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Adult versus pediatric eosinophilic esophagitis: important differences and similarities for the clinician to understand

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Eosinophilic esophagitis (EoE) is recognized as a common, allergy-associated cause of chronic esophageal symptoms affecting both children and adults. Research has begun to shed light on its epidemiology with consistent results from various geographical areas. Differences in clinical presentation, endoscopic aspects and response to treatment have all been reported for patients of different ages, and the question as to whether adult and pediatric EoE are manifestations of a single entity or in fact two distinct disorders has been posed. The most relevant differences between pediatric and adult EoE come from evolutionary changes in the consequences of the disease, including fibrous remodeling, and the ability to express symptoms. However, most studies support a common pathogenesis and similar histopathological features for adult and pediatric patients, being the same diagnostic criteria applied to them. This article comprehensively reviews the most recently published information and addresses important questions about the natural history of EoE.

Keywords: allergic esophagitis • corticosteroids • diet • dysphagia • eosinophilic esophagitis • food allergy

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Learning objectives

Upon completion of this activity, participants will be able to:

- Describe the epidemiology of EoE in adults and children, based on a review
- Compare the clinical features of EoE in adults and in children, based on a review
- Compare the pathophysiology of EoE in adults and in children, based on a review

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Eosinophilic esophagitis (EoE) is an emerging, chronic and antigen/immune-driven inflammatory disorder of the esophagus. Clinically, it is characterized by symptoms related to esophageal dysfunction while histologically it presents with eosinophil-predominant inflammation [1]. From its first descriptions in the literature a little over 20 years ago, EoE is currently recognized as a prevalent cause of chronic dysphagia and esophageal symptoms in both children and adults. In fact, EoE represents the second most common cause of chronic esophagitis (after gastroesophageal reflux) and the first cause of food impaction in young male patients. It is also considered to be the most common eosinophilic gastrointestinal disorder (EGID).

The natural history of EoE has not yet been clearly defined, but current knowledge considers it to be a chronic disorder in which esophageal symptoms persist or fluctuate over time while a dense esophageal eosinophilia generally remains despite prolonged treatment with proton-pump inhibitors (PPI) [2]. In addition, many patients often have a history of dysphagia, sometimes lasting for years before the diagnosis of EoE is finally established. Apart from these observations, more precise knowledge about the natural history of EoE and the underlying mechanisms leading to the perpetuation of this inflammation is still limited [1].

Several studies have found differences in the way EoE affects children and adults, giving rise to the question as to whether adult and pediatric EoE are manifestations of a single entity or in fact two distinct disorders [3]. This article aims to review the most relevant differences and similarities between adult and pediatric EoE by comprehensively reviewing the most recently published information and addressing important questions about the natural history of EoE.

Epidemiological aspects of EoE

During the 1980s, the presence of esophageal eosinophilia was considered to be a pathognomonic sign of gastroesophageal reflux disease (GERD) [4,5]; however, therapies based on controlling acid exposure were ineffective, especially in children. Paradoxically, the recognition of EoE as a distinct clinicopathological disorder came after the quasi-simultaneous reporting of an American and an European case series characterizing the disease in adult patients [6,7]. Since then, the number of studies on EoE has increased continuously and exponentially. Cases of EoE have been reported from all continents except Africa. While it is predominately found in Westernized countries and geographical areas with a higher socioeconomic development, modern life-style does not seem to be the only factor responsible. Moreover, though EoE seems to be more common among caucasians and it is reported that it predominantly affects males, it can affect patients of every race, age and gender. It has recently been shown that, compared with African–Americans, caucasians pediatric patients are significantly older at diagnosis and less likely to present with failure-to-thrive. However, clinical, endoscopic and histopathological features of EoE patients do not significantly differ by either race or gender [8].

In the past few years, several authors have estimated the epidemiology of EoE, but mainly within the pediatric population; such data on adult EoE are much scarcer. Thus, in 2006, the prevalence of pediatric EoE in Australia was estimated to have increased 18-fold over the previous 10 years [9]. In Philadelphia (USA), this increase was 35-fold [10]. Whether these observations reflect a true increase in incidence or simply increased awareness or frequency of endoscopic explorations has also been discussed.

Data on the incidence and prevalence of adult EoE have come almost exclusively from the USA and Switzerland, but the high concordance between them bolsters their findings. In any case, epidemiological figures vary widely for both pediatric and adult populations.

With regard to adult EoE patients, in 2005, Straumann *et al.* analyzed a large series of adult patients in Switzerland who were followed for 16 years [11]. The authors estimated an annual incidence of 1.4 per 100,000 inhabitants, with an increasing tendency in the last years. This registry was reevaluated in 2011, when it reported a rise in the annual incidence rate up to 2.45 per

100,000 [12]. In parallel, the prevalence of EoE also increased in the period between both analyses from 23 to 42.8 patients per 100,000 inhabitants [11,12].

For pediatric EoE, the reported figures are notably higher. For example, in one region of Ohio (USA), the incidence of adult EoE during the period between 2000 and 2003 was calculated by Noel *et al.* to be nine to 13 new cases per 100,000 inhabitants while the prevalence among children for the same period was estimated to be 42.9 per 100,000 inhabitants [13]. A recent survey-based study estimated the overall prevalence of EoE in the USA to be 52 cases per 100,000 inhabitants [14]. The same study also showed that the prevalence of EoE seemed to be higher in urban areas than in suburban and rural settings; geographically it was more common in the northwestern states [14].

A possible relationship between climate and the epidemiology of EoE has also been recently reported, with an analysis of an esophageal biopsy database demonstrating a higher prevalence of EoE in cold climate zones of the USA than in tropical or arid zones [15]. Diagnosis of EoE may also present seasonal variations since significantly more adult cases were diagnosed during the spring and summer than in the fall and winter months [16]. Moreover, esophageal bolus food impaction in atopic patients was demonstrated to be significantly higher in the summer and fall than in winter [17]. Climatic influences over immune system regulation, variations in exposure to air-borne allergens and the role of pollution associated with industrial development in promoting esophageal allergies all require further research.

It should also be noted that epidemiology data may be influenced by the eosinophil count threshold considered for EoE diagnosis, which has varied widely in the past. Retrospective analysis of a series of biopsies from 1992 to 1999 showed that 29% of children diagnosed with 'esophagitis' presented at least 15 eosinophils/hpf along with additional histopathological features that led to a retrospective diagnosis of EoE [18]. This particular study also showed that during the study period the incidence of EoE remained relatively stable in spite of a marked increase in the number of endoscopic exams performed. In any case, the rise in the incidence of EoE in recent years has grown faster than the increase in the number of endoscopic procedures carried out [12].

Allergy study results in EoE patients

EoE has been clearly associated with allergies in both children and adults, with peripheral eosinophilia occurring in 50% of patients [1] and elevated serum IgE levels being present in three out of four patients [1,19]. The majority of EoE patients present a family and/or personal allergic background, commonly presenting with asthma, rhinitis, conjunctivitis and eczema with variable frequency [1]. Moreover, food and aeroallergen sensitization have been commonly described in patients of all ages [12,20]. However, even though food-specific IgE or skin prick test (SPT) results were positive in over 80% of adult patients [21], elimination of foods that gave positive results failed to achieve disease remission [22]. In contrast, response to a food elimination diet resulted effective in patients who had exhibited negative allergy test results [23], indicating a dissociation between IgE based food allergy test results and actual EoE trigger foods.

In studies on children, only a single research group achieved EoE remission after excluding foods for which patients had demonstrated sensitization in SPT and atopic patch tests (APT) [24].

Interesting results have been also reported with regard to air-borne allergens [3]. For example, adult patients seem to present a higher proportion of IgE-mediated positive allergy results than children in whom sensitization to both indoor and outdoor antigens have been documented [20,25]. Both types of antigens have been demonstrated to cause experimental EoE [26]. As noted above, seasonal variation in the diagnosis and severity of EoE has been reported for both children [27] and adults [16], and after that, some researchers have posed that airborne-antigens may trigger and help to maintain EoE, even when no clinical human trials have been conducted to undoubtedly demonstrate air-borne allergens as EoE triggers.

In conclusion, although SPTs, serum IgE tests and food APTs can be used to help identify food sensitizations associated with EoE, none has definitively proven useful in diagnosing or managing EoE. For now, food triggers can only be identified by documenting disease remission after specific food antigen elimination followed by EoE recrudescence on the reintroduction of these specific trigger foods.

Clinical aspects of EoE

EoE has been described in patients of various ages, from 1 to 98 years-old [28]. In both children and adults it has been described as a predominantly male disorder, being at least three-times more frequent in males than in females [28]. It is important to note that symptoms leading to endoscopy vary considerably between pediatric and adult patients, more than any other aspect of the disease.

With regard to pediatric forms of EoE, the first descriptions of GERD-related symptoms in the literature were predominantly reported in children. Another early finding was that the treatment of GERD with antisecretive drugs or fundoplication proved ineffective in pediatric patients that presented with eosinophilic infiltration of the esophagus [29]. A nation-wide database in the USA identified heartburn and abdominal pain/dyspepsia as the main reported symptoms in 38.1 and 31% of children suffering from EoE, respectively [28]. Other symptoms commonly reported for children includes nausea, gagging, regurgitation, chest pain, sialorrhea, decreased appetite or food aversion, delayed growth, sleep difficulties and respiratory complaints (cough, stridor, sinusitis, obstruction and pneumonia) [3,30].

Only older children and adolescents usually present with dysphagia for solids and food impaction, which are also the most common indications for endoscopy in adult patients [28,31,32].

In some series [28,33], chronic or intermittent dysphagia occurs in more than 70% of adult cases; however, food impaction is the symptom that most often leads to a diagnosis (56–88% of cases) [34]. While less frequent, reflux symptoms are also commonplace [35], with more than 30% of patients suffering from swallow-independent retrosternal pain, occasionally exacerbated after consuming alcoholic beverages and usually undistinguishable

from that appearing in GERD. It has not yet been clearly established whether this may be triggered by increased esophageal acid-sensitivity in these patients [3,36]. Overall, symptoms may persist for a long time, up to 4–5 years, before a diagnosis is reached [1,33,37], so it is tempting to speculate that an early diagnosis of EoE after reflux-related symptoms, especially in adolescents and young adults could lead to a decrease in dysphagia, food impaction and strictures late in life.

Differences in symptoms according to patient age have been explained by elaborating a time sequence in which symptoms develop chronologically, depending on the patient's ability to communicate symptoms associated with esophageal dysfunction [13,38]. Thus, smaller children (who cannot report dysphagia) present with irritability and a number of eating disorders including food aversion or failure-to-thrive; later symptoms include vomiting, regurgitation and both chest and abdominal pain, mimicking GERD. In children aged 11 years and older, the condition manifests with dysphagia and food impaction. Patients with an atopic background or food-allergies have been shown to present with more severe esophageal symptoms and food impaction [39].

It should be noted that both pediatric and adult EoE patients usually develop adaptive strategies to guarantee feeding in spite of symptoms. These strategies often consist of eating at a very slow pace, taking much longer than the rest of the family to complete a meal, holding food in the mouth and prolonged chewing and usually drinking after each bite, especially in the case of more problematic foods such as dry rice and fibrous meat (chicken and veal). Parents and/or patients should thus be asked at great length for this type of behavior during anamnesis.

Although younger EoE patients sometimes exhibit retarded growth, EoE does not seem to influence the final height of patients, who usually have no clinical or histological signs of malnutrition at diagnosis or during the evolution of the disease. Although an increased risk of infection has been reported in some cases [40], EoE does not seem to have an impact on life expectancy, with no deaths from the disease being described to date. The development of adaptive strategies for coping with chronic symptoms by patients appears to be the key factor in this regard. Likewise, no association with an increased risk of developing malignant or premalignant lesions has been identified, although observational studies do not cover a long enough periods to categorically confirm this [41].

Quality of life & psychosocial repercussions

Chronic diseases usually affect patients' quality of life (QoL), forcing them to adopt adaptive strategies that usually modify their daily lives in terms of psychosocial or behavioral functioning. At the same time, adherence to dietary or pharmacological treatments can greatly influence the outcome of chronic disorders. Recently, researchers have started assessing all these aspects with regard to EoE.

Health-related QoL has recently been analyzed in pediatric EoE patients of different ages, leading to the conclusion that certain aspects not captured in standard questionnaires were often expressed by the children themselves. These included feelings of being different from their family and peers, feelings with regard to diet and medication adherence, difficulties with eating food and worry about symptoms and the illness [42]. Interestingly, patients often reported different concerns from those of their parents or parent proxies. In order to capture the full impact of EoE on children, the newly developed QoL-evaluation tools also incorporate both histological findings and reported parent-proxy outcomes [43], together with symptoms. Still, although the ability of pediatric EoE symptom scores to predict histological esophageal inflammation remains undetermined [44,45], they can be useful in distinguishing between active and inactive EoE and between EoE and GERD [45].

No data are available on the QoL of children with EoE as they progress into adulthood, even though the lack of a cure for EoE (despite the existence of effective treatments) means that pediatric patients will continue to face ongoing symptoms, evaluation and disease management strategies throughout their lives. For this reason, a healthcare program to help guide the transition from pediatric to adult-focused gastroenterology has recently been proposed [46]. The long-term clinical outcomes of pediatric EoE patients as they enter early adulthood has also recently been assessed with the aid of a case control study in which EoE patients (identified by retrospectively reviewing a pathology database) were asked to answer a battery of questionnaires more than 15 years after histological diagnosis [39]. Three out of four patients, the majority of whom did not receive adequate treatment for EoE at initial presentation, had persistent dysphagia and food impaction as adults, and expressed a significantly worse QoL than matched chronic esophagitis and healthy control subjects.

Adult EoE also has a great impact on several psychological and social domains. In a recent study relying on semistructured interviews regarding adult patients' experiences with the illness, patients expressed their concerns about the disease, their difficulty swallowing and the impact of EoE on their social interactions [47]. As a result of these findings, these same researchers developed the Adult Eosinophilic oesophagitis QoL questionnaire as a reliable, disease-specific measure of health-related QoL based on 37 items with five subscales: eating/dietary impact, social impact, emotional impact, disease anxiety and choking anxiety [48].

Finally, treatment adherence has recently been analyzed specifically in pediatric EGID, including EoE. The study found a high variability in adherence rates for EGID patients, with the adherence to medications being the most problematic aspect, reaching only up to 30%. Food allergen exposure presented with a 33% of nonadherence prevalence, while tube-feeding revealed excellent adherence rates [49]. Those pediatric patients who demonstrated clinically significant symptoms of depression were significantly more likely (odds ratio: 7.27) to demonstrate medication nonadherence than nondepressed patients [50].

Endoscopic findings

The delay in describing and understanding EoE has probably been favored by the discrete and nonspecific endoscopic findings exhibited by a large proportion of patients; indeed, a third to a quarter of all EoE patients present normal exams. Therefore, reaching a

diagnosis of EoE requires clinicians to maintain a high degree of suspicion, conduct careful esophageal examinations, and to always take biopsies, even if the mucosa appear to be normal or if other potential causes of dysphagia are identified, such as stenosis [34]. A number of endoscopic findings have been described for EoE, among them rigid esophageal rings, which occasionally reduce organ caliber and are referred to as 'trachealization', and transient esophageal rings, also known as feline furrows or 'felinization'. Nodularity and granularity of the mucosal surface and exudative mucosal lesions, either in the form of whitish papules or with varying sizes and large exudative fibrinoid lesions, are also frequently described [1,51]. These white lesions resemble Candida infection, but their histological analysis reveals them to be eosinophilic abscesses. Other findings include the loss of the mucosal vascular pattern, longitudinal folds or 'corrugated' esophagus, diffuse esophageal strictures and mucosal fragility, which when severe can present a 'crêpe paper' appearance and cause tears and lacerations with vomiting during endoscopic procedures. Because these findings have also been described in other esophageal diseases, none of them can be considered pathognomonic for EoE [52,53].

Studies specifically comparing EoE-associated endoscopic findings between children and adults are not available, although some experts have suggested that in children, signs of active acute inflammation such as edema and exudate predominate, while manifestations of chronic inflammation such as rigid rings and strictures occur more frequently in adults [3]. Endoscopic dilation procedures are also more common in the latter [54].

Histopathological features

The presence of eosinophils in the esophageal epithelium has been reported in several pathological esophageal conditions and should be assessed within the patient's clinical and pathological context. Under normal conditions, eosinophils are not commonly found in esophageal epithelia and, when present, their quantity constitutes a crucial component in the diagnosis of EoE [3]. Eosinophilic infiltration in EoE involves the entire esophagus, but often in a patchy manner, requiring multiple biopsies at different levels for an accurate diagnosis. Various studies have reported that the density of eosinophilic infiltration is similar in the distal and proximal thirds of the esophagus [51] in both pediatric [55] and adult patients [34,41,56]; a good diagnostic strategy thus involves collecting samples from both of these thirds. Comparisons between various studies are difficult since the usual assessment entails counting the number of eosinophils in more densely inflamed fields using a 400× power lens (number per high power field or hpf). This is a nonstandardized measure because the area included in an hpf varies from one microscope manufacturer to the next. Unfortunately, exact cell density quantification with the aid of stereology has only been used in very few studies on adult patients [34,57,58].

One analysis of an American pathology database showed that while there was no significant difference in the peak mucosal eosinophil count between age groups or genders, patients with dysphagia had significantly higher counts [28]. In this context, a direct correlation between endoscopic severity (whitish exudative lesions on the esophageal surface), histological severity (detachment of the most superficial epithelial strata) and the density and activation of eosinophilic inflammatory infiltration has also been reported for adult EoE patients [34]. Moreover, the number of eosinophils in the lamina propria is also higher in EoE patients [56,59], with a count of more than 5 per hpf considered to be an exclusive characteristic of EoE [60]. It is difficult to establish whether eosinophil density in esophageal mucosa varies over time since contradictory information has been reported for children and adults [18,41].

Other inflammatory cells found in the inflammatory infiltrate typical of EoE have been assessed after immunohistochemical staining. These include mast cells, which exhibit increased density in both pediatric [61–64] and adult patients [6,57,65,66], a feature that has been proposed as a differentiating element from GERD [67]. Intraepithelial $CD3^+$ T lymphocytes are also significantly increased in both children [55,68] and adults [69] with EoE. These cells may be present with comparable densities, with $CD8^+$ cells being predominant in all age groups [55,57]. The density of antigen-presenting Langerhans cells has also been demonstrated to be slightly higher in pediatric [55] and adult [70] EoE patients in comparison with GERD patients; differences after treatment with fluticasone propionate treatment were also noted.

Fibrous remodeling in EoE

Eosinophilic inflammation of the airways leads to structural changes known as remodeling. The most clinically relevant components of this phenomenon are smooth muscle hypertrophy and collagen subepithelial deposition since they can lead to the narrowing of the bronchia and impairment of respiratory function. Fibrous remodeling has been demonstrated in both pediatric [71] and adult EoE patients [56,72]; while it constitutes a reversible phenomenon in the former [59], it tends to persist in the latter [56,72]. In addition to digestive motor disturbances [73], fibrous remodeling also explains the strictures commonly associated with EoE and the obstructive symptoms found in many reported cases.

Fibrosis in EoE is directly related to eosinophilic activation, as evaluated with the aid of immunohistochemistry against major basic protein [74]. Eosinophil-released major basic protein increases gene expression of FGF-9, a cytokine implicated in the proliferative response after tissue damage [75]. Eosinophils also produce and secrete high amounts of CCL18, a type-2 chemokine implicated in fibrous remodeling of the lungs through fibroblast proliferation and collagen deposition, and the expression levels of which have been shown to be increased in EoE [56]. However, the most widely studied cytokine in promoting fibrous remodeling is TGF-β1, the expression of which was found to be upregulated in both pediatric [71] and adult [56,76] EoE patients, but which was reduced after steroid treatment [56,76].

Treatment of EoE in pediatric & adult patients

Despite the increasing importance and incidence of EoE in all age groups, the authors currently lack a commonly accepted algorithm for treating patients, mostly because the adequate management of these patients has been controversial. In addition, few randomized controlled studies have been conducted and very little is known

of the long-term effects of the different therapies to modify the natural history of the disease and the associated subepithelial fibrosis.

Dietary therapies

Dietary therapies are based on eliminating all putative EoE trigger antigens from the patient's diet. Evidence as to the effects of dietary intervention was first provided by studies involving pediatric patients. The findings demonstrated the food-allergy nature of the disease, which was clinically and endoscopically resolved after feeding the children exclusively with an amino-acid based formula lacking any antigenic capacity. Further studies focused on identifying and subsequently restricting from the diet those foods, which specifically triggered EoE after being identified through allergy testing. Thus, satisfactory results were obtained in 2005 after using SPT and APT in a pediatric EoE series; in these subjects an average of five foods had to be restricted [24] in order to maintain disease remission. However, when other researchers tried to reproduce these results in both children and adults [77], they failed, probably because APTs are not standardized tests. The next dietary approach consisted of eliminating six foods from the diet that were most likely to trigger food-allergies, regardless of individual allergy test results. In 2006, Kagawalla *et al.* excluded cows' milk protein, soy, wheat, eggs, peanuts and seafood from a cohort of 35 pediatric EoE patients, achieving a treatment efficacy of 74% after 6 weeks [78]. In a similar study, sequential food reintroduction with endoscopic and biopsy monitoring led to the identification of specific food triggers in pediatric EoE patients [79]. This strategy has also been used in adult patients with similar efficacy in achieving EoE remission in three out of four patients [80,81]. In addition, long-term maintenance of disease remission was demonstrated in all adult patients who continued to avoid specific EoE food triggers [81].

There is an increasing consensus that specific serum IgE and allergy tests are useless in identifying EoE food triggers; however, given the high prevalence of other allergic manifestations in EoE, including anaphylaxis, allergy tests are recommended for all patients [1], and allergists should be consulted, especially when food allergy, dietary treatment and other allergic disorders are being considered in these patients. Correct identification and treatment of aeroallergen-mediated allergies appears to be crucial because of the important role they play in many patients.

All patients who successfully achieve clinical and histopathological remission after food restriction should undergo a sequential food reintroduction protocol in order to both avoid nutrition deficiencies and identify food triggers. It is recommended to initially reintroduce those foods less likely to cause EoE, such as fruits and vegetables, in the case that they have been restricted. After that, the foods more likely to cause EoE should be sequentially reintroduced, carrying out endoscopies in a scheduled program or as soon as patients present esophageal symptoms. Only by this method can offending foods be identified and definitively restricted from a patient's diet. Cows' milk has been identified as the most frequent cause of EoE in both children and adults, causing disease recurrence in approximately 70% of patients 6 weeks after being reintroduced in the diet [79–81], followed by wheat and eggs. North American and Spanish studies on six-food elimination diets have differed, with the latter excluding additional foods. Thus, legumes, which were not tested as a cause of EoE in North America, were shown to trigger EoE in 20% of Spanish adult patients. This fact raises the question of whether exclusion diets should be tailored to each specific region and are based on the staple diets where the patient is being treated. Large multicenter transatlantic studies are needed to address these questions.

PPI

EoE is defined by the persistence of eosinophilic inflammation after acid suppression. PPIs, which are generally ineffective as a sole therapy in EoE patients [1], may be useful in controlling GERD-related symptoms that are frequently associated with EoE. Moreover, there have been isolated reports in both pediatric and adult patient series that have demonstrated the efficacy of PPI in reversing eosinophilic inflammation [82–84], giving rise to the term 'PPI-responsive EoE' [1] and renewing interest in studies on the anti-inflammatory properties and barrier-healing role of PPI in patients with the disease.

Systemic & topical corticosteroids

Systemic and topical corticoids are effective therapies in both children and adults, leading to symptomatic relief and the disappearance of inflammatory infiltration in a high proportion of patients. However, the disease commonly recurs after the drugs are withdrawn. A prospective controlled trial demonstrated that topical fluticasone was just as effective as prednisone in achieving histological and symptomatic EoE remission; therefore, because the latter more frequently causes serious side effects, prolonged use of systemic steroids should be avoided and only recommended for occasional use in severely ill patients and in emergency situations.

First used in pediatric patients [85], topically administered oral fluticasone propionate is now widely used in EoE and has demonstrated high efficacy in both children [55,56] and adults [57,58]. When administered in short courses it causes few side effects, the most notable being an increased risk of pharyngeal-esophageal fungal infections. Given the chronic nature of EoE, maintenance treatment with fluticasone propionate should be considered after achieving disease remission. However, there are no definitive data on its safety and possible side effects, especially in the case of children, in whom bone mineral density and adrenal suppression should be monitored.

In the past few years, viscous budesonide has emerged as an alternative treatment for both children [86] and adults [72] with EoE, having proven to be safe and effective. Ciclesonide has also recently been added to the pharmacological armory for treating EoE [87]. There is limited agreement regarding the dosages in which topical steroids should be used. For example, the recommended dose for fluticasone propionate ranges from 88 to 440 µg, two- to four-times daily or 440–800 µg twice daily. For viscous budesonide recommended dosages vary between 1 mg per day for children under 10 years of age and 2 mg per day for older

patients. In addition to its presentation in inhaler form, a liquid form of fluticasone propionate designed for nasal administration and more easily swallowed by patients is also commercially available [56,88]. The duration of induction therapy with topical corticosteroids is 12 weeks in most studies. Optimal dosages for maintenance therapy with topical corticosteroids have not yet been defined, especially in children. However, a dose of 0.25 mg of budesonide twice daily for 50 weeks was shown to maintain histological remission in 50% of adults treated.

Other drugs

The mast cell stabilizer, disodium cromoglycate, has shown no therapeutic benefit in patients with EoE [10]. High doses of the leukotriene receptor antagonist montelukast likewise demonstrated no histological benefit, although it did relieve EoE symptoms in adults. In the case of pediatric EoE patients, only three out of eight subjects showed at least partial clinical response to this treatment; unfortunately, histological efficacy was not evaluated in every patient [89]. Finally, because montelukast was not efficient in maintaining the histopathological or clinical response achieved by topical steroids in adult EoE patients, the use of leukotriene inhibitors is not recommended for treating either adult or pediatric patients [1].

Biological therapies based on monoclonal antibodies have also been assessed in EoE. Thus, while the anti-TNF-α infliximab was found to have no beneficial effects in adult EoE patient [90], the anti-IL-5 monoclonal antibody mepolizumab, which was analyzed in randomized controlled trials in both adult [91] and pediatric [92] patients, was shown to significantly reduce tissue eosinophils; nevertheless, clinical improvement was minimal. Recently, reslizumab produced similar findings in assays in pediatric EoE patients [93], in which demonstrated a significant histologic response but no significant clinical response when compared with placebo.

Finally, in a pilot study that included two adult patients with steroid-dependent EoE and one more with eosinophilic gastroenteritis also involving the esophagus, the immunosuppressant azathioprine/6 mercaptopurine was found to be effective in the remission of symptoms and eosinophilic infiltration during treatment periods of 3–8 years [94].

Endoscopic treatment

From the earliest documented cases, mechanical dilation with through-the-scope hydropneumatic balloons or Savary bougies has been employed as a treatment option for EoE, similar to the way it is used in other cases of rigid or fibrous esophageal strictures. However, the early literature described a high risk of complications after dilating EoE patients [95]. Several predictive factors for complications during dilation have recently been identified, including a long evolution of dysphagia, the existence of esophageal stenosis, and high eosinophil density [96]. Complications were also significantly associated with a younger age and repeated procedures [97], as well as with luminal narrowing in the upper and middle esophageal thirds, a luminal stricture incapable of being traversed with a standard upper endoscope, and the use of Savary bougies [98]. More recently, in two retrospective, uncontrolled studies conducted on adult EoE patients, the safety of esophageal dilation in a total of 363 dilation procedures was reassessed [97,98]. Both studies reported low complication rates in contrast with the high rates of perforation described in earlier EoE literature. Moreover, none of the perforations reported in these two studies required surgical intervention. Still, the safest recommendation is to consider endoscopic dilation only in cases in which symptoms and/or a reduced esophageal caliber persists despite topical steroid or dietary therapies. The procedure should preferably be done when the active inflammatory infiltrate has been eliminated or significantly reduced [33], and it should be carried out gently under sedation to avoid provoking Boerhaave syndrome if the technique is tolerated badly [98]. A final recommendation is to use medium-sized hydropneumatic balloons with smaller calibers than those used in other forms of strictures.

Endoscopic dilation is mostly used in adult EoE patients and has been reported only as exceptional therapy in children [99]. It should be noted that because endoscopic dilation is a mechanical procedure with no effect on the underlying inflammatory process [100], its efficacy is probably limited over time. From the studies published to date, the duration of its effect cannot be properly estimated, although it usually ranges from 3 to 12 months. Still, it is common for patients to undergo repeated dilations, in some cases up to nine times, to control their symptoms [97,101,102]. A number of patients undergoing endoscopic dilation also receive concomitant drug therapy, which may mask the clinical effects of endoscopic therapy alone [97].

Expert commentary: unresolved aspects & proposed new research methods

EoE presents both differences and many similarities when affecting children and adults. The discovery and characterization of this disease have progressed in parallel with studies on various series of children and adults with the disease. However, EoE's natural history has yet to be unequivocally defined, and until recently, it was not clear whether adult and pediatric EoE were manifestations of a single entity or two distinct diseases. This review shows that, 20 years after its initial description, the consensus is that pediatric and adult EoE constitute a single disease. Most research supports a common EoE pathogenesis for adult and pediatric patients; in all age groups EoE has the same demographic predisposition to affect caucasian male patients who frequently have an associated atopic background. Moreover, patients of different ages share common histopathological findings, with the same diagnostic criteria being applied in all cases.

The most relevant differences between children and adults come in part from evolutionary changes in disease consequences and the ability of the patients to express symptoms. In this sense, the differences observed in the endoscopic findings of children and adults may be related to the longer evolution of the disease in the latter, which often entails greater fibrous remodeling of the organ and leads to more severe histological changes and increased frequency of stenosis. Esophageal dilations via endoscopy are thus reported more often in adult patients. In this sense, it should be

noted that the later a patient suffering from EoE is diagnosed, the more likely fibrosis may occur.

More similarities than differences have been reported regarding patient response to the remaining therapy modalities. Topical steroids, for example, have proven to be highly effective in both children and adults. The slightly lower efficacy observed in children treated with swallowed inhaled steroids is probably due to difficulties in coordinating the 'push and swallow' sequence; this drawback has largely been overcome through the use of viscous liquid formulas. It is also interesting to note that the various available dietary interventions for EoE produce similarly effective results in children and adults, ranging from 88 to 70% [10,24,29,78,80,81]. It is thus clear that in approximately three out of four EoE patients, the disease is triggered and maintained exclusively by food, with the remaining quarter of cases attributable to air-borne allergens, either alone or together with food allergies.

Despite the fact that our knowledge about the epidemiology of EoE comes from the past few years, very consistent and concordant results in this regard have been reported from different continents. Although the incidence of the disease is relevantly higher among children, adult-onset EoE has now been definitively recognized, with a high proportion of adults reporting symptoms for several years before diagnosis. Moreover, various series of pediatric patients have evolved in recent years and are now being attended in adult clinics. The impact of EoE on QoL and other related aspects has thus captured the interest of clinicians in recent years, leading to the increasing recognition of the psychosocial consequences of the disease. As a result, satisfactory control of symptoms or inflammation is no longer the only aspect of the disease to be considered. This calls for a global and comprehensive management of EoE patients over the next few years.

Five-year view

The history of EoE has evolved rapidly, from being considered a rare disease just over 10 years ago to being recognized as a pathology as common as Crohn's disease. In fact, EoE is now usually taken into account in the differential diagnosis of dysphagia. However, significant advances are needed before we can achieve prolonged remission of the disease with a minimal use of drugs. In addition, despite wide recognition of the disease, EoE patients still usually suffer an inacceptable diagnostic delay. The intermittent presentation of symptoms, which may be misinterpreted as manifestations of GERD, and the unwillingness of patients, especially children, to undergo endoscopic examinations partly explain this diagnostic delay. A high level of suspicion and awareness of EoE on the part of families and physicians is thus essential for ensuring adequate referral of patients to the gastroenterologist or allergist. The latter, together with the pathologist, are crucial in the diagnosis and management of the disease.

The low sensitivity of allergy tests in predicting the causal food agent in the majority of patients who later undergo food reintroduction treatment [78,80] leads us to conclude that IgE-mediated allergies may not be the main pathophysiological mechanism in EoE; instead, a delayed hypersensitivity reaction against common, regularly consumed foods appears to be more likely [73]. Studies based on challenge through sequential reintroduction of single foods with repeated endoscopies and biopsies to identify the offending foods are impractical and have important drawbacks; therefore, the development of non- or minimally invasive markers to replace the need for multiple endoscopies is a top priority.

Drugs specifically developed and approved for use in EoE patients in whom diet therapy cannot be instituted should also be developed within the next few years. This is especially important because, even though the efficacy and safety of different synthetic steroids in EoE has been well documented, all patients are currently being treated outside of standard indications.

In summary, early and accurate diagnosis, effective treatment and long-lasting remission of EoE are crucial goals in the next few years in order to effectively modify the natural history of both pediatric and adult EoE.

Key issues

- Eosinophilic esophagitis (EoE) is a prevalent cause of chronic esophageal symptoms in both children and adults, representing the second cause of chronic esophagitis and the major cause of food impaction in young male patients.
- The incidence of EoE has increased in the past few years; it predominantly affects young caucasian male patients, but can affect patients of any race or age.
- Differences in symptoms according to patient age have been explained by invoking a time sequence in which symptoms may develop chronologically according to the patient's ability to communicate esophageal dysfunction.
- Although no specific studies are available, experts suggest that signs of active acute inflammation, such as edema and exudates, predominate in children, while manifestations of chronic inflammation, such as rigid rings and strictures, occur more frequently in adults. Endoscopic therapeutic procedures are more common in adults.
- Esophageal inflammatory infiltrate is similar in both pediatric and adult EoE patients. The phenomenon of fibrous remodeling has been reported in both groups; this is reversible in children, but tends to persist in adults.
- There are no differences regarding patient response to currently used therapy modalities between pediatric and adult EoE patients.

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Medscape EDUCATION

Adult versus pediatric eosinophilic esophagitis: important differences and similarities for the clinician to understand

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Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. Based on the review by Drs. Lucendo and Sánchez-Cazalilla, which of the following statements about the epidemiology of eosinophilic esophagitis (EoE) in adults and children is most likely correct?
   - ☐ **A** EoE predominantly affects black women
   - ☐ **B** EoE only affects young white males
   - ☐ **C** In older women, EoE is the leading cause of food impaction and the second leading cause of chronic esophagitis
   - ☐ **D** EoE is a common, allergy-associated cause of chronic esophageal symptoms with increasing incidence in the past few years

2. Your patient is a 5-year-old white male thought to have EoE. Based on the review by Drs. Lucendo and Sánchez-Cazalilla, which of the following statements about the clinical features of EoE in children compared with in adults is most likely correct?
   - ☐ **A** He is more likely to have manifestations of chronic inflammation than of active acute inflammation
   - ☐ **B** Children are more likely to have edema and exudates, whereas adults are more likely to have rigid rings and strictures
   - ☐ **C** Children are more likely than adults to undergo endoscopic therapeutic procedures
   - ☐ **D** Response to recommended therapeutic modalities for this patient is likely to differ considerably from therapeutic response in adults

3. Based on the review by Drs. Lucendo and Sánchez-Cazalilla, which of the following statements about pathophysiology of EoE in adults and children is most likely correct?
   - ☐ **A** Esophageal inflammatory infiltrate is similar in both pediatric and adult EoE patients
   - ☐ **B** Fibrous remodeling has not been reported in children with EoE
   - ☐ **C** Fibrous remodeling is almost always reversible in adults
   - ☐ **D** Analysis of an American pathology database showed significant differences in the peak mucosal eosinophil count between adults and children with EoE