) monoclonal antibodies. They target eosinophils by binding to IL-5 and interfering with its ligation to IL-5Rα expressed mainly on the eosinophil membrane [73, 74]. Mepolizumab was tested in children and adults with eosinophilic esophagitis, resulting in a reduction of esophageal eosinophils and peripheral eosinophilia; how-

ever, no clinical improvement was reported [75]. In a small clinical trial with reslizumab a clinical improvement was observed in patients with EoGE. However, rebound eosinophilia and clinical relapse were seen after the discontinuation of the treatment [76]. Further randomized, controlled trials are needed in order to clarify the efficacy of mepolizumab and reslizumab in EGIDs.

Omalizumab is a humanized anti-IgE monoclonal antibody that binds to free IgEs and prevents their binding to Fc-ε-RI, leading to inhibition of mast cell and basophil activation [77]. Currently, omalizumab is not recommended for EGIDs treatment because the clinical improvement and the reduction of serum IgE levels do not correlate with changes in peripheral or tissue eosinophilia [78]. This suggests that blocking IgE alone may not be effective to treat EoGE and EoC.

7.3.4. Immunosuppressant and Anti-TNF-α Therapies

Inflammatory bowel diseases (IBD) therapies, including mesalamine, azathioprine, and anti-TNF- α agents are trialed in small case series and case reports of patients with severe EGIDs. The use of mesalamine is anecdotal and described in few patients with EoC [79]. Azathioprine might have steroid-sparing effects; it is described to be efficacious in patients with EoGE and acute abdomen at the same dose used in patients with IBD (2– 2.5 mg/kg) [80].

Infliximab and adalimumab are two antibodies directed against the tumor necrosis factor-α (TNF-α), widely used in the treatment of IBD and rheumatological diseases. While infliximab is a chimeric immunoglobulin-G1 antibody while adalimumab is totally humanized. The use of anti-TNF-α agents in the treatment of severe adult EoE has been explored with poor results [81]. However, Turner *et al*. described the efficacy of anti-TNF-α agents (both infliximab and adalimumab) in children with refractory eosinophilic gastroenteritis and colitis [82].

7.4. Novel Therapies

Recently, Song *et al*. showed a reduction of the eosinophilic inflammation and an improvement in the gastrointestinal disease in murine models of EoGE treated with a novel antibody directed against CCR3, an eotaxin receptor [83].

OC000459 is a selective chemoattractant receptor- homologous molecule on Th-2 cell (CRTH2) antagonist. CRTH2 is a prostaglandin D2 (PGD2) receptor, expressed by Th-2 cells, eosinophils, and basophils, that mediates eosinophil chemotaxis and recruitment. In a randomized, double-blind, placebo-controlled trial of adult patients with severe and active EoE, Strauman *et al*. showed that OC000459 reduced tissue eosinophils but did not improve esophageal lesions [84]. There are no studies on OC000459 in patients with EGIDs.

7.5. Fecal Microbiota Transplantation

The most effective and well-studied indication for fecal microbiota transplantation (FMT) is recurrent and severe Clostridium difficile infection [85]. There is only one case report that describes the efficacy of FMT in a man with severe, refractory and stricturing EoGE presenting with long-term diarrhea [86]. At this time, there is insufficient evidence to recommend FMT for EGIDs and other gastrointestinal diseases, and further studies are needed.

7.6. Surgery

Bowel obstruction is a consequence of eosinophilic inflammation in muscle layers. Several case reports described that the diagnosis of EGIDs occurs after resection of the obstructing segment, recurring to laparotomy or laparoscopic surgery [26]. However, in most cases, bowel obstruction is reversible with corticosteroid treatment. Bowel perforation is a severe complication of eosinophilic duodenitis and gastritis; in these cases, surgery is absolutely required [26, 29].

8. NATURAL HISTORY

There are few data on the clinical follow-up of EGIDs, especially in children. A recent study analyzed the clinical presentation and long-term follow-up of a cohort of 43 adult patients with EoGE [23], identifying three different patterns of disease course:

1. A single flare characterized by the presence of gastrointestinal symptoms for less than 6 months (42%);
2. A recurring course-disease defined by at least two relapses (37%);
3. A chronic course-disease characterized by the presence of gastrointestinal symptoms for more than 6 months without a period of remission (21%).

The detected risk factors of clinic relapse are the absence of spontaneous remission and high peripheral eosinophilia [23]. In a follow-up study of patients with EoGE, Reed *et al* showed that about one-third of patients remained in long-term remission, while other patients present a persistent or progressive disease [17]. Further large studies are needed to understand the natural history of eosinophilic gastrointestinal diseases and the possible risk factors associated to worst prognosis. Walker *et al*. recently suggested a possible algorithm for the management of EGIDs [46].

CONCLUSION

EGIDs represent a heterogeneous group of disorders that selectively affects the different segments of the gastrointestinal tract and are characterized by eosinophilic inflammation in the absence of known causes for eosinophilia. Intestinal biopsy is the diagnostic gold standard of EGIDs, and it should be performed in all patients with recurrent or persistent gastrointestinal symptoms and peripheral eosinophilia. More detailed knowledge and more widespread tendency of pathologists to count eosinophils in biopsy specimens improved and increased the diagnosis of EGIDs. While pediatric EoE is a well-defined disease with established guidelines, further studies are needed in order to better define epidemiology, pathogenesis, diagnosis and prognosis of EGIDs distal to esophagus. Moreover, standard guidelines for the diagnosis and management of EoGE and EoC are still lacking. Actually, recommended and efficacious treatment of EGIDs are corticosteroids, but some patients might present a steroid-dependent or resistant disease. Most of the patients with EGIDs show a benign course of their disease; however, fur-

ther investigations about the natural history of EGIDs are needed.

LIST OF ABBREVIATIONS

ECP	=	Eosinophil Cationic Protein
EGIDs	=	Eosinophilic Gastrointestinal Diseases
EoC	=	Eosinophilic Colitis
EoE	=	Eosinophilic Esophagitis
EoG	=	Eosinophilic Gastritis
EoGE	=	Eosinophilic Gastroenteritis
FMT	=	fecal Microbiota Transplantation
GI	=	Gastrointestinal
HES	=	Hypereosinophilic Syndrome
IBD	=	inflammatory Bowel Disease
MBP	=	Major Basic Protein
RANTES	=	Regulation upon Activation Normal T-cell Expressed and Secreted
TGF	=	transforming Growth Factor
TNF	=	Tumor Necrosis Factor

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REVIEW
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Diet Therapy in Eosinophilic Esophagitis. Focus on a Personalized Approach

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Eosinophilic esophagitis (EoE) is a chronic allergic disease defined by a marked eosinophilic inflammation and symptoms of esophageal dysfunction. EoE is a heterogeneous disease and severely impacts the quality of life of affected patients. The current therapeutic management of EoE is based on two cornerstones: medication and diet therapy, both effective but limited by several critical issues. The choice of one or the other therapy might depend on the different disease phenotypes (allergic vs. non-allergic, inflammatory vs. fibro-stenotic), patient's age (adult vs. childhood-onset), food habits, patient/family preference, and familiar financial resource. Diet therapy is a successful treatment but limited by low patient adherence, the need for several endoscopies, food restrictions, psychosocial impact, and potential nutritional deficiencies. All these limitations could be effectively overcome with multidisciplinary and personalized management. This review summarizes the most recent evidence on the dietary elimination approaches and will provide a practical guide to clinicians in managing and implementing dietary therapy for patients with EoE.

Keywords: eosinophilic esophagitis, diet, food allergens, food-reintroduction, personalized therapy, multidisciplinary approach, phenotype, endotype

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INTRODUCTION

Eosinophilic esophagitis (EoE) is the most characterized eosinophilic gastrointestinal disorder (EGID) and is a chronic/remittent allergic disease, defined by a marked eosinophilic inflammation and symptoms of esophageal dysfunction (1, 2). Currently, the diagnosis of EoE requires the presence of more than 15 eosinophils per high power field (eos/HPF) in the endoscopically obtained esophageal biopsies in patients with suspicious symptoms (1, 2).

It is estimated that EoE affects about 0.5-1/1,000 patients in the USA, varying widely across the different Countries and mostly prevailing in Caucasian patients and male sex (3). However, in the last 20 years, several epidemiological studies showed a significant increase in the epidemiology of EGIDs, partially related to improved medical awareness and knowledge through modern diagnostic instruments (4–6). It was also postulated that changes in environmental factors may have contributed to the significant increase in EoE epidemiology (7). Recently, Navarro et al. found that the pooled prevalence of EoE is 34.4 cases/100,000 inhabitants and is higher for adults than for children (42.2/100,000 vs. 34/100,000) (5). The pooled incidence rate was 6.6/100,000 people per year in children and 7.7/100,000 in adults (5).

Genome-wide association studies have identified multiple susceptibility genes associated with EoE risk and a complex model of disease inheritance. EoE is a multifactorial disease typically characterized by a type 2 (T2) inflammation (8). The impaired epithelial barrier function plays a pivotal role in the pathophysiology of EoE, inducing the release of alarmins (thymic stromal lymphopoietin, IL-15, IL-33), which then activates the type 2 innate lymphoid cells (ILC2) and basophils. The subsequent release of IL-4, IL-5, and IL-13 recruits and expands the eosinophilic inflammation. The consequences of this sustained inflammation include tissue remodeling and esophageal dysfunction. Esophageal fibrosis begins in the early phases of the disease course, initially involving the *lamina propria* (6). Fibrosis has been found in 57–88% of young patients and children and 89% of adult patients with EoE (9). However, the increased esophageal stiffness, due to subepithelial fibrosis and muscular hypertrophy, clinically occurs with food impaction and dysphagia, symptoms that are typically reported by adult patients (**Figure 1**) (9). Although the pathogenesis is not entirely understood and is likely non-IgE-mediated, food allergens are known to trigger EoE, stimulating the already dysregulated immune cells through the impaired esophageal epithelial barrier (10, 11). Most patients with EoE are allergic to 1–3 foods that trigger esophageal inflammation, according to Koch's postulate (12). Esophageal inflammation is resolved once the food(s) is removed from the diet, and reproducibility reactivates it when the culprit allergen(s) is reintroduced (10, 12–14). Recent and conflicting studies have also supported the potential role of aeroallergens in the pathogenesis of EoE, with evidence mostly limited to case series and case reports (8, 15).

Since EoE was first recognized as a distinct clinical entity in the mid-1990's, several signs of progress were achieved. However, there are diagnostic and therapeutic aspects that should be investigated, and one of these concerns the diet therapy and nutritional assessment of patients with EoE. To date, most data on nutritional management came from the single center's experience rather than comparative clinical trials. This review summarizes the most recent evidence on the dietary elimination approaches and will provide a practical guide to clinicians in managing and implementing dietary therapy for patients with EoE.

CLINICAL FEATURES AND HETEROGENEITY OF EOE

EoE is a heterogeneous disease with variable symptoms and severity, comorbidities (atopic vs. non-atopic), treatment response, and natural history. Moreover, EoE severely impacts both adults and children's quality of life (QoL) (16, 17). Notably, EoE symptoms vary with age (1). Toddler and young children generally experienced food refusal, feeding difficulties, and recurrent vomiting and/or regurgitation. On the contrary, school-aged children reported abdominal/epigastric pain, refractory gastroesophageal reflux, whereas adolescents and adults present dysphagia and food impaction. Symptoms, endoscopic and histological findings, and response to treatments reflect the typical evolution of the EoE inflammation through time, as reported in **Figure 1**. In this context, different clinical patterns or phenotypes have been identified (16). The "inflammatory" pattern is generally observed in childhood and is defined by the endoscopic evidence of edema, erythema, linear furrowing, and the prevalent eosinophilic esophageal inflammation in histologic samples (16, 18, 19). On the other hand, the "fibro-stenotic" and "fibrotic" phenotypes primarily affect adolescents and adults with dysphagia and food impaction (16, 18–20). These phenotypes are endoscopically characterized by fixed esophageal rings and/or strictures resulting from tissue remodeling and esophageal fibrosis (16, 18–20). The clinical and histological heterogeneity might reflect and partially explain the heterogeneous response to available therapies (16). While diet and medical therapies may reduce tissue fibrosis in childhood, this remodeling process may persist despite the resolution of inflammation in adulthood (6). Recently, Shoda et al. identified three potential endotypes of EoE, using a machine learning approach to analyze histological, endoscopic, and molecular features of US patients with EoE. The first endotype (EoEe1) was recognized in 35% of the cohort and was mainly characterized by a minimal eosinophilic inflammation and steroid responsiveness. The EoEe2 endotype affected 29% of patients and showed a prevalent T2 inflammation, pediatric-onset, and a low steroid response. Finally, 36% of the EoE cohort (EoEe3) presented an adult-onset and structuring disease (16, 21). Therefore, according to this endotype classification, patients with the EoEe1 endotype might successfully be treated with diet and steroid therapy, and children with the EoEe2 endotype might benefit from the anti-T2 immune agents (i.e., dupilumab) (22). Finally, adult patients with the EoEe3 endotype are more challenging to treat with available therapies; thus, esophageal dilatations are the only current solution to esophageal stenosis (22). In the future, a validated endo-phenotype classification of EoE will provide better disease management and aim physicians to develop a personalized medicine using targeted treatments.

HOW TO MANAGE EOE

The current therapeutic management of EoE is based on two cornerstones: the medication (proton pump inhibitors [*PPIs*] and topical corticosteroids) and diet therapy, both effective but limited by different critical issues (2, 17, 18). Patients with EoE should be maintained on monotherapy when effective (2, 23). However, if monotherapy fails or loses its efficacy, a combination therapy (diet + topical steroid) may be indicated (24). Although not already approved, biological therapy with dupilumab showed promising results in adults with EoE, improving symptoms, esophageal inflammation, and distensibility (25).

When correctly administered (1 mg/kg/day, twice daily), PPIs are effective in about 50% of children with EoE. The long-term effectiveness of PPIs is still debated and might be related to specific genetic polymorphisms (26, 27). However, disease remission might appear more sustained in patients with the inflammatory phenotype than those with the fibro-stenotic or stenotic phenotype (19, 26, 27). Therefore, as widely

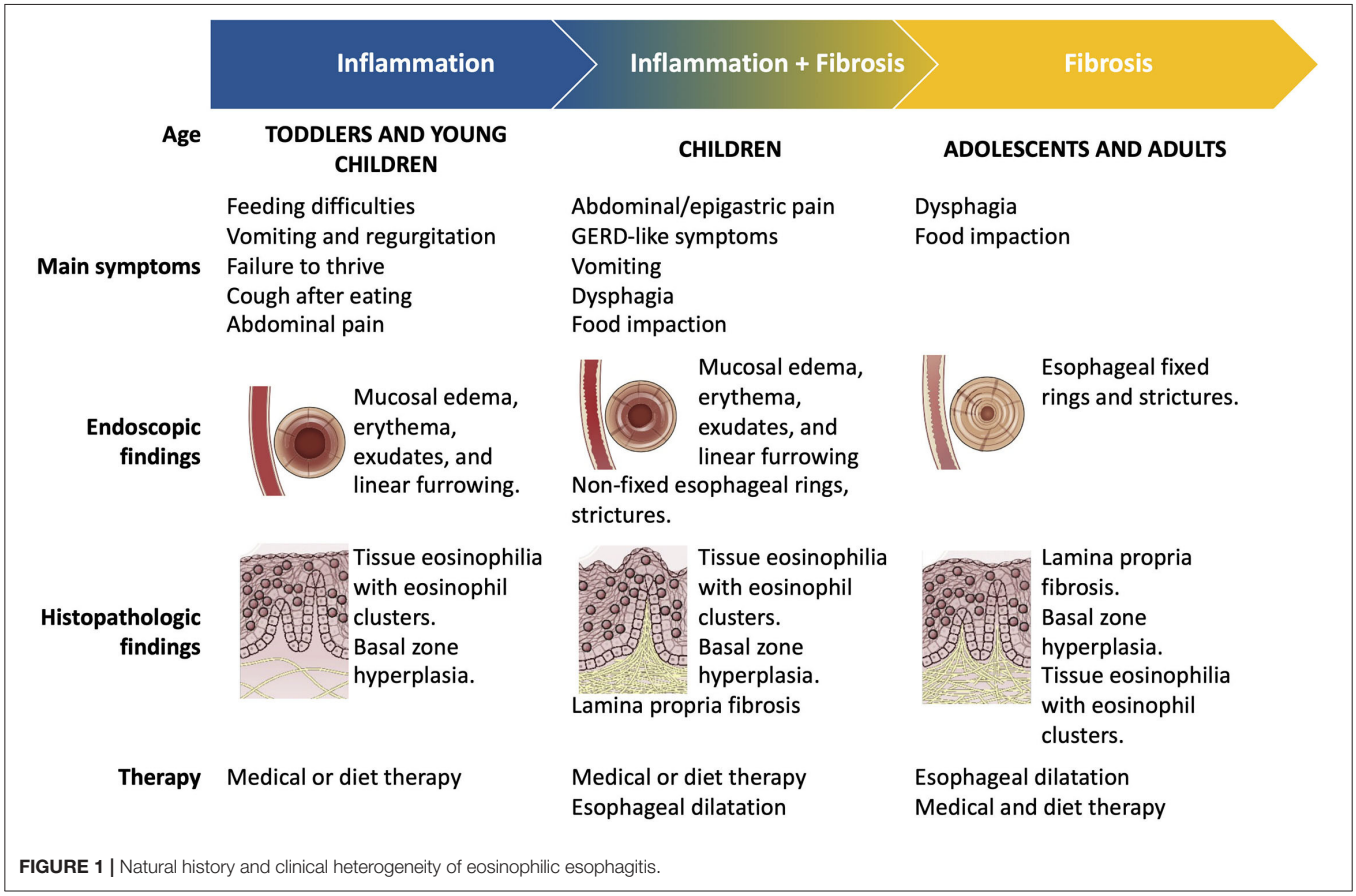

FIGURE 1 | Natural history and clinical heterogeneity of eosinophilic esophagitis.

reported, PPI response is not homogeneous and prolonged in all patients (27).

Current formulations of topical corticosteroids have not yet been approved by the Food and Drug Administration (FDA) (27). However, in 2017, the European Medicines Agency (EMA) authorized orodispersible budesonide for adults with EoE (https://www.ema.europa.eu/en/documents/assessment-report/jorveza-epar-public-assessment-report_en.pdf). Slurry budesonide and swallowed fluticasone are both effective to induce EoE remission. However, their long-term use is compromised by patient adherence and side effects (19, 27). Although topical corticosteroids are generally safe and well-tolerated, long-term administration is complicated mainly by esophageal candidiasis in 1–3% of patients (19, 27). Moreover, there have been sporadic reports of decreased cortisol levels, minor anthropometric growth changes, and low bone mineral density; thus, physicians may consider periodic monitoring for growth, adrenal, and bone metabolism (27). When complete remission is achieved, topical corticosteroid treatment should be administered at the minimal effective dosage to reduce the risk of potential long-term side effects. On the other hand, a brief cycle of oral/systemic corticosteroid is also suggested for controlling refractory esophageal inflammation (28).

In 1995, Kelly et al. successfully demonstrated the efficacy of the exclusive aminoacid-based formula diet in children with EoE (29). Since this attempt, several studies have evaluated the therapeutic role of elimination diets. Three main dietary approaches, such as the elemental, empiric, and allergy test-directed elimination diets, have been proposed with variable efficacy rates and specific advantages and disadvantages (**Table 1**) (2, 28). Although the therapeutic choice mainly depends on clinician experience and patient's needs, several clinical aspects must be considered before prescribing a diet therapy, especially in children.

TABLE 1 | Diet therapies of eosinophilic esophagitis.

Diets	Specific recommendation	Results
Elemental diet	Elemental formula	Adults and children ~ 90%
Elimination diet		
6-food	Cow's milk, wheat, eggs, soy/legumes, seafood, nuts	Adults 52–70% Children 74%
4-food	Cow's milk, wheat, eggs, soy/legumes	Adults 52–70% Children 74%
2-food	Cow's milk, wheat	Adults and children 43%
1-food	Cow's milk	Adults and children 44–70%

IgE, immunoglobulin E.

DIET THERAPY

What Clinicians Should Know Before Prescribing a Diet Therapy

According to international guidelines, the diet approach is considered the first-line treatment of EoE and is as effective as medication therapy (2, 28). It is widely demonstrated that foods are the primary triggers of EoE; indeed, food elimination diets (FEDs) have demonstrated complete remission of EoE, with higher rates (>90%) in patients treated with elemental diet than empirical FEDs and test directed diets (12). However, FEDs are challenging and are not risk-free. Patients on diet therapy may potentially develop nutritional deficiencies, eating disorders and experience a low QoL and high psychological impacts. Before prescribing a FED, allergists and gastroenterologists should consider several clinical aspects, such as (1) disease-severity and patient's nutritional status, (2) presence of maladaptive feeding behaviors or/and food allergies, (3) family and patient preferences, and (4) financial resources (27). Then, clinicians should widely explain to patients and their families the advantages and disadvantages of diets to choose judiciously (7, 27). Children and adults, candidates for diet therapy, should also be informed of the need to undergo several endoscopic and clinical evaluations to confirm or assess disease remission (2, 28). Patients and parents of children with EoE should know that more restrictive diet therapies (elemental and empirical FED) may be expensive and alternative foods may be often found only in specialty stores (30). On the other hand, clinicians should guarantee a strict follow-up with upper GI endoscopy to evaluate the remission 6–12 weeks after diet beginning and each food reintroduction (2, 28). Moreover, physicians should consider patients' food habits, such as eating at home/work or school canteen, reliance on pre-prepared foods, and cultural issues (12).

At baseline, patients with active EoE are generally not malnourished (31). However, toddlers and young children may present growth failure and feeding issues that are not a contraindication for an elimination diet after a comprehensive assessment of the nutritional status (32). As reported in different pediatric studies, a significant proportion of children with EoE has other coexisting allergic diseases, including multiple IgE-mediated food allergies (33–35). These patients generally are not the best candidates for FEDs, as the extensive food restrictions may compromise patient's compliance and negatively impact on QoL (14).

Elemental Diet

The elemental diet consists in removing all foods. Thus, patients are exclusively fed with an aminoacid-based formula for at least 6 weeks (2, 28, 36). The elemental diet is the most effective treatment, and several studies reported high complete remission rates in children and adults with active EoE (37). EoE patients treated with the elemental diet experienced a significant reduction in their symptoms and achieved complete histologic remission in 90 and 94% of pediatric and adult cases, respectively (**Table 1**). Moreover, the highest efficacy rates are primarily observed in patients with a non-stricturing phenotype (27, 38–41).

TABLE 2 | Advantages and disadvantages of elemental diet.

Advantages	Disadvantages
• Rapid and complete remission in 2 weeks • Better acceptance in young children and toddlers • Rescue therapy or temporary solution in adults with non-stricturing EoE • Pediatric formulas are almost nutritionally complete • Nutritional supplement	• Poor palatability and low patient's compliance • The administration through NG or G-tube may induce feeding skills regression • High cost and insurance coverage • Less effective in stricturing EoE

EoE, eosinophilic esophagitis; G, gastric; NG, nasal gastric.

The elemental diet is a fundamental therapeutic option, especially in severe EoE cases. However, the elemental diet is not the first-line approach for its limitations in most cases (12). Elemental diet is often proposed as rescue therapy or temporary solution in adults and adolescents with refractory EoE when all other treatments alone or in combination have failed (12, 27). In toddlers or young children with active EoE complicated by failure to thrive, the elemental diet is generally considered a valid and useful therapeutic option with the highest patient compliance (12, 27). In severe disease or when large volumes of the aminoacid-based formula are required to meet the caloric needs and restore the good nutritional status, nasal-gastric (NG) or gastric (G) tube feeding is a temporary solution (42). These interventions should be discouraged in the long-term treatment, especially in children with feeding disorders, because they are often fraught with difficult solid food oral reintroduction and progressive feeding skills regression (12). In children with multiple food triggers and subsequent high diet restrictions, elemental formulas can also be used as supplements of protein and energy necessary for adequate growth and puberty spurt (12).

Although the elemental diet can induce a rapid disease-remission in only 2 weeks, several disadvantages limit its adherence (**Table 2**) (43). The poor palatability, highly restrictive nature, costs, and psychosocial isolation are the main reasons for treatment discontinuation and low compliance (12, 17, 27). To remedy these issues, the elemental diet is often modified, introducing one or two less allergenic foods (generally vegetables or fruits) in addition to the aminoacid-based formula (12, 27). Moreover, elemental formulas are also available in flavored and unflavored formulations to address patient taste and preferences (12). Pediatric elemental formulas are nutritionally complete but do not contain dietary fiber. Thus, fiber supplements (free of known allergens) should be prescribed in patients who develop or are more prone to constipation (12).

Food Elimination Diets

Empirical FED

In general, more foods are eliminated from the diet, more likely the remission is achieved at the first endoscopy. FED is the most widely used diet treatment for EoE. The first proposed

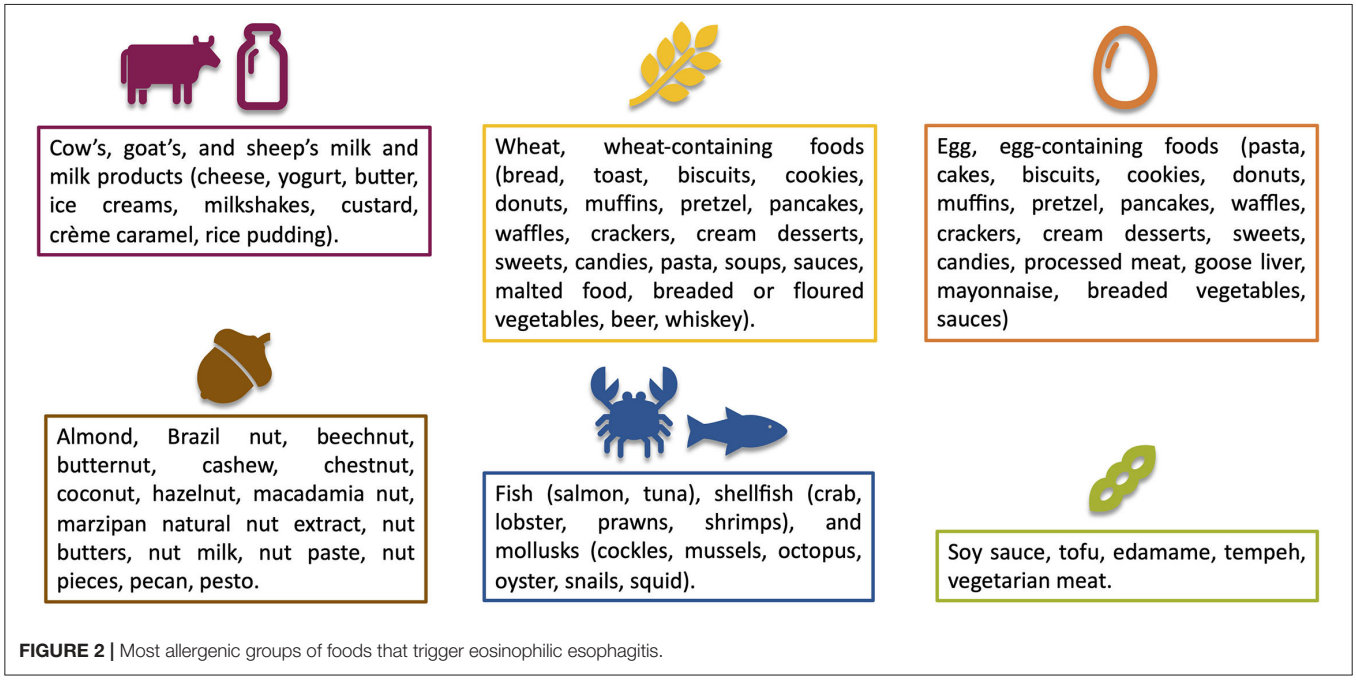

FIGURE 2 | Most allergenic groups of foods that trigger eosinophilic esophagitis.

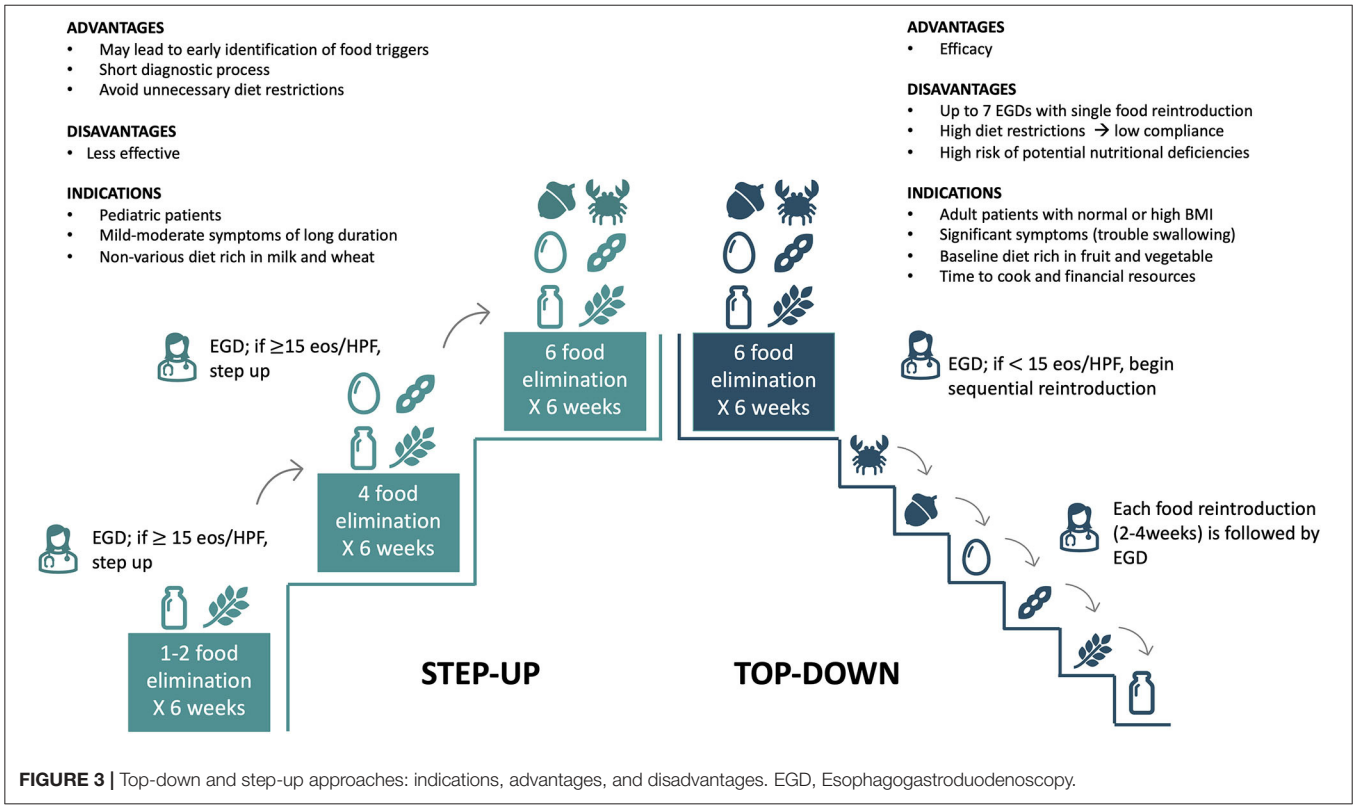

FIGURE 3 | Top-down and step-up approaches: indications, advantages, and disadvantages. EGD, Esophagogastroduodenoscopy.

FED was founded on avoiding the six most common food-triggers of EoE in the Western diet, such as milk, wheat, egg, soy/legumes, peanut/tree nuts, and seafood/fish (**Figure 2**) (44). Patients should be advised that all these foods should be avoided both in fresh and backed forms (12). The 6-FED effectively induces histologic remission in about 74% of children and 70% of adults with EoE (**Table 1**) (45). Studies assessing the efficacy of 6-FED have been fundamental to find that the most common food triggers are cow's milk (up to 85% of the pediatric cases), followed by wheat/gluten (up to 60%), egg, and soy/legumes

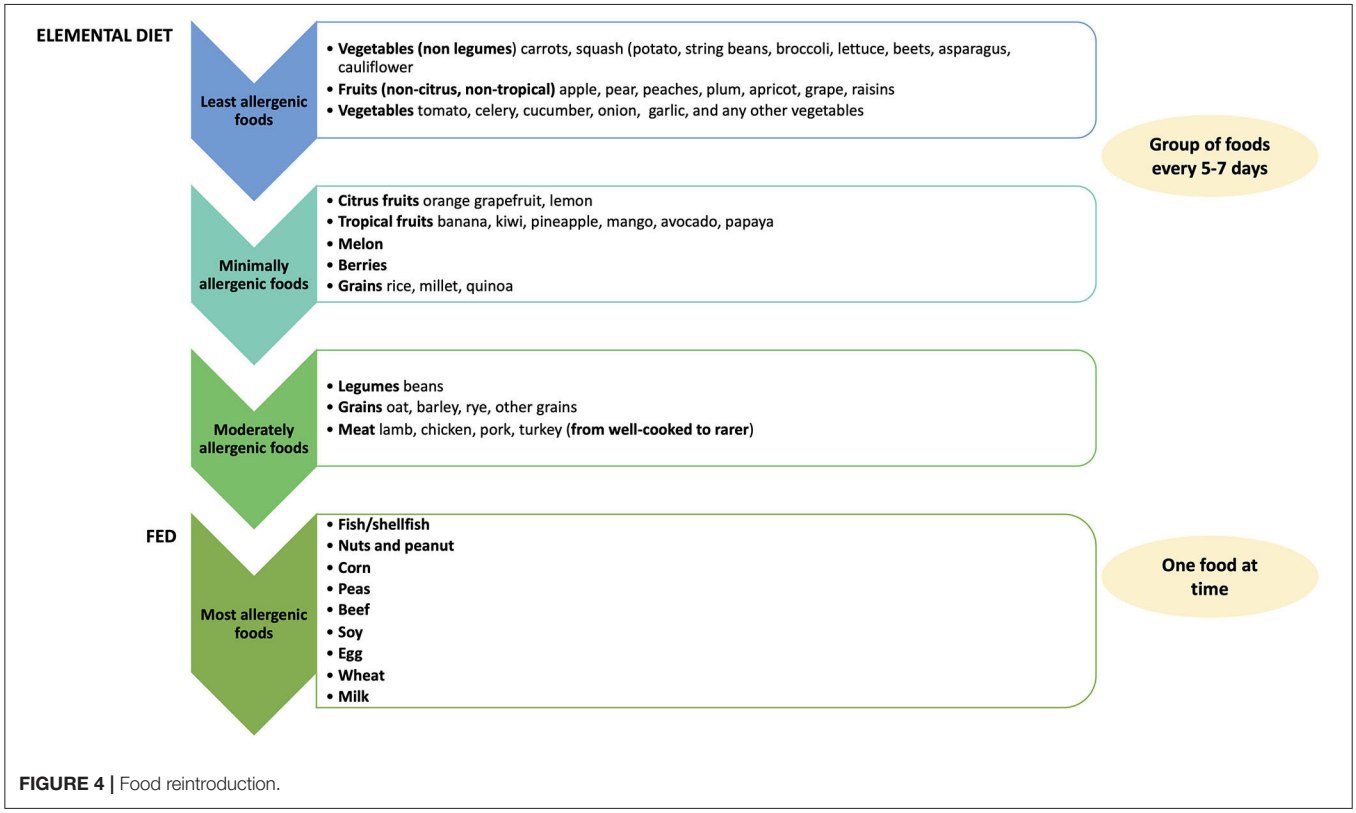

FIGURE 4 | Food reintroduction.

with geographic variations, primarily due to the different food cultures (37). Consequently, nuts and fish/seafood rarely trigger EoE. Therefore, most of the patients who histologically recover with 6-FED were allergic to only 1–3 foods (19).

Although 6-FED is less restrictive than the elemental diet, it still can be challenging to avoid all the six groups of foods. Several drawbacks limit the adherence to 6-FED due to the high level of dietary restriction and the need of frequent upper GI endoscopies to identify the culprit food(s) (12). For these reasons, 6-FED is generally not considered the ideal therapeutic approach in most EoE patients. Therefore, subsequent studies proposed and assessed the utility of less restrictive FEDs that consisted of avoiding the most common food triggers. 4-FED (milk, wheat, egg, and soy/legumes-free diet) induced histologic remission in 64 and 54% of children and adults, respectively (46, 47). In studies evaluating the efficacy of 4-FED, milk and wheat were the most common triggers of EoE (12). Children and adults avoiding these two foods (2-FED) achieved complete remission in 40 and 44% of cases, respectively. The elimination of cow's milk (1-FED) demonstrated disease-remission rates of 44–51% in pediatric patients (27). In a recent systematic review with meta-analysis, the overall efficacy of a milk-free diet was about 70% (45).

There are two strategies for avoiding foods in FED with different indications, strengths, and weaknesses (**Figure 3**) (12, 27). FED can be managed with a *top-down approach* removing milk, wheat, egg, soy/legumes, peanut/tree nuts, and seafood/fish (6-FED) simultaneously. If disease-remission is achieved (<15 eos/HPF), the avoided foods can be sequentially added to the patient's diet, with clinical evaluations and esophageal-gastroduodenoscopy after each reintroduction, to identify the true allergenic trigger(s) (12, 22). Although more effective, this approach is limited by several endoscopic procedures (at least six), high diet restrictions, and potential nutritional deficiencies that may negatively impact patient and family compliance (12, 22). Moreover, a more restrictive diet requires high financial resources and time for buying and preparing alternative meals. For these reasons, the top-down approach is generally indicated in adult patients with severe esophageal symptoms limiting the normal feed (i.e., swallowing issues), adequate/high body mass index (BMI), and without nutritional deficiencies (12). Recently, Molina-Infante et al. tested a prospective *step-up approach* to empiric food elimination (13). The step-up approach consists of the initial elimination of one (1-FED) or two (2-FED) more common allergenic foods (milk and wheat) (13). If a complete remission is not achieved, diet is further restricted to a 4-FED and eventually to 6-FED (13). Although less effective, this dietary approach leads to faster and earlier identification of food triggers [one to four GI endoscopies to identify food trigger(s)] than the top-down approach, avoiding unnecessary diet restrictions (12, 13, 27). A step-up approach is generally preferred in children and adolescents with mild-moderate GI symptoms, a diet rich in milk and wheat, and signs of impaired growth or BMI (**Figure 3**).

Allergy-Test Directed Elimination Diet

EoE is a T2 immune-mediated disease, where IgEs do not have a specific pathogenetic role. Based on the results of skin

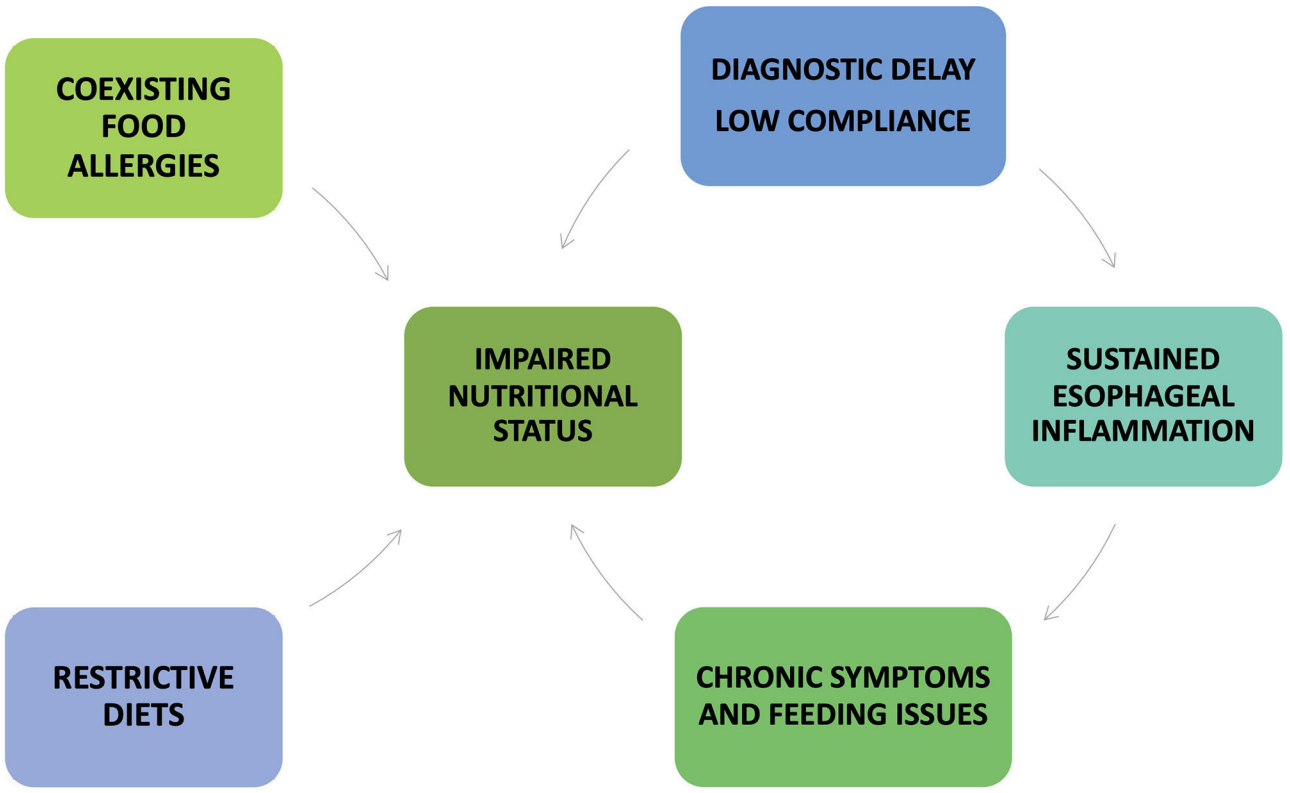

FIGURE 5 | Factors that may negatively impact the nutritional status of patients with eosinophilic esophagitis.

prick tests and atopy patch tests, Spergel et al. reported that about 75% of children achieved a significant improvement in EoE symptoms and esophageal inflammation (48). However, subsequent studies found that atopy patch tests, skin prick tests, food-specific serum IgEs did not reliably predict food triggers and did not have a clear role in evaluating patients with EoE (49, 50). Moreover, a meta-analysis revealed that this diet approach induces histologic remission in 45.5% of patients, and efficacy rates were significantly lower in adults than in children (45). According to this evidence, current American and European guidelines do not recommend allergy test-based dietary elimination therapies (2, 28, 51).

HOW TO MANAGE FOOD REINTRODUCTION AND LONG-TERM TREATMENT?

When a FED (empirical food elimination or elemental diet) is implemented, the GI endoscopy should be performed after 6–12 weeks to assess the histologic remission (2, 30). Once clinical and histologic remission is achieved, a single food or food group is gradually reintroduced based on the specific diet approach. The endoscopy should be made after 4–6 weeks each reintroduction to confirm or exclude disease remission and before proceeding to other food reintroduction (2, 28, 43). Food reintroduction should start from the less allergenic foods (fruits and vegetables) to the most common food triggers (52). In patients treated with elemental diet or 6-FED, Cianferoni et al. recommended reintroducing the high-risk foods (milk, wheat, soy, and/or egg) one at a time, whereas medium-risk foods (legumes, seafood, nuts) may be re-administered at one time, and low-risk foods (fruit and vegetables) may be reintroduced in groups every 5–7 days (**Figure 4**) (12, 52). If symptoms do not recur after reintroducing 4–5 new foods from one group, endoscopy is performed 1–2 months later (52). On the contrary, if patients become symptomatic or relapse after reintroducing a specific food, that food is definitively excluded from the diet (52).

If EoE children achieve complete disease remission on a free-milk diet (1-FED), cow's milk and milk-containing products (included all mammalian milk and partially and extensively hydrolyzed formulas) should be removed from the diet. However, it is reported that some patients can tolerate baked milk products that may be tried in the diet followed by an upper GI endoscopy. Notably, children sensitized (positive food-specific IgEs or skin test) to previously tolerated foods removed from the diet because of EoE triggers, should be referred to a pediatric allergist before the reintroduction at home (12). As already reported in patients with atopic dermatitis, children with EoE may develop IgE-mediated immediate hypersensitivity to food previously identified as the causative agent for EoE (53, 54).

TABLE 3 | Nutritional assessment [Adapted from Cianferoni et al. (12)].

Nutritional assessment	Parameters	Health care specialist
Clinical history	Symptom onset Food-related symptoms Extraesophageal manifestations and comorbidities	Gastroenterologist Allergist Pediatrician
Anthropometric data	Weight Height BMI	Gastroenterologist Allergist Pediatrician Nutritionist
Patient diet and feeding habits	Breakfast, lunch, snacks, dinner (food diary) Food variety	Nutritionist
Identification of feeding issues	Description of a typical meal; food and texture preferences. Swallowing issues Delayed onset of oral-motor skills	Nutritionist
Identification of eating disorders, behavioral issues, and neurological diseases	Unmotivated weight loss Nervous anorexia Anxiety Depression Fear of eating in public Fear of food impaction Autism spectrum disorders	Psychologist
Coexisting allergic and non-allergic comorbidities	Gastroesophageal reflux diseases Coeliac disease Inflammatory bowel diseases Esophageal atresia IgE and non-IgE mediated food allergies Food intolerances Atopic dermatitis	Gastroenterologist Allergist Pediatrician
Biochemical assessment	Complete blood count Iron status (serum ferritin, iron, total iron-binding capacity, hemoglobin) Bone metabolism (calcium, phosphate, vitamin D, alkaline phosphatase)* Micronutrient deficiency (folate, vitamin B12, zinc, selenium, electrolytes) Macronutrient deficiency (albumin, prealbumin, total protein, blood urea nitrogen, creatinine)	Gastroenterologist Allergist Pediatrician Nutritionist
Compliance to therapy	Follow-up EGD with biopsies Clinical scores	Gastroenterologist Allergist Pediatrician

No current guidelines exist on DEXA use in patients on a milk-free diet or topical steroid therapy (12).
BMI, body mass index; EGD, esophageal-gastroduodenoscopy; IgE, immunoglobulin E.

A significant group (∼20%) of adults and children treated with an elimination diet do not respond to the dietary approach, even after mostly eaten trigger foods are removed, or a more restrictive 6-FED is implemented. In these cases, after assessing the patient's compliance, combination therapy with FED + PPI is generally recommended, or clinicians may add a topical corticosteroid and gradually expand the diet, reintroducing foods (12).

Due to its chronic/remittent nature, EoE requires lifelong therapy (2, 28). Patients following a dietary regimen should be widely informed of the need for repeated follow-up endoscopies. Food reintroduction in patients treated with a 6-FED requires at least six endoscopies and several months to identify the culprit food(s). In children exclusively fed with the aminoacid-based formula, the food-reintroduction process is even longer and loaded by several endoscopies. Once the culprit food(s) is identified, the long-term diet therapy is only based on exclusively avoiding the food(s) responsible for esophageal inflammation (55). In adults, the strict avoidance of trigger food(s) maintains a complete remission (clinical and histologic remission) for up to 3 years (43, 56). Notably, the prolonged elimination of a food or a group of trigger foods might induce potential nutritional deficiency.

NUTRITIONAL CONSIDERATIONS AND PATIENT EDUCATION

Several factors may negatively impact the nutritional status of patients with EoE (**Figure 5**).

Firstly, children with EoE generally present symptoms that may limit the adequate nutritional intake, such as recurrent vomiting and regurgitation, abdominal pain, lack of appetite, low volume and/or poor variety food intake, grazing, and spitting food out (31). Patients with chronic esophageal inflammation develop compensative feeding habits (i.e., drinking a lot during meals, eating slowly, chewing carefully, cutting food into small pieces, lubricating foods with sauces or liquids), or avoiding some foods (meat, crusty bread, pills) (20). Moreover, young children fed for a long time with liquid formula do not engage masticatory muscles and are at increased risk of delayed onset of oral-motor skills (57).

Secondly, EoE is often delayed or misdiagnosed. It is reported that diagnostic delay mainly occurs in the first two decades of life and is more likely associated with tissue remodeling complications, such as esophageal rings and strictures, and further prolong the GI symptoms and feeding discomfort (58, 59).

Although occurring in pediatric patients, esophageal strictures generally complicate the disease course in adulthood since esophageal fibrosis becomes an irreversible process more challenging to treat with available therapies (58). Patients with previous food impaction episodes may have a high risk of developing anxiety and eating disorders, compromising the adequate nutrient intake (17, 60). Therefore, chronic GI symptoms, compensative feeding habits, eating disorders may all complicate the nutritional status of EoE patients, especially if they are children.

Thirdly, the coexistence of multiple (IgE and non-IgE mediated) food allergies might be a further reason for failure to thrive and undernutrition. On the other hand, long-term restrictive FEDs may compromise adequate micronutrient intake, although they do not appear to worsen child growth or BMI (31, 61). For these reasons, in children treated with 1- or 2-FED, regular clinical follow-up is recommended to identify

TABLE 4 | Nutritional deficiencies associated with food elimination and appropriate substitutions [Adapted from Bashaw et al. (66)].

	Milk	Wheat	Egg	Soy	Nuts	Fish/shellfish
Macronutrient						
Protein	X		X	X	X	X
Fat	X		X	X	X	X
Fiber		X			X	
Micronutrient						
Calcium	X			X		
Vitamin D	X		X			X
Iron		X		X		X
Zinc		X		X	X	X
Copper					X	X
Selenium		X	X		X	X
Vitamin A	X		X			
B1—Thiamin		X		X		
B2—Riboflavin	X	X		X		
B3—Niacin		X		X	X	
B5—Pantothenic acid	X		X			
B6—Pyridoxine		X		X		
B7—Biotin		X	X			
B9—Folate		X		X	X	
B12—Cobalamin	X		X			X
Iodine	X					X
Substitutions	Meats, legumes, whole grains, nuts, fortified foods, and beverages	Fortified foods, fruits, vegetables, other grains (barley, oat, rice, corn, rye, millet, teff, quinoa, buckwheat, amaranth)	Meats, legumes, whole grains (gluten-free)	Meats, other legumes, fortified beverages	Meats, seeds, legumes	Meats, legumes, seeds, fortified beverages

early potential nutritional deficiency and growth impairment (**Table 3**).

Finally, the low compliance to therapy is the main reason for therapeutic failure and persistent active inflammation (17).

Nutritionists have a crucial role in evaluating nutritional status (**Table 3**). A nutritionist should meticulously evaluate the diet of patients (i.e., veggie or lactose-free diets) to determine the degree of exposure to high-risk groups of foods and the potential nutritional and psychological effects of their elimination (62, 63). Before beginning a diet therapy and during the follow-up period, clinicians should periodically assess the nutritional status of patients and rule out the potential nutritional deficiency. Then, clinical (symptoms, comorbidities, feeding habits/disorders) and anthropometric data should be collected and carefully evaluated to address the best therapeutic choice.

EoE may appear with failure to thrive, one of the most described complications in young children (64, 65). Moreover, the risk of nutritional deficiency and impaired growth also increases with the restrictive nature of the diet and the number of removed foods. Vitamin D deficiency is widespread in Western Countries and is frequently found in patients with chronic inflammatory diseases, including allergic disorders (31). Although published studies are often conflicting, patients with EoE are at high risk of impaired bone metabolism and vitamin D deficiency due to the intrinsic nature of the esophageal inflammation, long-term treatment with topical corticosteroids, and FED (31). Iron deficiency anemia may be a consequence of selective diets. The fear of new food impaction episodes leads patients to voluntarily remove the culprit food (especially steak). If failure to thrive or nutritional deficiencies are suspected, biochemical tests (i.e., bone and iron metabolism, serum albumin, and prealbumin) should be performed. When a micro- or macronutrient deficiency is confirmed, nutritional supplements should be promptly provided (**Table 4**) (66).

Another critical point concerns the patient's education. Clinicians should carefully inform patients and their families regarding what they can eat and provide the appropriate (written or online) resources for additional information (12). Moreover, patients should also be advised on the risk of potential allergen contaminations. According to the specific European legislation (https://www.mise.gov.it/index.php/it/impresa/competitivita-e-nuove-imprese/industria-alimentare/etichettatura-alimentare), clinicians should provide information on packaged foods and educate patients and families to read and correctly interpret the labels of food products. European law established that major food allergens must be declared and reported in the labels of packaged food or available to consumers for non-packaged foods (catering, fresh and cooked foods) (12). Ingredients may change

over time, and labels of regularly consumed food should be read each time (12). Fourteen significant allergens must be identified and reported in labels: cereals containing gluten (wheat, rye, barley, oats, spelled, and Kamut), crustaceans, eggs, fish, peanut, soy, milk (including lactose), nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamia, pecan nuts, pistachio nuts, and walnuts), celery, mustard, sesame, sulfites, lupin, and mollusks (https://www.mise.gov.it/index.php/it/impresa/competitivita-e-nuove-imprese/industria-alimentare/etichettatura-alimentare). The precautionary allergen labeling ("may contain") is not mandatory for European law (12). However, the risk of allergen cross-contamination and trace exposure for foods reporting this warning is variable and still not established in EoE patients (12).

HOW TO IMPROVE PATIENT'S COMPLIANCE: THE ROLE OF THE MULTIDISCIPLINARY TEAM

The chronic nature of EoE, comorbidities, long-term restrictive therapies and strict endoscopic follow-up are the main stressful factors for patients and their families (17). Therefore, it is evident that EoE significantly impacts the QoL of both pediatric and adult patients (17). The complexity and the clinical heterogeneity of this emerging chronic disease implies the need for a multidisciplinary approach, including allergist, pediatrician, gastroenterologist, nutritionist, and psychologist to manage these patients (**Table 3**) (31). In high specialized Centers, all these specialists should be present during the entire course of the disease and guarantee the transition from the pediatric to the adult setting. Allergists should identify other coexisting atopic comorbidities (eczema, allergic rhinitis, asthma, food/drug allergy, and anaphylaxis) and provide adequate treatment if symptoms are not controlled. Allergy assessment is also fundamental to prevent potential IgE-mediated reactions when foods (especially milk) are reintroduced. Strict clinical and endoscopic follow-up is required to evaluate patient compliance, long-term treatment side effects, and assess disease remission. Notably, children with severe disease, multiple food allergies, non-allergic comorbidities (such as esophageal atresia or genetic disorders) or treated with elimination diets (elemental diets or empirical FEDs) require a regular pediatric evaluation of their growth and nutritional status. Finally, psychological support should be provided when behavioral, mood diseases, or eating disorders are suspected (17).

CONCLUSION

EoE is an emerging chronic allergic disease with a relevant impact on the health care system and patients' QoL. Although the pathogenesis is not entirely understood, EoE is a T2 inflammatory disease mainly triggered by food allergens. Diet therapy and medications are both first-line treatments. The choice of one or the other therapy depends on the disease phenotypes (allergic vs. non-allergic, inflammatory vs. fibro-stenotic), patient's age (adult vs. childhood-onset), food habits, patient/family preference, and familiar financial resource. Diet therapy is a successful treatment but limited by low patient adherence, the need for several endoscopies, food restriction, psychosocial impacts, and potential nutritional deficiency. All these limitations could be effectively overcome with multidisciplinary and personalized management. Considering the clinical heterogeneity of EoE, future efforts should be addressed to personalize treatments. Multidisciplinary management, a personalized approach, and proactive education on the importance of treatments and regular endoscopic follow-up may be the keys to a more successful therapeutic strategy.

AUTHOR CONTRIBUTIONS

MV reviewed the literature and wrote the manuscript. MDF reviewed the literature and the manuscript. AL, GLM, ADS, MVL, and CMR revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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children

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Review

A Practical Update on Pediatric Eosinophilic Esophagitis

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Abstract: Eosinophilic esophagitis (EoE) is an emerging atopic disease of unknown etiology limited to the esophagus. The pathogenesis is still understood and is likely characterized by type 2 inflammation. Food allergens are the primary triggers of EoE that stimulate inflammatory cells through an impaired esophageal barrier. In children and adolescents, clinical presentation varies with age and mainly includes food refusal, recurrent vomiting, failure to thrive, abdominal/epigastric pain, dysphagia, and food impaction. Upper-gastrointestinal endoscopy is the gold standard for diagnosing and monitoring EoE. EoE therapy aims to achieve clinical, endoscopic, and histological ("deep") remission; prevent esophageal fibrosis; and improve quality of life. In pediatrics, the cornerstones of therapy are proton pump inhibitors, topical steroids (swallowed fluticasone and viscous budesonide), and food elimination diets. In recent years, much progress has been made in understanding EoE pathogenesis, characterizing the clinical and molecular heterogeneity, and identifying new therapeutic approaches. Notably, clinical, molecular, endoscopic, and histological features reflect and influence the evolution of inflammation over time and the response to currently available treatments. Therefore, different EoE phenotypes and endotypes have recently been recognized. Dupilumab recently was approved by FDA and EMA as the first biological therapy for adolescents (≥12 years) and adults with active EoE, but other biologics are still under consideration. Due to its chronic course, EoE management requires long-term therapy, a multidisciplinary approach, and regular follow-ups.

Keywords: adolescents; allergy; children; eosinophilic esophagitis; food elimination diet; proton pump inhibitor; quality of life; topical steroids

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1. Introduction

Eosinophilic esophagitis (EoE) is a chronic/remittent, antigen-mediated disease involving the esophagus [1]. The first case of EoE was described in 1978 by Landres et al. and was considered an esophageal motility disorder [2]. Subsequently, esophageal eosinophilia was considered a feature of gastroesophageal reflux disease (GERD) [3]. EoE was only recognized as a distinct clinical entity by Attwood and Straumann in the early 1990s [4,5]. Since then, several efforts and progress have been made to understand the pathophysiology and natural history of this clinically heterogeneous disease, which significantly impacts patients' quality of life and health care systems.

2. Epidemiology

EoE has evolved from a rare to a frequent upper gastrointestinal tract disease commonly encountered in pediatric clinical practice [6]. The global prevalence of EoE is 0.5–1 cases/1000 persons [6]. In children, the pooled incidence of EoE is 6.6 cases/100,000 persons each year, whereas the overall prevalence is 34 cases/100,000 children [6]. In the Netherlands, the incidence rates increased from 0.01/100,000 (95% CI: 0.0–0.04) in 1995 to 3.16/100,000 (95% CI: 2.90–3.44) in 2019 [7]. The prevalence of pediatric EoE varies from 2.3/100,000 in Denmark to 90.7/100,000 in Ohio [6].

In recent years, several studies have reported a relevant increase in EoE epidemiology, especially in children living in developed countries [8–15]. This phenomenon occurred parallelly with the dramatic increase in the prevalence of allergic disorders observed over the last few decades [16,17]. Economic development combined with high welfare status, the wide distribution of food resources, and improvements in hygienic conditions may potentially contribute to EoE pathogenesis, which is multifactorial. Although some genetic polymorphisms are known to increase the risk of EoE, environmental factors, including a diet rich in modified and enriched foods, are probably the most crucial players in disease development [6,18].

3. Pathogenesis

EoE is a multifactorial disease in which genes and environment are pathogenetic factors [18]. Their intricate interaction alters the esophageal epithelial barrier, allowing abnormal exposure to allergens (primarily foods) and other luminal components [19]. The impaired barrier leads to the local release of alarmins, including the thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33, which drive the differentiation of T helper 2 (Th2) effector cells and the consequent production of Th2 cytokines (IL-4, IL-5, IL-9, and IL-13) and eosinophil recruitment [20,21]. IgEs, crucial in several atopic diseases, do not have a primary role in EoE pathogenesis [18]. The inflammatory *milieu* in children with active EoE is also characterized by increased angiogenesis, which was demonstrated through evidence of high levels of angiogenic factors, including vascular endothelial growth factor (VEGF), vascular adhesion molecule-1 (VCAM-1), angiogenin, and IL-8 [21].

The role of genetics in EoE pathogenesis was suggested owing to clinical evidence, which has showed that EoE prevalence varies among sex (male: female ratio = 3:1) and ethnicity (EoE is more common in White than Black or Hispanic children) [22,23]. Moreover, having a first-degree family member with EoE is a known risk factor (OR 16.3; 95% CI, 9.4–28.3), which is markedly higher in monozygotic than in dizygotic twins (41% vs. 22%) [24,25]. Despite this evidence, twin studies report a low disease concordance, highlighting the crucial role of environmental factors. The effect of genetics seems to occur in conjunction with environmental factors, including early-life exposures [18]. Early life is a critical period in which the developing immune system and gut microbiota mature and become susceptible to environmental exposures [18]. A few studies have focused on the role of early-life exposures [26–30]. Formula feeding, neonatal intensive care admission, prematurity, maternal fever, early antibiotic or acid suppressant use, and cesarean delivery were all considered putative early risk factors of EoE [18].

Genome-wide association (GWA) studies allowed the identification of different genetic loci involved in the expression of Th2 inflammatory cytokines and the regulation and functioning of esophageal epithelial barrier proteins [31–34]. Desmosomes, tight and adherence junctions, filaggrin, and desmoglein-1 ensure esophageal barrier integrity. Genetic variations in these genes have been reported in EoE patients [35]. The most potent association concerns the expression of dysregulated calpain 14 (CAPN14), an enzyme exclusively expressed in the esophagus and involved in barrier regulation via the IL-13 pathway [31–33]. Other polymorphisms were detected in EoE patients and are mainly related to the Th2 immune response, eosinophil chemotaxis, and cell adhesion [31,36–38]. GWA studies have also identified other genetic *loci* likely contributing to EoE development, including TSLP, EMSY, LRRC32, STAT6, and ANKRD27 [18,31]. These genetic loci are

mainly involved in T helper 2 inflammation and epithelial barrier function and integrity. Interestingly, EoE may complicate the course of different monogenic, inherited diseases. Connective tissue disorders, including Marfan syndrome and Ehlers-Danlos syndromes, share a common pathogenic mechanism through the dysregulation of the TGF-β signaling. Children with autosomal dominant hyper-IgE syndrome (HIES) and Netherton syndrome have a high risk of EoE development [39,40].

Despite the progress achieved so far, a complete understanding of the molecular pattern will help to further classify patients into endotypes defined by a specific pathophysiologic disease mechanism and to personalize treatments. In this context, using a machine learning approach, Shoda et al. analyzed patients' histological, endoscopic, and molecular features with EoE, identifying three endotypes. The EoEe1 endotype was recognized in 35% of enrolled patients and was mainly signed by minimal eosinophilic inflammation and responsiveness to topical steroids. The EoEe2 endotype affected 29% of patients, showing prevalent Th2 inflammation, pediatric onset, and low steroid response. The third endotype (EoEe3) was reported in 36% of patients, characterized by adult-onset and strictures [41]. Identifying these endotypes has important clinical implications because they reflect the response to currently available treatments. Indeed, patients with the EoEe1 endotype may be treated with FED and topical steroids, while children with the EoEe2 endotype may benefit from anti-Th2 immune agents (i.e., dupilumab) [42]. The available therapeutic tools for patients with the EoEe3 endotype and strictures are limited; hence, esophageal dilations are the only therapy for esophageal strictures [42].

4. Diagnosis

EoE is characterized by symptoms of esophageal dysfunction and $\geq$15 eosinophils per high power field (eos/HPF) in endoscopically obtained biopsies [43]. In patients with esophageal eosinophilia, other causes of esophageal eosinophilia should always be ruled out, particularly GERD, coeliac disease, Crohn's disease, achalasia, HIES, and drug hypersensitivity. Pediatricians should diagnose EoE based on a combination of symptoms and histological and endoscopic findings, as no single feature is sufficient to establish a definitive diagnosis. Therefore, the essential diagnostic instruments are (1) a detailed medical history, (2) a correct evaluation of endoscopic features, and (3) an accurate histological examination. Upper-gastrointestinal (GI) endoscopy is currently the gold standard for diagnosing and monitoring EoE [43]. Therefore, there is a critical need for noninvasive tools and biomarkers to replace such invasive—but essential—instruments. Despite several efforts to identify potential noninvasive biomarkers, none were included in the guidelines [44,45].

Another critical point is that EoE is often delayed or misdiagnosed, especially in the first two decades of life [46]. A longer diagnostic time in children significantly impairs growth and is associated with esophageal tissue remodeling and subepithelial fibrosis, which appear with esophageal rings and strictures [47].

4.1. Clinical Features and Heterogeneity of EoE

It has been widely reported that EoE symptoms vary with age [1]. In infants and toddlers, the symptoms of esophageal dysfunction generally appear as feeding difficulties, food refusal, recurrent vomiting, or regurgitation. Older children often report abdominal or epigastric pain and refractory gastroesophageal reflux. Adolescents and adults report dysphagia (first for solid foods, then for liquids) and food impaction episodes [1]. Atypical symptoms have also been reported in EoE patients, such as a recurrent cough in children and heartburn and/or chest pain (including exercise-induced chest pain) in adolescents and adults. Children and adolescents can also develop compensative feeding habits, such as eating slowly, chewing carefully, drinking a lot during meals, cutting food into small pieces, lubricating foods with liquids, and avoiding some foods (meat, bread, and pills) [47]. Adolescents and older children can be worried about eating in public places and thus may develop anxiety disorders. Failure to thrive is a potential complication observed in

EoE children due to selective feeding, food refusal, recurrent vomiting, or the occurrence of eating disorders. EoE should be generally suspected in children with gastrointestinal symptoms (reflux, abdominal pain, vomiting) not responsive to conventional therapies, especially if these are related to changes in eating behavior or disorders. Suspicious symptoms or conditions that may help to suspect EoE are summarized in Table 1.

Table 1. Suspicious symptoms of EoE in children.

Infants and Young Children	Older Children	Adolescents
Regurgitation that does not recover with formula thickening, splitting of feedings, or acid suppressants.	GERD-like symptoms that do not recover with acid suppressants.	GERD-like symptoms that do not recover with acid suppressants.
Young children who prefer creamy or smoothed foods, soups, or liquids and avoid solid meals.	Children with selective feeding (avoiding more solid foods like meat and crusty bread).	Dysphagia for solids, then for liquids
Toddlers with speech delay	Children who drink a lot during meals to help food *bolus* progression.	Food impaction episodes
Young children with failure to thrive not related to more common diseases (food allergy, celiac disease, recurrent infections, or other chronic conditions)	Children who eat slowly compared to their siblings or friends.	Eating disorders
Non-surgical causes of recurrent vomiting	Epigastric/abdominal pain that is not responsive to conventional therapies for functional gastrointestinal disorders.	Selective feeding, avoidance of solid food or pills
Non-neurological dysphagia	Episodes of food impaction	Anxiety about eating in public places
Recurrent cough/wheezing	Non-neurological dysphagia for solid food	Adolescents eat slowly compared to their siblings or friends.
Gagging or coughing with feeding	FIRE symptoms	FIRE symptoms
	Recurrent cough	Heartburn or chest pain episodes

FIRE, food-induced immediate response of the esophagus; GERD, gastroesophageal reflux disease.

Notably, clinical, endoscopic, and histological features reflect and influence the evolution of inflammation over time and the response to currently available treatments. Therefore, different EoE phenotypes have been recognized so far [47]. The "inflammatory" phenotype is typically observed in childhood and is characterized by the endoscopic finding of edema, erythema, linear furrowing, and prevalent eosinophilic infiltration found through histology [47–50] (Figure 1). The "fibro-stenotic" phenotype affects adults, who typically experience dysphagia and food impaction episodes [47–50]. This phenotype is defined by fixed esophageal rings and/or strictures found through endoscopy and results from tissue-remodeling phenomena [47–50] (Figure 1). While food elimination diets (FED) and medical therapies may revert esophageal fibrosis in children, this remodeling process may persist despite the resolution of esophageal inflammation in adults [51].

Several studies have shown that patients with EoE have concomitant allergic comorbidities, such as allergic rhinitis, asthma, atopic dermatitis, and IgE-mediated food allergy [36]. The prevalence of asthma reaches 60% of prevalence in pediatric series [52]. The prevalence of IgE-mediated food allergy varies from 25% to nearly 70% [53,54]. Eczema was also significantly more frequent in EoE patients than in controls [53,54]. These findings have led many researchers to consider EoE the final step of the atopic march [55]. Conversely, several non-atopic comorbidities are associated with EoE, including inflammatory bowel diseases, connective tissue disorders, autism and attention deficit hyperactivity disorders, esophageal atresia, celiac disease, and the monogenic disorders previously reported [52,56,57]. Eosinophilic gastrointestinal disorders, particularly EoE, have been found in different inborn errors of immunity, including common variable immunodeficiency and

HIES [58]. Using a cluster analysis approach, Votto et al. identified and explored the clinical heterogeneity of eosinophilic gastrointestinal disorders (EGIDs), finding two clinical phenotypes of pediatric EoE. Cluster 1 was mainly composed of patients with allergic comorbidities (allergic rhinitis was the prevalent disease), high levels of total serum IgE, and blood peripheral eosinophils. Conversely, Cluster 3 consisted of non-allergic children with a history of neonatal intensive care admission, probably related to the high frequency of congenital malformations observed in this subgroup (such as esophageal atresia) [59].

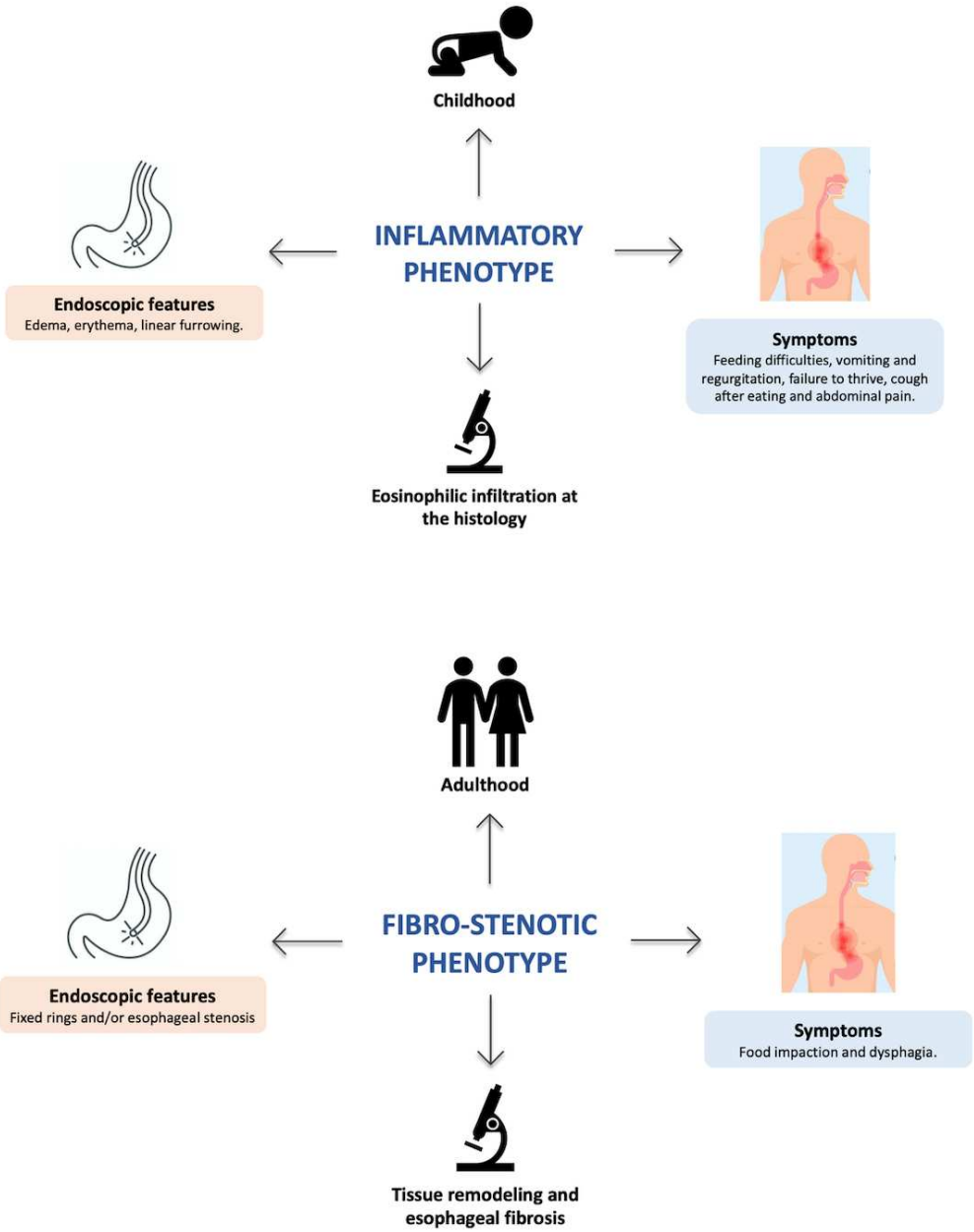

Figure 1. Features of the inflammatory and fibro-stenotic phenotypes.

Recently, Biedermann and colleagues identified and described in adult EoE patients a new clinical syndrome called "food-induced immediate response of the esophagus" or FIRE [60]. FIRE symptoms are highly pronounced, unpleasant, and even painful and are strictly linked to the contact of a specific food trigger with the esophagus, usually appearing a few minutes (<5 min) after ingestion. Symptoms have a limited duration and generally resolve in less than 30 min. The primary identified triggers are fruits, vegetables, and drinks. FIRE might be compared to the pollen food allergy syndrome (PFAS) of

the esophagus [60,61]. FIRE has been described in only one pediatric case [62]. The prevalence of FIRE in children may be underestimated because symptoms are challenging to distinguish from EoE, PFAS, and GERD [62].

4.2. Endoscopic and Histological Features

Upper-GI endoscopy is the gold standard for EoE diagnosis. In children, esophageal-gastro-duodenoscopy (EGD) is always performed in a hospital setting and with general anesthesia.

Several endoscopic findings can be recognized in children and adolescents. A graded endoscopic score system has recently been developed to standardize endoscopic findings [63]. The endoscopic reference score (EREFS) is a sum and scoring of the five most prominent endoscopic features of EoE:

- Edema (E), i.e., the loss of vascular markings (present 1, absent 0);
- Rings (R) or esophageal trachealization (none 0, mild 1, moderate 2, severe 3);
- Exudates (E) or white plaques (none 0, mild 1, severe 2);
- Furrows (F) or vertical lines (none 0, mild 1, severe 2);
- Strictures (S) (present 1, absent 0).

Edema, exudates, and furrows are considered inflammatory components, whereas rings and strictures reflect fibrotic components. An EREFS score of less than two corresponds to endoscopic remission.

Due to the need for repetitive endoscopic evaluations with multiple biopsies and the consequential high costs and psychological burden, minimally invasive methods to diagnose and monitor EoE have recently been proposed. Unsedated transnasal endoscopy was applied in clinical trials; it resulted in a feasible, safe, and cost-effective procedure for children, providing direct visualization of the esophagus and correct acquisition of biopsy samples [64]. Other, less invasive instruments are being validated in pediatric EoE monitoring, such as Cytosponge and endoFLIP to assess mucosal inflammation and esophageal stiffness and motility, respectively.

Unlike other GI tracts, the normal esophagus is entirely devoid of eosinophils. Histologically, $\geq$15 eosinophils in one HPF are necessary for defining EoE and active disease [43]. Other histological findings have been observed in eosinophilic esophagitis, such as spongiosis (dilation of intercellular spaces), increased mast cell and lymphocyte numbers, basal zone hyperplasia, and papillary elongation [65]. Recently, Collins et al. developed a histological scoring system (EoE-HSS) that analyzes several histologic features: eosinophil density and abscess, basal zone hyperplasia, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis [65]. Although EoE-HSS allows the complete evaluation of all mucosal inflammatory components, its diffusion and application in general and pediatric clinical practice is still limited.

5. Therapy

EoE treatment aims to control symptoms and esophageal inflammation and prevent complications. Current therapeutic options can be distinguished into three categories defined by three Ds: drugs (medical therapy), diet (the elimination of trigger foods), and esophageal dilation [1]. The only currently approved treatment options for EoE are budesonide effervescent tablets, approved for use by adults in most European countries, and dupilumab, approved by the FDA and EMA for patients $\geq$12 years old [66]. Therefore, treatments routinely used in pediatric clinical practice, like proton pump inhibitors (PPIs) or topical corticosteroids, are not approved for EoE and are prescribed off-label. Choosing the best treatment is not always straightforward and depends on disease-related aspects (severity, the presence of stenosis and comorbidities, nutritional status) but primarily on patient-related factors (the presence of eating and/or mood disorders, financial resources, motivation, lifestyle) (Figure 2).

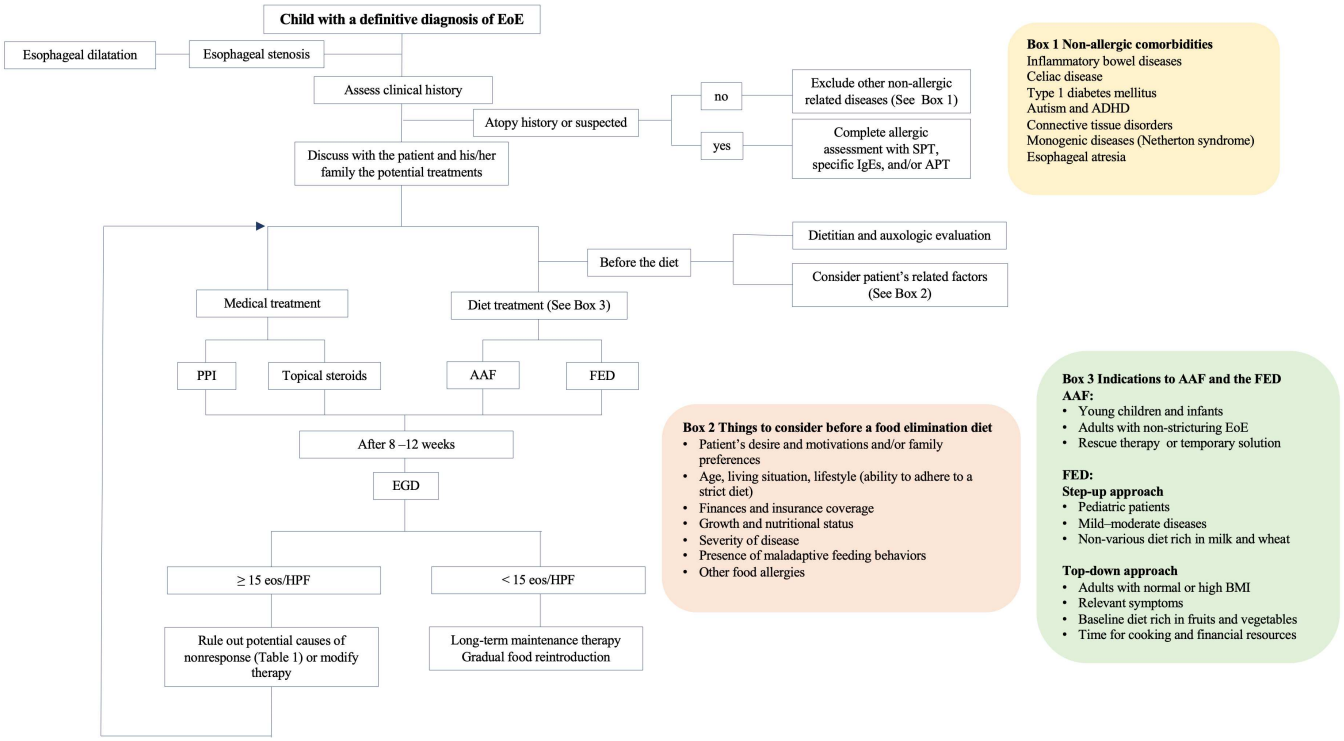

Figure 2. Proposed algorithm for EoE management in children. AAF: aminoacidic based formula; ADHD: attention deficit hyperactivity disorder; ATP: atopy patch test; BMI: body mass index; EGD: esophagogastroduodenoscopy FED: food elimination diet; HPF: high power field; PPI: proton pump inhibitor; SPT: skin prick test.

5.1. Pharmacological Therapy

5.1.1. Topical Corticosteroids

Topical corticosteroids are effective in inducing EoE remission. Oral steroids can clinically and histologically treat EoE. However, they have significant and well-known side effects if used in the long term. Given the chronicity of EoE, long-term treatment with oral or systemic steroids is not recommended [43]. Meta-analyses of topical corticosteroids demonstrated the superiority of swallowed fluticasone or viscous budesonide compared to a placebo in resolving esophageal eosinophilia, endoscopic findings, and GI symptoms [67–69]. Moreover, some evidence has shown that oral budesonide can reverse esophageal fibrosis [70]. Despite regular therapy, the increase in esophageal eosinophil counts has also been described in steroid-refractory or -resistant cases [71,72].

There are many unresolved questions about the chronic use of topical steroids. There is no consensus regarding dosage, formulation, frequency, or how to obtain remission using the minimal dose. Long-term side effects are the primary concern, although they have been widely evaluated. Indeed, no studies have been conducted regarding bone health, growth, or adrenal function in children treated with swallowed steroids for longer than one year [73]. The most common side effect of topical steroids is oral and esophageal candidiasis [74]. Thus, further studies are necessary to understand the potential systemic side effects of these therapies in children.

Topical corticosteroids are typically administered once or twice daily, and dosing depends on age and disease severity (Table 1). Patients should spray fluticasone without a spacer in the back of their mouth and swallow the dose. No eating or drinking is allowed 30 min after administering the medication [73].

5.1.2. Proton Pump Inhibitors

The response rates to PPI therapy can vary widely from 30% to 70% [43]. In a meta-analysis of 32 studies on PPI treatment, 50.5% of patients achieved histologic remission [75].

The dosages that are effective in EoE treatment are 1–2 mg/kg in children and 40 mg of omeprazole (or equivalent dosages for other PPIs) once or twice daily in adults (Table 2). The mechanism of action of PPIs in EoE is still unclear. PPIs are well-established inhibitors of H+/K+-ATPase expressed by the gastric parietal cells. Thanks to their pharmacological effect, PPI reduces acidic injury to the esophagus and restores epithelial damage. PPIs also show anti-inflammatory properties, directly inhibiting epithelial STAT6, a key transcription factor for the secretion of pro-inflammatory Th-2 chemokines and cytokines [76,77]. Although the occurrence of PPI use in childhood is higher than that of topical steroids, the possible long-term effects of these medications have not been evaluated in EoE patients. Potential adverse effects (increased risk of fractures, intestinal dysbiosis, or deficiencies in certain micronutrients) should be considered during follow-up.

Table 2. Pharmacological therapy of EoE in children and adolescents.

	Proton Pump Inhibitors (PPIs)	Slurry Budesonide	Swallowed Fluticasone	Dupilumab
Dose	Children: 1 mg/kg/day. Adolescents: 20–40 mg/day.	<10 years: 1 mg/day. >10 years: 2 mg/day.	<10 years: 440 mcg twice daily. >10 years: 880 mcg twice daily.	>12 years (weight > 40 kg): 300 mg/weekly.
Specific instructions	Twice daily. 30 min before meals.	Mixed with sucralose (5 g of sucralose), honey, or 2.5 mL aminoacidic formula per mg of budesonide to make a total volume of 8–12 mL.	Do not use the spacer. Do not inhale.	Pre-filled syringe or pre-filled pen for home administration.
General considerations	Initial treatment of 8–12 weeks. Effective in 54% of children.	Second dose administered at bedtime. Avoid eating/drinking 30 min after use. Safe and well tolerated.		Before beginning: - exclude parasitic (helminth) infection; - assess the vaccination status (patients should not receive a live vaccine right before or during treatment); - exclude pregnant status.
Long-term maintenance therapy	PPIs are generally safe. The response is sustained in inflammatory phenotype (70%).	Esophageal candidiasis 4–5%. Consider periodic monitoring for adrenal insufficiency, bone metabolism, and growth. The strategy is to decrease the dose to the lowest adequate level. Limited data on optimal dosage and side effects of long-term use		No long-term data. The most common side effects include injection site reactions, upper respiratory tract infections, cold sores in the mouth or on lips, and joint pain (arthralgia).

PPI, proton pump inhibitor.

5.1.3. Biologic Therapies

The increasing knowledge of EoE pathogenesis has allowed several therapeutic targets to be identified and tested. The humanized antibodies against IL-5, such as mepolizumab and reslizumab, were tested in three controlled trials in children and adults with active EoE, demonstrating reduced tissue eosinophilia and a favorable safety profile. Unfortunately, clinical improvement was minimal [78–80]. A phase III trial using benralizumab, a monoclonal antibody against the IL-5 receptor, remains active [80,81].

Two randomized clinical trials (RCTs) with the anti-IL-13 agent and one with the anti-IL-4 receptor antagonist dupilumab showed promising results [82,83]. In a phase II study, a monoclonal antibody against IL-13 improved endoscopic and histological disease activity in the short and long term. Dupilumab is currently the most advanced biologic therapy in EoE treatment. Dupilumab is a humanized monoclonal antibody that binds to the α subunit of the IL-4 receptor and can be found in both IL-4 and IL-13 [84]. In the phase III study, dupilumab significantly relieved symptoms, reduced eosinophil counts, and improved esophageal distensibility [80]. Therefore, the FDA, then the EMA, recently approved dupilumab for treating adolescents (≥12 years) and adults with active EoE. RCTs are active in children younger than 12 years, but preliminary results showed promising

results and a good safety profile, with a slight increase in respiratory infections in the treated group compared to the placebo one (Table 3).

Table 3. Active trials on biological therapies in children and adolescents with EoE.

NCT Number	Intervention	Population	Status	Phase
NCT04394351	Dupilumab vs. placebo	1–11 years old	Active—not recruiting	Phase 3
NCT05247866	Dupilumab in food reintroduction	6–25 years old	Recruiting	Phase 4
NCT04991935	Cendakimab vs. placebo	12–75 years old	Recruiting	Phase 3
NCT04753697	Cendakimab	12–75 years old	Recruiting	Phase 3
NCT05583227	Tezepelumab vs. placebo	12–80 years old	Recruiting	Phase 3

5.2. Diet Therapies

5.2.1. Elemental Diet

In 1995, Kelly et al. applied the elemental diet (ED) to a small group of children with active EoE, and it was the first effective treatment to be proposed [85]. In the ED, all foods are removed. Patients are fed exclusively with the amino-acid-based formula for at least six to eight weeks [43,86,87]. The ED is the most effective diet therapy [43]. High complete remission rates were reported in children with active disease and an inflammatory phenotype found via endoscopy [88]. Patients with esophageal stenosis had the lowest efficacy rates [89–93]. In children, the ED significantly improves esophageal symptoms and results in a complete histologic remission in about 90% of cases. Therefore, ED is considered a good and valuable therapeutic option in infants and young children, who show the highest treatment compliance (Table 3) [94]. The ED also provides a source of proteins and calories necessary for adequate child growth and puberty spurt, meaning it can be especially proposed for children with EoE triggered by multiple food allergens [94]. The ED is sometimes proposed as a rescue therapy or a "bridge" treatment in adult patients and adolescents with a refractory disease [89,94]. Some authors recently proposed a "modified" ED, adding a few less-allergenic foods (vegetables or fruits) to the diet, thus improving patient acceptance and psychological impact [89,94]. Although the ED is highly effective and induces a rapid remission (of two weeks), unfortunately, its compliance is limited by several disadvantages [95]. The main reasons for low compliance and discontinuation are the unpalatable taste, high costs, and restrictive nature, causing psychosocial isolation for the child [89,94,96]. For these reasons, the ED is not a first-line approach in older children and adolescents, except in severe pediatric cases [94].

5.2.2. Empirical Food Elimination Diet (FED)

The FED is the most commonly prescribed diet therapy for EoE. The FED was first proposed to avoid the six primary food triggers of EoE in Western countries. The six-FED (or 6-FED) includes eliminating cow's milk, wheat/gluten, egg, soy/legumes, peanut/tree nuts, and shellfish/fish [97]. In pediatric studies, the efficacy of 6-FED (assessed according to histologic remission) is about 74% [98]. In childhood, milk is the main food trigger, recognized in up to 85% of cases and followed by wheat/gluten (up to 60% of cases), egg, and soy/legumes. As reported for IgE-mediated food allergy, there is geographic variation in EoE food triggers [88]. Legumes and soy are indeed an uncommon trigger in Spain [88]. Equally, nuts and fish/seafood rarely trigger esophageal inflammation.

Although 6-FED is less restrictive than the ED, avoiding all six food groups can be challenging. Adherence to 6-FED is often limited by several drawbacks due to the relevant dietary restrictions and the need for frequent EGDs to identify the trigger food(s) and assess disease remission [94]. Therefore, 6-FED is not the ideal treatment option in childhood (Table 4). More recently, less restrictive food elimination diets (removing the most common trigger foods) have been proposed and evaluated. It was demonstrated that most patients who clinically and histologically recover with 6-FED are then allergic to only

one or two foods [50]. Kagalwalla et al. reported that the elimination of four (4-FED) foods (cow's milk, wheat, egg, and soy/legumes) induced histologic remission in 54% of treated children [99,100]. Moreover, children avoiding milk and wheat (2-FED) achieved complete remission in 40% of cases. Finally, adopting a diet free from cow's milk (1-FED) was effective in 44–51% of pediatric patients [89]. In a recent systematic review with meta-analysis, the overall efficacy of 1-FED was about 70% [98]. In this context, Molina-Infante et al. proposed a step-up approach based on the elimination of one (1-FED) or two (2-FED) more-allergenic foods (generally milk and wheat) [101]. If complete remission is not achieved, the diet is further restricted to four and six foods [101]. This approach should be preferred in children because it leads to faster and easier identification of the culprit food(s), thus reducing the number of EGDs and diet restrictions.

Table 4. Diet treatments of EoE in children and adolescents.

Diet Therapy	Rationale	Indications	Advantages	Disadvantages
Elemental diet (ED)	Exclusive administration of aminoacidic-based formula. Modified ED: one or two less-allergenic foods (vegetables or fruits) are permitted.	Toddlers or young children with severe active EoE. Severe cases. Rescue therapy in severe/refractory cases or temporary solutions.	Rapid remission in 2 weeks. Higher compliance in infants and toddlers. Pediatric amino-acid-based formulas are almost nutritionally complete.	Poor palatability. Low compliance among children and adolescents. Feeding skill regression may be observed in children with NG or G-tube. Amino-acid-based formulas are expensive and not covered by insurance. Less effective in patients with stricturing EoE.
Empiric food elimination diet (FED)	Step-up approach (From 1–2-FED to 6-FED)	Pediatric patients. Moderate symptoms. A diet rich in milk and wheat.	Early identification of trigger food. Short diagnostic process. Avoid unnecessary diet restrictions.	Less effective.
	Top-down approach (From 6-FED to 1–2-FED)	Adults and adolescents with normal or high BMI. Severe symptoms. Baseline diet rich in fruits and vegetables. There is much time to prepare alternative meals and high financial resources.	More effective.	Up to 7 endoscopies, one after every single food reintroduction. Several diet restrictions. Low compliance. Risk of nutritional deficiencies.

BMI, body mass index; ED, elemental diet; FED, food elimination diet; NG, nasogastric.

5.2.3. Allergy-Test-Directed Elimination Diet

IgEs do not have a pathogenetic role in EoE. Thus far, the evidence has demonstrated that food-specific serum IgEs, atopy patch tests, and skin prick tests do not reliably predict food triggers [43,102]. A meta-analysis reported that an allergy-test-directed elimination diet induces histologic remission in about 45% of patients, with higher efficacy rates in children than adults [98]. According to this evidence, current American and European guidelines do not recommend this diet approach [43,102].

6. EoE Follow-Up

EoE is a chronic disease that requires lifelong therapy and monitoring [43,102]. The absence of guidelines and consensus recommendations limits the long-term management of EoE. In children, follow-up should include the regular assessment of symptoms, growth, nutritional status, endoscopic alterations, and histological abnormalities. Treatment response should be assessed around 8–12 weeks after initiating a novel treatment or after each relevant therapeutical change [103]. Under remission and solid adherence to treatment, the EGD should be performed once per year.

Patients treated with the FED or ED should be widely informed of the need for several EGDs to assess disease remission when each food or group of foods is reintroduced. Food reintroduction is a long process that requires several months to identify the culprit food(s).

Patients treated with 6-FED generally undergo at least six endoscopies [104]. In patients exclusively fed with the amino-acid-based formula, food reintroduction is an even longer process that requires numerous EGDs.

A recent study demonstrated that, in children, topical steroids can be safely and effectively reduced to the lowest effective dose after a successful induction therapy [105].

6.1. Nutritional Issues and Assessment

Several factors may negatively influence nutritional status and caloric intake. EoE children generally show GI symptoms, like vomiting or food refusal, that may limit adequate dietary intake [106]. Children and adolescents who experience food impaction episodes present a high risk of developing eating or mood disorders, which may further compromise adequate nutrient and caloric intake [96,107]. The coexistence of multiple food allergies may further complicate the nutritional status and growth of EoE children. Long-term and restrictive food elimination diets may compromise adequate micronutrient intake, although they do not seem to worsen child growth or body mass index (BMI) [106,108]. Nutritionists play an essential role in EoE children's care. The nutritionist should determine the degree of exposure to EoE trigger foods and the potential nutritional effects of their elimination, meticulously evaluating the patient's diet and family eating habits [109,110]. Before beginning an empirical food elimination diet and during the follow-up, pediatricians and nutritionists should periodically assess children's nutritional status and growth and rule out potential nutritional deficiencies.

Another critical point of EoE follow-up concerns patient and family education. Pediatricians should carefully inform and educate affected patients and families regarding what they can safely eat or cannot eat, avoid cross-contaminations, and provide the appropriate resources for additional information [94]. Parents and children should also be advised on the risk of potential food cross-contamination. Based on the specific local legislation, patients and parents should also be educated and sensitized to interpret foodstuff labels correctly [94]. The precautionary allergen warning ("may contain") is not obligatory in some countries [94]. The potential risk of trace exposure or allergen contamination is still debated, and it has not been evaluated in EoE patients [94].

6.2. Multidisciplinary Assessment

The multidisciplinary team, including the pediatric allergist, gastroenterologist, endoscopist, nutritionist, and psychologist, is crucial in pediatric EoE management [106] (Figure 3). At highly specialized centers, these pediatric specialists should be enrolled at the first visit and during the follow-up evaluations, guaranteeing the transition from the pediatric to the adult setting. Pediatric allergists should identify and treat coexisting atopic diseases (allergic rhinitis, eczema, asthma, IgE-mediated food allergy, and drug allergy). Allergy assessment is also addressed to stratify the potential risk of IgE-mediated reactions when foods previously eliminated (especially cow's milk) are reintroduced into the child's diet [111].

Endoscopic and histologic abnormalities are not always associated with gastrointestinal symptoms, and children may be asymptomatic or mildly symptomatic despite active disease. Therefore, endoscopic follow-up is mandatory to evaluate disease remission and patient compliance. Regular multidisciplinary follow-up is also essential to rule out potential side effects of long-term treatments [111].

Children with suspected genetic diseases should also be assessed by a medical geneticist. In the case of a suspected hyper-IgE syndrome or Netherton syndrome, the involvement of a pediatric immunologist in the multidisciplinary team is mandatory.

The chronic nature of EoE, comorbidities, long-term therapies, and periodic EGDs are the main stressful factors for children and adolescents with EoE [96]. It has been demonstrated that EoE negatively impacts the QoL of patients [96]. Older children and adolescents may also develop eating disorders or anxiety mostly related to the fear of eating in public places or new food impaction episodes [96]. Therefore, psychological support

should be provided when behavioral disorders, eating disorders, or low compliance with therapies are suspected [96]. The psychological impact of EoE is still poorly understood, and more research is needed to assess the burden of neuropsychiatric disorders and their clinical manifestations (sleep disorders, low school performance, dysfunctional family relationships, anxiety, anorexia, or bulimia) and the psychological impact of families.

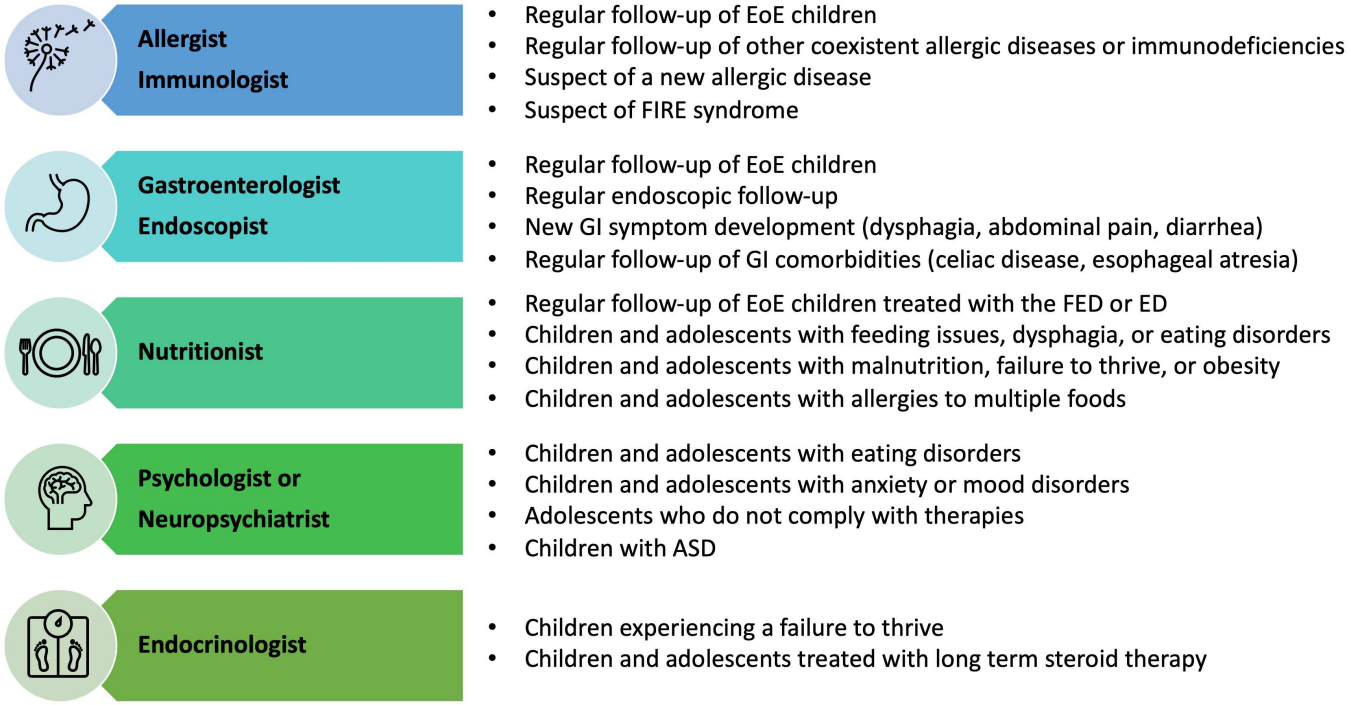

Figure 3. Indications to refer EoE patients to the specialists. ADS, autism spectrum disorders; ED, elemental diet; EoE, eosinophilic esophagitis; FIRE, food-immediate response to the esophagus; FED, food elimination diet.

7. Conclusions

EoE is an emerging chronic/remittent allergic disease with a meaningful impact on quality of life and health care systems. Despite several progresses, pediatric EoE management is still limited by gaps and unmet needs. Currently, no treatments have been approved for pediatric EoE management, and studies comparing the superiority of elimination diets with pharmacological therapies or assessing the long-term side effects are still unavailable. EoE follow-up is often limited by numerous drawbacks due to the need for several endoscopies for monitoring the disease, restrictive diets, or long-term pharmacological treatments. Therefore, there is a crucial need to:

1. Personalize treatments according to the molecular profile and clinical features of patients.
2. Assess the long-term effects of currently available therapies.
3. Identify noninvasive biomarkers and new molecular therapeutic targets.
4. Implement the use of less invasive tools to assess disease activity.
5. Improve the diagnostic process to identify the disease and prevent potential complications early.
6. Define international guidelines for long-term pediatric EoE management, focusing on the central role of a multidisciplinary approach.

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Summary

Eosinophilic gastrointestinal diseases (EGIDs) are emerging, heterogeneous, and chronic disorders affecting adults and children equally. Although several efforts have been made in the last decade to understand the pathophysiology and natural history of these diseases, many unmet needs still need to be solved. We investigated some of these aspects, achieving several notable findings.

We find that the epidemiology of non-EoE EGIDs in symptomatic patients is higher than that reported in observational studies or surveys, highlighting that these conditions are common and should be included in the differential diagnostic process of inflammatory GI diseases.

Although the pathogenesis is still unknown, EGIDs, particularly EoE, are allergic conditions related to early life and environmental risk factors. Diet is the most potent risk factor. A Western diet rich in sugar, fats, and ultra-processed foods may influence chronic non-communicable diseases, including food allergy and EoE. Moreover, we investigated the relationship between EGIDs and allergic disorders and oral immunotherapy, demonstrating a potential causal link, which is still being further investigated.

We collected data on patients with EGIDs followed at our Pediatric Hospital for five years, and we found that:

1. The epidemiology of these conditions is increased; thus, EGIDs are not rare diseases;
2. EGIDs affect patients with atopic comorbidities and children with non-atopic diseases, including autism spectrum disorders, esophageal atresia, and other congenital or genetic disorders, suggesting different potential phenotypes;
3. Symptoms are unspecific and depend on the site of intestinal inflammation.

Subsequently, we identified three potential phenotypes of pediatric EGIDs for the first time using a cluster analysis approach. Notably, we confirmed and characterized two subgroups of EoE patients, an atopic and non-atopic phenotype, with a relevant impact on clinical practice and potential significance in prognosis and response to therapy. In this context, we investigated and reviewed current evidence on the relationship between EGID and inborn errors of immunity (IEI), proposing a potential diagnostic algorithm to help clinicians suspect IEI in EGID patients and *vice versa* and prevent clinically relevant complications.

We also focused on the nutritional status of our EGID patients. Although there is a consistent risk of malnutrition, children with EGIDs are neither malnourished nor deficient in vitamin D compared with healthy controls. This successful finding is probably related to the multidisciplinary management ensured by the Center for Pediatric Eosinophilic Gastrointestinal Disorders. CPED collects an interdisciplinary team of pediatric allergists, gastroenterologists, endoscopists, and nutritionists.

We also reported the first pediatric case of FIRE. FIRE is the acronymous "food-induced immediate response of the esophagus" (FIRE) and is a novel syndrome characterized by an intense, unpleasant, or even painful retrosternal sensation occurring rapidly and reproducibly after esophageal contact with specific foods or liquids. To date, FIRE has been described in adults.

The clinical heterogeneity of EGIDs and the absence of specific noninvasive biomarkers are the main limitations to a prompt diagnosis and a shorter diagnostic process, especially in non-esophageal EGID cases. We identified that the diagnostic time is significantly associated with impaired child growth in children with EGIDs, highlighting that raising awareness among family pediatricians on EGIDs and promptly referring suspicious cases to specialized pediatric centers with a multidisciplinary team is fundamental. On the other hand, allergists and gastroenterologists should promptly consider GI endoscopy with correct biopsy sampling in all those children with

refractory GI symptoms, especially if complicated by atopy, peripheral eosinophilia, failure to thrive, or feeding issues.

EoE significantly impacts the quality of life of affected children, primarily because of the absence of noninvasive biomarkers and the need to periodically monitor treatment response with esophagogastroduodenoscopy. Consequently, identifying noninvasive biomarkers is an urgent need in pediatric EoE management. The last part of the Ph.D. research aimed to identify potential noninvasive biomarkers for EoE diagnosis and monitoring, assessing disease activity with the newly proposed set of outcome measures for improving the data quality of trials and observational studies (COREOS). We identified three promising noninvasive biomarkers for EoE diagnosis and surveillance using a panel of inflammatory, tissue, vascular, and eosinophil-derived markers. We found that interleukin (IL)-17 values predicted clinically, endoscopically, and histologically active disease. As reported in the asthma model, high expression of IL-17 might define a potential “Th-2 low" endotype, which might correspond to a severe and difficult-to-treat EoE phenotype. In the case-control comparison, galectin (GAL)-10 and transforming growth factor (TGF)-β values were significantly increased in EoE patients compared to healthy, non-allergic children. The results of this explorative prospective study are promising and open new scenarios in EoE diagnosis and surveillance that should be investigated with further and more extensive studies.

Additional scientific activity during the Ph.D.

Education

06/02/2023 – 06/02/2034

National Scientific qualification as an associate in the Italian higher education system, for the disciplinary field of 06/G1 - Pediatrics and child neuropsychiatry

Academic year 2020/2021

Advanced Training Course in Pediatric Gastroenterology

"Sapienza" University of Rome

Oct 18, 2021

European Examination in Allergology and Clinical Immunology

13th EAACI/UEMS Examination

European Academy of Allergy and Clinical Immunology

Jan 19, 2021

Master of High Qualification (MsC) in "Pediatric Immunopathology"

University of Pavia

Dec 31, 2020

Expert and teaching assistant in Pediatrics

Academic activity

Teaching, supplementary teaching, and student service activities

- General Pediatrics, Bachelor of Science in Medicine (1CFU)
- Childhood and Women Health, Harvey Medical Course (1CFU)
- General Pediatrics, Bachelor of Science in Dentistry (1CFU)
- Master's degree in Pediatric Nutrition and Nutraceuticals
- Master's degree in Clinical Allergology and Immunology of the Developmental Age
- Post-graduate degree in Pediatric Nursing

Co-supervisor of Medical degree project thesis

Thesis: *"Eosinophilic gastrointestinal disorders: The Experience of the Pediatric Reference Center of the University of Pavia.*" Candidate: Serena Anjali Pitigalage Kurera. University of Pavia, *Harvey Course.* Academic year 2020/21

Thesis: *"Diagnostic delay and its implications in pediatric eosinophilic gastrointestinal disorders."* Candidate: *Francesca Bertaina. Università degli Studi di Pavia, Harvey Course.* Academic year 2020/21.

Thesis*: "Orticaria cronica in età pediatrica: studio retrospettivo".* Candidate: Mattia Cristallo. *Università degli Studi di Pavia.* Academic year 2021/22.

Grants and Awards

"Pediatria Futura" Award 2021 from the Italian Society of Pediatrics (SIP)

Research: "Eosinophilic gastrointestinal disorders in children."

Participation in national and international research groups

- **Sub-investigator** of the multicenter clinical trial V1605-201/APTITUDE: "*A phase 2 study to evaluate the sensitivity, specificity, and safety of dbv1605, an off-the-shelf atopic patch test for the diagnosis of non-immunoglobulin-mediated cow's milk allergy in children.*"
- **Collaborator** of the international multicenter clinical study "*Comprehensive analyses of innate and adaptive immune responses during acute COVID-19 infection and convalescence*" sponsored by the National Institute of Allergy and Infectious Diseases, NIH.

- Sacco K, Castagnoli R, Vakkilainen S, Liu C, Delmonte OM, Oguz C, et al; NIAID Immune Response to COVID Group; Chile MIS-C Group; Pavia Pediatric COVID-19 Group, Cohen JI, Su HC, Kuhns DB, Lionakis MS, Snyder TM, Holland SM, Goldbach-Mansky R, Tsang JS, Notarangelo LD. Immunopathological signatures in multisystem inflammatory syndrome in children and pediatric COVID-19. Nat Med. 2022;28(5):1050-1062. doi: 10.1038/s41591-022-01724-3. **Collaborator**

- **Sub-investigator** of the DAISY multicenter clinical trial (No. 53718678RSV3001): "*A Study of Rilematovir in Infants and Children and Subsequent in Neonates Hospitalized With* Acute *Respiratory Tract Infection Due to Respiratory Syncytial Virus (RSV)*."
- **Sub-investigator** of the CROCUS multicenter clinical trial (No. 53718678RSV2002): "*A Phase 2, Double-blind, Placebo-controlled Study to Evaluate the Antiviral Activity, Clinical Outcomes, Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Relationships of Different Doses of JNJ-53718678 in Children equal to or greater than 28 Days and equal to less than 3 Years of Age With Acute Respiratory Tract Infection Due to Respiratory Syncytial Virus Infection*."
- **Sub-investigator** of the trial "*Double-blind, randomized, active-controlled, two-way cross-over, two-period, two treatment (indacaterol/mometasone furoate versus budesonide) study, with 12-week treatment duration each, to evaluate the efficacy and safety of indacaterol (acetate) / mometasone (furoate) compared to budesonide in terms of superiority in children from 6 to less than 12 years of age with asthma (CQMF149G2301)*"
- **Co-principal investigator** of the European study "*European Registry of Clinical, Environmental, and Genetic Determinants in Eosinophilic Esophagitis, EoE CONNECT*" promoted by the European Society of Eosinophilic Esophagitis (EUREOS) from 15-12-2021 to present.
- **Co-principal investigator** of a national, multicenter, retrospective, prospective study to evaluate pediatric gastrointestinal eosinophilic disorders (EGIDs), the GOLDEN Study from 10-02-2022 to present.
    - Votto M, Fasola S, Cilluffo G, Ferrante G, La Grutta S, Marseglia GL, Licari A. CLUSTER ANALYSIS OF CLINICAL DATA REVEALS THREE PEDIATRIC EOSINOPHILIC GASTROINTESTINAL DISORDER PHENOTYPES. *Pediatr Allergy Immunol*. 2022;33(2):e13746. doi: 10.1111/pai.13746.
    - Votto M, Naso M, De Filippo M, Marseglia A, Raffaele A, Marseglia GL, et al. FOOD-INDUCED IMMEDIATE RESPONSE OF THE ESOPHAGUS: A FIRST REPORT IN THE PEDIATRIC AGE. *Allergy. 2022;77(2):711-712. doi: 10.1111/all.15088.*
    - Votto M, Lenti MV, De Silvestri A, Bertaina F, Bertozzi M, Caimmi S, Cereda E, De Filippo M, Di Sabatino A, Klersy C, Raffaele A, Riccipetitoni G, Marseglia GL, Licari A, Brambilla I. EVALUATION OF DIAGNOSTIC TIME IN PEDIATRIC PATIENTS WITH EOSINOPHILIC GASTROINTESTINAL DISORDERS ACCORDING TO THEIR CLINICAL FEATURES. *Ital J Pediatr*. 2023 Jan 16;49(1):9. doi: 10.1186/s13052-023-01410-1.
    - Votto M, De Filippo, Caimmi S, Indolfi C, Raffaele A, Tosca MA, Marseglia GL, Licari A. A PRACTICAL UPDATE ON PEDIATRIC EOSINOPHILIC ESOPHAGITIS. *Children* 2023.
- **Co-principal investigator** of international and multicenter study "Severe Paediatric Asthma Collaborative in Europe_SPACE" from 28-06-2022 to present.
- **Local collaborator** of the multicenter study "Send-In Sample Collection to Achieve Genetic and Immunologic Characterization of Primary Immunodeficiencies" promoted by the National Institute of Health (NIH), Bethesda, USA.

Congress Activity

Lecturer, oral communications, and posters

- Tutors of the 2nd "Scuola Superiore SIP (Italian Society of Pediatrics). Rimini 27 November-2 December 2023.
- 78th National Congress of Italian Society of Pediatrics. Lecture: "Galectina-10 sierica: un nuovo e potenziale biomarcatore di esofagite eosinofila in età pediatrica." Turin, 25-28 October 2023. Lecturer
- Grand Round of the Italian Society of Pediatric Allergology and Immunology (SIAIP). Lecture: L'esofagite eosinofila in età pediatrica. Webinar. 28 September 2023. Speaker
- European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress 2023. Hamburg, 9-11 June 2023. Chair of "Targeting eosinophilic esophagitis" session.
- XXV National Congress of "Italian Society of Pediatric Allergology and Immunology (SIAIP)". Lecture: "Patologie eosinofile gastro-enteriche: seguire la clinica per pianificare gli accertamenti" Rome, 13-15 April 2023. Lecturer.
- Paviallergy 2023 Congress. Lecture: "Esofagite eosinofila: il punto di vista del pediatria." Pavia, 25 February 2023. Lecturer.
- SIDerP-SIAIP National Congress. Lecture: "Orticaria: le basi immunologiche." Bologna, 17 - 18 February 2023. Lecturer.
- Academic forum SIAIP. "Focus sulle patologie respiratorie e allergiche del bambino". Pavia, 30 November- 1st Dicember 2022. Tutor and Lecturer.

- “Scuola SIGENP per giovani ricercatori”. Lecture: "Cluster analysis reveals three pediatric eosinophilic gastrointestinal disorder phenotypes." Sorrento, 27 - 29 October 2022. Lecturer.
- Congress “Strategie terapeutiche innovative nelle patologie immuno-allergologiche nel bambino e nell'adulto. Ruolo dell’infiammazione di tipo-2. Gestione integrata del paziente tra ospedale e territorio.” Lecture: “Esofagite eosinofila: una patologia emergente in età pediatrica”. Pavia, 15 September 2022. Lecturer.
- Congress “Giornate Pediatriche Rhodensi” Lecture: “Malattie eosinofile dell’apparato gastrointestinale”. Rho, 9-10 September 2022. Lecturer.
- European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress 2021. 10-12 July 2021. Poster presentation.
- Congress “Incontri Serali 2022 Pediatria: Ospedale e Territorio rete pediatrica della scuola di specializzazione in Pediatria dell'Università degli studi di Pavia. 43° maggio pediatrico”. Lecture: “L’esofagite eosinofila: cosa deve sapere il Pediatra”. Pavia, 22 June 2022. Lecturer.
- EUREOS Online Update Course on Eosinophilic Esophagitis. Lecture: "Noninvasive markers in EoE" May 22, 2022. Lecturer.
- XXIV National Congress of Italian Society of Pediatric Allergology and Immunology (SIAIP). Lecture: “Esofagite Eosinofila: una patologia in evoluzione” Naples, 7-9 April 2022. Lecturer.
- Congress “Opinioni a confronto in Immuno-pneumo-allergologia Pediatrica.” Pavia, 5-6 October 2021. Discussant.
- European Academy of Allergy and Clinical Immunology (EAACI) Hybrid Congress 2021. 10-12 July 2021. Poster presentation.
- 76th National Congress of Italian Society of Pediatrics. Lecture: “Le patologie eosinofile gastrointestinali nel bambino.” 25-28 May 2021. Lecturer and award.
- XXIII National Congress of Italian Society of Pediatric Allergology and Immunology (SIAIP). Lecture: “Patologie eosinofile gastrointestinali e ITS.” 22-24 April 2021. Lecturer.

Congress scientific/organizing committee

- Congress “Opinioni a confronto in Immuno-pneumo-allergologia Pediatrica.” Pavia, 6 -7 October 2023.
- Congress “Opinioni a confronto in Immuno-pneumo-allergologia Pediatrica.” Pavia, 7 -8 October 2022.
- “Forum Nazionale delle Scuole di Specializzazione in Pediatria Specialità e Professione in Pediatria 17° edizione. 30 September 2022.
- Congress “Opinioni a confronto in Immuno-pneumo-allergologia Pediatrica.” Pavia, 5-6 October 2021.
- “Specialità e professione in pediatria, 16° edizione. Forum Nazionale delle scuole di specializzazione in pediatria.” 1 October 2021.
- “XXIII Congresso Nazionale della Società italiana di Allergologia ed Immunologia Pediatrica (SIAIP).” 22-24 April 2021.
- “Immunologia ed Allergologia pediatrica: dalla teoria alla pratica clinica.” Pavia, 7-9 November 2019.
- Congress “Opinioni a confronto in Immuno-pneumo-allergologia Pediatrica.” Pavia, 4-5 October 2019.

Affiliations to Scientific Societies

Scientific committee member

- Board Member of the Working Group on Eosinophilic Esophagitis of the European Academy of Allergy and Clinical Immunology (EAACI) 2022/24.
- Board Member of the Scientific Committee of Eosinophilic Diseases (Italian Society of Pediatric Allergy and Immunology) from March 2022 to present.
- Board Member of the Scientific Committee of Allergy Immunotherapy (Italian Society of Pediatric Allergy and Immunology)
- Member of EUROS (European Society of Eosinophilic Oesophagitis)
- Junior Member of EAACI (European Academy of Allergy and Clinical Immunology). Membership. Number: 20081.
- Junior Member of SIAIP (Italian Society of Pediatric Allergy and Immunology)
- Junior Member of SIGENP (Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition)
- Member of SIP (Italian Society of Pediatrics)

Editorial Roles

- Guest Editor of the Special Issue "Dietary Interventions in Immune Diseases" for Nutrients (in progress)

Guest Editor "New perspectives in pediatrics: from research to clinical practice." Acta Biomedica Vol. 93 Suppl. 3 (2022)

- Review Board for ***Frontiers in Pediatrics*** journal section Infectious Diseases-Surveillance, Prevention and Treatment. https://loop.frontiersin.org/people/977751/editorial
- Review Board for ***Nutrients***
- Review Board for ***Frontiers in Allergy***
- Junior Reviewer of ***Allergy*** and ***Pediatric Allergy and Immunology*** (PAI) journal

Publications during the Ph.D.

Publications in international indexed journals

1. Votto M, De Filippo, Caimmi S, Indolfi C, Raffaele A, Tosca MA, Marseglia GL, Licari A. A PRACTICAL UPDATE ON PEDIATRIC EOSINOPHILIC ESOPHAGITIS. *Children* 2023. ***IF2.4***

2. Castagnoli R, Taietti I, Votto M, Naso M, De Filippo M, Marseglia A, Montagna L, De Amici M, Avanzini MA, Montagna D, Marseglia GL, Licari A; Italian Primary Immunodeficiency NETwork (IPINET). CLINICAL AND IMMUNOLOGICAL PHENOTYPES OF SELECTIVE IGM DEFICIENCY IN CHILDREN: RESULTS FROM A MULTICENTER STUDY. *Pediatr Allergy Immunol*. 2023 Sep;34(9):e14015. doi: 10.1111/pai.14015. ***IF 4.4***

3. Taietti I, Votto M, De Filippo M, Naso M, Montagna L, Montagna D, Licari A, Marseglia GL, Castagnoli R. SELECTIVE IGM DEFICIENCY: EVIDENCE, CONTROVERSIES, AND GAPS. *Diagnostics (Basel)*. 2023 Sep 4;13(17):2861. doi: 10.3390/diagnostics13172861. ***IF 3.6***

4. Pitsios C, Rossi CM, Terreehorst I, Heffler E, Votto M, Konstantinou GN, Alvarez-Perea A, Bakirtas A, Apostolidou E, Antolin-Amerigo D, Nikolopoulos GK, Pfaar O, Cianferoni A. EOSINOPHILIC ESOPHAGITIS AS A SIDE-EFFECT OF ALLERGEN IMMUNOTHERAPY: PROTOCOL FOR A SYSTEMATIC REVIEW AND META-ANALYSIS. *Eur Ann Allergy Clin Immunol*. 2023. doi: 10.23822/EurAnnACI.1764-1489.311. ***IF 2.3***

5. Andrenacci B, De Filippo M, Votto M, Prevedoni Gorone MS, De Amici M, La Grutta S, Marseglia GL, Licari A. SEVERE PEDIATRIC ASTHMA ENDOTYPES: CURRENT LIMITS AND FUTURE PERSPECTIVES. *Expert Rev Respir Med*. 2023 Jul-Dec;17(8):675-690. doi: 10.1080/17476348.2023.2254234. ***IF 3.9***

6. Votto M, De Filippo M, Marseglia A, Brambilla I, Marseglia GL, Licari A. APPLYING A NEW SET OF CORE OUTCOME MEASURES FOR SEVERE PEDIATRIC ASTHMA IN REAL-LIFE: A SINGLE-CENTER EXPERIENCE. *Pediatr Pulmonol*. 2023 Aug 2. doi: 10.1002/ppul.26619. ***IF 4.09***

7. Carucci L, Votto M, Licari A, Marseglia GL, Berni Canani R. FOOD ALLERGY: CAUSE OR CONSEQUENCE OF PEDIATRIC EOSINOPHILIC ESOPHAGITIS? POTENTIAL IMPLICATIONS OF ULTRAPROCESSED FOODS IN PREVENTION AND MANAGEMENT. *Front. Allergy*. 2023 Jun 29. doi: 10.3389/falgy.2023.1138400 **Co-first author.**

8. De Filippo M, Fasola S, Tanno LK, Brambilla I, Votto M, Grutta S, Marseglia GL, Licari A. OPTIMIZING UNDERSTANDING OF FOOD-INDUCED ANAPHYLAXIS PHENOTYPES THROUGH CLUSTERING ANALYSIS. *Clin Exp Allergy*. 2023 Jun 12. doi: 10.1111/cea.14358. ***IF 6.1***

9. Votto M, Lenti MV, De Silvestri A, Bertaina F, Bertozzi M, Caimmi S, Cereda E, De Filippo M, Di Sabatino A, Klersy C, Raffaele A, Riccipetitoni G, Marseglia GL, Licari A, Brambilla I. EVALUATION OF DIAGNOSTIC TIME IN PEDIATRIC PATIENTS WITH EOSINOPHILIC GASTROINTESTINAL DISORDERS ACCORDING TO THEIR CLINICAL FEATURES. *Ital J Pediatr*. 2023 Jan 16;49(1):9. doi: 10.1186/s13052-023-01410-1. ***IF 3.288***

10. Votto M, Castagnoli R, Marseglia GL, Licari A, Brambilla I. COVID-19 AND AUTOIMMUNE DISEASES: IS THERE A CONNECTION? *Curr Opin Allergy Clin Immunol*. 2023 doi: 10.1097/ACI.0000000000000888. ***IF 3.142***

11. Votto M, Naso M, Brambilla I, Caimmi S, De Filippo M, Licari A, Marseglia GL, Castagnoli R. EOSINOPHILIC GASTROINTESTINAL DISEASES IN INBORN ERRORS OF IMMUNITY. *J. Clin.* Med. 2023, 12, 514. https://doi.org/10.3390/jcm12020514. ***IF 4.964***

12. De Filippo M, Votto M, Caminiti L, Carella F, De Castro G, Landi M, Olcese R, Panasiti I, Vernich M, Barberi S, Ciprandi G, Marseglia GL. OMALIZUMAB AND ALLERGEN IMMUNOTHERAPY FOR RESPIRATORY ALLERGIES: A MINI-REVIEW FROM THE ALLERGEN-IMMUNOTHERAPY COMMITTEE OF THE ITALIAN SOCIETY OF PEDIATRIC ALLERGY AND IMMUNOLOGY (SIAIP). *Allergol Immunopathol (Madr). 2022. Accepted, In press.* **Corresponding author** ***IF 1.667***

13. De Filippo M, Votto M, Albini M, Castagnoli R, De Amici M, Marseglia A, Pizzo A, Marseglia GL, Licari A. PEDIATRIC ANAPHYLAXIS: A 20-YEAR RETROSPECTIVE ANALYSIS. *Journal of Clinical Medicine*. 2022; 11(18):5285. doi:10.3390/jcm11185285. **Co-first author.** ***IF 4.964***

14. Votto M, Achilli G, De Filippo M, Licari A, Marseglia A, Moiraghi A, Di Sabatino A, Marseglia GL. PEDIATRIC CHRONIC SPONTANEOUS URTICARIA: A BRIEF CLINICIAN'S GUIDE. *Expert Rev Clin Immunol*. 2022 Jul 14. doi: 10.1080/1744666X.2022.2101999. ***IF 4.473***

15. Votto M, Naso M, Clemente AM, De Filippo M, Gargiulo G, Granone V, et al. EOSINOPHILIC ESOPHAGITIS AN UPDATE IN CHILDREN. *Acta Biomed*. 2022 Jun 6;93(S3):e2022034. doi: 10.23750/abm.v93iS3.13068. ***IF 1.352***

16. Votto M, Santi V, Bajeli M, De Filippo M, Deidda E, De Stefano E, et al. SAFETY OF BIOLOGICAL THERAPY IN CHILDREN AND ADOLESCENTS WITH SEVERE ASTHMA DURING THE COVID-19 PANDEMIC: A CASE SERIES. *Acta Biomed*. 2022 Jun 6;93(S3):e2022053. doi: 10.23750/abm.v93iS3.13073. ***IF 1.352***

17. De Filippo M, Magri P, Bossi G, Brambilla I, Castagnoli R, Mascolo A, et al. CLINICAL AND EPIDEMIOLOGICAL FEATURES OF PEDIATRIC PATIENTS WITH COVID-19 IN A TERTIARY PEDIATRIC HOSPITAL. *Acta Biomed*. 2022 Jun 6;93(S3):e2022039. doi: 10.23750/abm.v93iS3.13074. ***IF 1.352***

18. Brambilla I, Rossi F, Pistone C, Licari A, De Filippo M, Votto M, et al. PSEUDOHYPOPARATHYROIDISM: A DIAGNOSIS TO CONSIDER ONCE A PTH ELEVATION IS DETECTED. *Acta Biomed*. 2022 Jun 6;93(S3):e2022194. doi: 10.23750/abm.v93iS3.13072. ***IF 1.352***

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20. Brambilla I, Bellanca E, Pistone C, De Filippo M, Votto M, Tondina E, et al. PEDIATRIC OBESITY: A MINI-REVIEW FOR PEDIATRICIAN. *Acta Biomed*. 2022 Jun 6;93(S3):e2022197. doi: 10.23750/abm.v93iS3.13078. ***IF 1.352***

21. Rossi CM, Lenti MV, Merli S, Licari A, Votto M, Marseglia GL, et al. PRIMARY EOSINOPHILIC GASTROINTESTINAL DISORDERS AND ALLERGY: CLINICAL AND THERAPEUTIC IMPLICATIONS. *Clin Transl Allergy*. 2022 May 23;12(5):e12146. doi: 10.1002/clt2.12146. ***IF 3.57***

22. Votto M, Fasola S, Fasola, Cilluffo G, Ferrante G, La Grutta S, et al. CLUSTER ANALYSIS OF CLINICAL DATA REVEALS THREE PEDIATRIC EOSINOPHILIC GASTROINTESTINAL DISORDER PHENOTYPES. *Pediatr Allergy Immunol*. 2022. doi: 10.1111/pai.13746 (in press). ***IF 6.377***

23. De Filippo M, Votto M, Benazzo M, Gitto E, Salpietro A, Pagella F, et al. HOT TOPICS IN PEDIATRIC CHRONIC RHINOSINUSITIS. *Journal of Biological Regulators and Homeostatic Agents.* 2022;36: 183–190. ***IF 1.506***

24. Castagnoli R, Brambilla I, De Filippo M, Votto M, Montagna D, Montagna L, et al. PEDIATRIC COVID-19 – A REVIEW. *Journal of Biological Regulators and Homeostatic Agents.* 2022;36: 177–183. ***IF 1.506***

25. Sacco K, Castagnoli R, Vakkilainen S, Liu C, Del Monte O, Oguz C, et al. IMMUNOPATHOLOGICAL SIGNATURES IN MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN AND PEDIATRIC COVID-19. *Nat Med* (2022). doi:10.1038/s41591-022-01724-3. **Collaborator.** ***IF 49.962***

26. Votto M, Naso M, De Filippo M, Marseglia A, Raffaele A, Marseglia GL, Licari A. FOOD-INDUCED IMMEDIATE RESPONSE OF THE ESOPHAGUS: A FIRST REPORT IN THE PEDIATRIC AGE. *Allergy.* 2022;77(2):711-712. doi: 10.1111/all.15088. ***IF 13.146***

27. Votto M, Delle Cave F, De Filippo M, Marseglia A, Marseglia GL, Brazzelli V, Licari A. RAPID RESPONSE TO DUPILUMAB TREATMENT IN CHILDREN WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS: A CASE SERIES. *Pediatr Allergy Immunol*. 2022;33 Suppl 27:31-33. doi: 10.1111/pai.13623. ***IF 6.377***

28. Votto M, Bonitatibus G, De Filippo M, Pitigalage Kurera SA, Brambilla I, Guarracino C, De Amici M, Marseglia GL, Licari A. NUTRITIONAL STATUS IN EOSINOPHILIC GASTROINTESTINAL DISORDERS: A PEDIATRIC CASE-CONTROL STUDY. *Pediatr Allergy Immunol*. 2022;33 Suppl 27:47-51. doi: 10.1111/pai.13628. ***IF 6.377***

29. De Filippo M, Votto M, Caminiti L, Panasiti I, Carella F, De Castro G, Landi M, Olcese R, Vernich M, Marseglia GL, Ciprandi G, Barberi S. SAFETY OF ALLERGEN-SPECIFIC IMMUNOTHERAPY IN CHILDREN. *Pediatr Allergy Immunol*. 2022;33 Suppl 27:27-30. doi: 10.1111/pai.13622. ***IF 6.377***

30. Signorino C, Votto M, De Filippo M, Marseglia GL, Galli L, Chiappini E. DIAGNOSTIC ACCURACY OF XPERT ULTRA FOR CHILDHOOD TUBERCULOSIS: A PRELIMINARY SYSTEMATIC REVIEW AND META-ANALYSIS. *Pediatr Allergy Immunol*. 2022;33 Suppl 27:80-82. doi: 10.1111/pai.13637. ***IF 6.377***

31. Votto M, De Filippo M, Lenti MV, Rossi CM, Di Sabatino A, Marseglia GL, Licari A. DIET THERAPY IN EOSINOPHILIC ESOPHAGITIS. FOCUS ON A PERSONALIZED APPROACH. *Front. Pediatr.* 2021 doi: 10.3389/fped.2021.820192 *Accepted. In press* ***IF 3.418***

32. Castagnoli R, Licari A, Votto M, Ciprandi G, Marseglia GL. ASSOCIATION BETWEEN TREATMENT AWARENESS AND UNCONTROLLED ASTHMA IN ADOLESCENTS. *Lung India*. 2022 Jan-Feb;39(1):84-85. doi: 10.4103/lungindia.lungindia_213_21. PMID: 34975061. ***IF 0.768***

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34. Votto M, De Filippo M, Castagnoli R, Delle Cave F, Giffoni F, Santi V, Vergani M, Caffarelli C, De Amici M, Marseglia GL, Licari A. NON-INVASIVE BIOMARKERS OF EOSINOPHILIC ESOPHAGITIS. *Acta Biomed*. 2021 Nov 29;92(S7):e2021530. doi: 10.23750/abm.v92iS7.12401.

35. De Filippo M, Votto M, Brambilla I, Castagnoli R, Montagna L, Caffarelli C, Cardinale F, Miraglia Del Giudice M, Tosca M, Caimmi S, Licari A, Marseglia GL. ALLERGY AND COVID-19. *Acta Biomed.* 2021 Nov 29;92(S7):e2021522. doi: 10.23750/abm.v92iS7.12402.

36. Tosca MA, Schiavetti I, Ciprandi G; "ControL'Asma" Study Group. ASTHMA SEVERITY PERCEPTION IN ITALIAN CHILDREN: A NATIONWIDE CROSS-SECTIONAL STUDY. *Health Sci Rep.* 2021;4:e383. doi:10.1002/hsr2.383. **Collaborator.** ***IF 1.56***

37. Tosca MA, Schiavetti I, Ciprandi G; the "ControL'Asma" Study Group. THE ROLE OF BRONCHODILATION TESTING IN CHILDREN AND ADOLESCENTS WITH ASTHMA IN CLINICAL PRACTICE. *J Asthma*. 2021 Sep 21:1-3. doi: 10.1080/02770903.2021.1980582. **Collaborator.** ***IF 1.849***

38. Votto M, De Filippo M, Licari A, Caimmi S, Marseglia GL, Davidovich S, Slawatyniec I, Fraticelli S, Barruscotti S, Brazzelli V. ATYPICAL ERYTHEMA *ANNULARE CENTRIFUGUM* IN A CHILD WITH COELIAC DISEASE. *Clinical Case Reports*. (Accepted May 15, 2021).

39. Tosca MA, Schiavetti I, Ciprandi G; "ControL'Asma" Study Group. THE CHALLENGE OF ASTHMA CONTROL GRADING IN CLINICAL PRACTICE. *Respir Investig*. 2021:S2212-5345(21)00109-X. doi: 10.1016/j.resinv.2021.06.001. **Collaborator.** ***IF 2.24***

40. Votto M, Raffaele A, De Filippo M, Caimmi S, Brunero M, Riccipetitoni G, Marseglia GL, Licari A. EOSINOPHILIC GASTROINTESTINAL DISORDERS IN CHILDREN AND ADOLESCENTS: A SINGLE-CENTER EXPERIENCE. Dig Liver Dis. 2021:S1590-8658(21)00341-8. doi: 10.1016/j.dld.2021.06.027. ***IF 4.088***

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43. Savasta S, Bassanese F, Hruby C, Foiadelli T, Siri B, Gori V, Votto M, Tinelli C, Marseglia GL. ABSENCE OF LINGUAL FRENULUM IN CHILDREN WITH EHLERS-DANLOS SYNDROME: A RETROSPECTIVE STUDY OF FORTY CASES AND LITERATURE REVIEW OF A TWENTY YEARS LONG DEBATE. *Minerva Pediatr (Torino).* 2021;73(3):230-235. doi: 10.23736/S0026-4946.19.05530-0. ***IF 1.312***

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45. Votto M, De Filippo M, Licari A, Marseglia A, De Amici M, Marseglia GL. BIOLOGICAL THERAPIES IN CHILDREN AND ADOLESCENTS WITH SEVERE UNCONTROLLED ASTHMA: A PRACTICAL REVIEW. *Biologics.* 2021;15:133-142. doi: 10.2147/BTT.S252574. ***IF 2.719***

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9. De Filippo M, Ciprandi R, Marseglia G, Votto M, Ciprandi G, Licari A**.** ANXIETY AND DEPRESSION IN ADOLESCENTS WITH SEVERE ASTHMA AND THEIR CAREGIVERS. *Allergy*. 2020; 75:S109. ***IF 8.706.*** EAACI (*European Academy of Allergy and Clinical Immunology*) *Virtual Congress* 2020.

Chapters of books

Ugazio A.G., Marseglia G.L. (2023). "Immunologia e allergologia pediatrica "– Third Edition (Italian). Pacini Editore ISBN: 978-88-3379-472-3.

Chapters:

- Severe asthma
- Cough
- Eosinophilic gastrointestinal diseases
- Biologic drugs in allergy
- Nutraceuticals and vitamins
- SARS-CoV-2 infection and the immune system
- Clinical manifestations and therapeutic approach of pediatric COVID-19
- COVID-19, asthma, and allergies

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