Eosinophilic Esophagitis: Example of an Emerging Allergic Manifestation?

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Abstract
Over the past decade, there has been a significant increase in the number of children and adults with eosinophilic esophagitis (EE). This recently recognized form of chronic pan-esophagitis is characterized by dense eosinophilic infiltration of the esophageal mucosa. EE is closely associated with male gender and allergic disorders, such as food allergy, eczema and asthma. The diagnosis relies on demonstration of increased numbers of eosinophils (≥15 per high power field) in esophageal biopsies. There is clinical overlap between EE and gastroesophageal reflux disease (GERD). Patients with EE typically present with reflux symptoms but are unresponsive to proton pump inhibitor therapy. While dysphagia, regurgitation and retrosternal pain are the clinical hallmarks of EE, many patients are asymptomatic. Treatment aims to prevent long-term complications, such as acute food bolus impaction or esophageal strictures. In childhood, treatment relies on elemental or elimination diets. Skin prick and atopy patch testing have proved useful in guiding specific dietary elimination. In adolescents and adults, broad-based elimination diets are commonly not tolerated or may be ineffective. These patients may respond to swallowed corticosteroid aerosols or other immune-modulating drugs. Further prospective clinical trials are needed to outline the most effective long-term treatment of EE.

Introduction
In 1995, Kelly et al. [1] first described eosinophilic esophagitis (EE) as a new diagnostic entity, separate from gastroesophageal reflux disease (GERD). In a series of 10 children with presumed refractory reflux esophagitis, resolution or significant improvement of the condition was achieved after treatment with amino acid-based formula. The unifying diagnostic feature in
these patients was significant esophageal mucosal eosinophilia. The clinical response to hypoallergenic formula, in conjunction with a history of eczema and asthma in many of the patients, raised the question whether EE was an allergic disorder. Subsequent sophisticated laboratory studies have confirmed that the condition is mediated by T helper-2 lymphocytes and closely associated with IgE sensitization to food or inhalant allergens [2].

Over the past decade, several epidemiological studies have demonstrated a significant increase in the number of children and adults with EE [3–6]. This trend appears to parallel the general increase in the prevalence of other pediatric allergic disorders, in particular eczema and food allergy. It is, however, unclear to what extent increased recognition and improved access to endoscopies have contributed to the apparent prevalence increase [7]. A recent population-based study from Sweden has shown that EE is a relatively common condition which affects about 1% of adults, including a large proportion of asymptomatic individuals [6].

Despite recent advances in understanding EE, significant clinical dilemmas and uncertainties remain, particularly regarding the natural history of untreated EE and its most effective long-term treatment [8]. This review aims to provide an outline of the pathophysiology, epidemiology, clinical presentation, prognosis and treatment of EE in children and adults. Areas in need of further investigation will be highlighted.

**Definition and Diagnostic Criteria**

The diagnosis of EE is based on clinicopathological criteria and always requires esophageal biopsies. These are generally obtained by fiberoptic esophagastroduodenoscopy. In the past, there has been considerable diversity between clinical centers in the pathology method used to quantify eosinophils in esophageal biopsies. In an attempt to formalize the diagnostic criteria for EE, a consensus panel has suggested that the diagnosis of EE requires the presence of at least 15 eosinophils per high power field at 400× magnification [2]. Histological changes should be present in the entire esophagus, an important difference to distal acid-peptic reflux esophagitis. Basal cell layer hyperplasia is usually present in EE [2]. Furthermore, eosinophilia is typically limited to the esophagus, and mucosal eosinophils are not increased in other parts of the gastrointestinal tract. Apart from these histological criteria, the diagnosis requires the presence of symptoms that fail to respond to proton pump inhibitor treatment (generally for 4 weeks) and/or normal esophageal 24-hour pH monitoring [2].

**Pathogenesis**

Our understanding of the mechanisms involved in the pathobiology of EE has evolved rapidly, based on sophisticated animal experiments [9, 10] as
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well as human gene array analysis [9]. Similar to eczema and asthma, EE has been shown to be a T helper-2 lymphocyte-driven disorder, with upregulation of interleukins (IL) 4, 5 and 13 [2, 9, 10]. The number of mucosal mast cells is increased, but their exact role is poorly understood [2]. The normal esophageal mucosa is devoid of eosinophils. The migration of eosinophils to the esophagus is under the control of three critical effector molecules: IL-5, IL-13 and eotaxin-3. Eotaxins are important chemoattractants for eosinophils [2]. Human gene array studies have demonstrated that the gene for eotaxin-3 is markedly upregulated in EE [11]. It has been speculated that susceptibility to EE may, in part, be explained by polymorphisms in the eotaxin-3 gene [11]. Familial clusters of EE have been described, but the exact susceptibility loci for familial and sporadic EE require further clarification [12].

Basal layer thickening is a key histological feature in patients with EE [2]. Local IL-5-induced eosinophilia has been shown to play a central role in this process [13]. Several eosinophil mediators, e.g. vasoactive peptides, platelet-activating factor or eosinophil-derived neurotoxin may disrupt the integrity of submucosal neuronal networks and promote lower esophageal sphincter dysfunction and esophageal dysmotility. Thickening of the esophageal mucosa in EE may also contribute to esophageal peristaltic dysfunction [14]. Subepithelial remodeling and deposition of extracellular matrix proteins, such as collagen, have also been demonstrated in patients with EE [15]. This process is of concern as it may cause progressive scarring, strictures and potentially result in permanent narrowing of the esophagus.

In experimental models, intratracheal egg challenge in ovalbumin-sensitized mice has been shown to elicit esophageal eosinophilia [9], suggesting that EE is a food antigen-driven process. This observation aligns with a high prevalence of IgE- and non-IgE-mediated food allergy in pediatric patients with EE [2]. Inhalant allergens, e.g. grass pollen, also appear to be of importance [16], but play a greater etiological role in adults than in children. Sensitization to grass and tree pollen may explain some seasonal variability in symptom severity, mucosal eosinophilia and incidence of EE [17]. A significant proportion of patients have evidence of neither food nor inhalant sensitization, and EE in this subset of patients does not appear to be associated with atopic disorders. Animal experiments have shown that the intratracheal administration of IL-13, in the absence of co-stimulation with food or inhalants, is able to elicit EE in mice [10]. The pathophysiology of non-atopic EE requires further clarification.

There is debate whether GERD plays an etiological role in the pathophysiology of EE [7, 18]. It has been speculated that acid-peptic mucosal injury may impair the mucosal barrier function and allow food allergens or other noxious substances to enter into subepithelial layers [18]. This, in turn, could promote sensitization and food protein-induced eosinophilic inflammation. Case reports have suggested that acid suppression alone may reduce distal
esophageal mucosal eosinophilia in some patients [19]. However, as a rule, the symptoms of EE are refractory to medical acid suppression.

**Epidemiology**

Until recently, no population-based prevalence data for EE in children and adults were available. The condition predominantly affects males. Meta-analysis of the gender distribution in several published studies found that 66% of children (mean age 8.6 years) and 76% of adults (mean age 38 years) with EE are male [2]. Familial clusters of individuals with EE have been described, spanning several generations [12]. Sporadic cases of EE do not appear to align with ethnicity or specific geographic regions.

Early case reports suggested that EE was a relatively rare finding in children and adults. It is, however, likely that EE occurred prior to its first recognition [1] under different diagnostic labels, usually GERD. Prevalence studies have mainly been based on data from tertiary centers. An American study from 2000–2003 found a slowly rising prevalence of 0.9–1.3/10,000 children and adolescents [3]. A recent West Australian study calculated a similar prevalence of 0.89/10,000 children in 2004, which represents a marked increase from 0.05/10,000 children 10 years earlier [2]. The magnitude of this increase seems to exceed the effects explained by increased recognition or improved access to gastroscopy [3, 4].

Two recent studies have attempted to generate population-based prevalence estimates for EE. The Kalixanda study [6], a large population-based study in Swedish adults (mean age 54 years), found EE in approximately 1% of study subjects. In that random sample of 1,000 adults, 11 patients had evidence of definite or probable EE in distal esophageal biopsies. Of these, approximately half were asymptomatic. 75% of patients with definite and 43% of probable EE were male. A recent American study retrospectively evaluated a large number of upper gastrointestinal biopsies through a national pathology provider [5]. Of 74,162 patients, 363 patients (0.48%) had a histological diagnosis of EE. Again, there was a strong male preponderance (OR 3.0, 95% Cl 2.4–3.8). The prevalence of 0.48–1.3% found in these studies was considerably higher than previously anticipated, suggesting that asymptomatic disease in adults is common. The clinical significance of asymptomatic EE remains uncertain.

**Clinical Presentation**

The presentation of EE in infants, children and adults varies considerably (table 1). In general, patients present with symptoms suggestive of GERD but fail to respond to treatment with acid-suppressant medications (i.e. proton
pump inhibitors) or fundoplication. A significant proportion of patients may be completely asymptomatic, and the diagnosis is often made as an incidental finding, e.g. endoscopy for suspected celiac disease [20]. Infants may develop significant feeding aversion, distressed behavior or failure to thrive. Dysphagia for solid foods and esophageal food bolus impaction are the most characteristic symptoms associated with EE, particularly in older children and young adults [2, 21, 22]. While in childhood the development of dysphagia is highly suggestive of EE, in adults the differential diagnosis of dysphagia is more varied (table 1). A recent study assessed the prevalence of EE in adults (aged 18–60 years) with dysphagia [22]. In that study, 33/222 (15%) of adult dysphagia patients had histological evidence of EE in mid-esophageal biopsies.

Table 1. Clinical features, complications, differential diagnosis and treatment of children and adults with eosinophilic esophagitis

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Infants and children</th>
<th>Adolescents and adults</th>
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<tr>
<td></td>
<td>frequent regurgitation</td>
<td>frequent regurgitation</td>
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<tr>
<td>Feeding difficulties/refusal</td>
<td></td>
<td>dysphagia for solids</td>
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<tr>
<td>Dysphagia for solids</td>
<td></td>
<td>heartburn/retrosternal pain</td>
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<td>Chest and abdominal pain</td>
<td></td>
<td></td>
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<tr>
<td>Complications</td>
<td>failure to thrive</td>
<td>food bolus impaction</td>
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<tr>
<td></td>
<td>food bolus impaction</td>
<td>strictures</td>
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<td></td>
<td>Candida esophagitis</td>
<td>diffuse esophageal narrowing</td>
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<td></td>
<td></td>
<td>esophageal perforation</td>
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<tr>
<td></td>
<td></td>
<td>Candida esophagitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Herpes simplex esophagitis</td>
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<tr>
<td>Differential diagnosis</td>
<td>gastroesophageal reflux disease</td>
<td>gastroesophageal reflux disease</td>
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<tr>
<td></td>
<td>infantile colic</td>
<td>barrett’s esophagus</td>
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<td></td>
<td>ingested foreign body</td>
<td>adenocarcinoma</td>
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<td></td>
<td>eosinophilic gastroenteritis</td>
<td>scleroderma</td>
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<td></td>
<td>hypereosinophilic syndromes</td>
<td>eosinophilic gastroenteritis</td>
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<tr>
<td></td>
<td></td>
<td>hypereosinophilic syndromes</td>
</tr>
<tr>
<td>Medical treatment</td>
<td>elemental diet (amino acid-based formula)</td>
<td>swallowed corticosteroid aerosols (fluticasone, budesonide)</td>
</tr>
<tr>
<td></td>
<td>multiple food elimination diet</td>
<td>systemic corticosteroids</td>
</tr>
<tr>
<td></td>
<td>swallowed corticosteroid aerosols (fluticasone, budesonide)</td>
<td>proton pump inhibitors</td>
</tr>
<tr>
<td></td>
<td>systemic corticosteroids</td>
<td>role of elimination diets unclear</td>
</tr>
<tr>
<td></td>
<td>proton pump inhibitors</td>
<td>proton pump inhibitors</td>
</tr>
<tr>
<td></td>
<td>need for treatment of asymptomatic cases unclear</td>
<td>need for treatment of asymptomatic cases unclear</td>
</tr>
</tbody>
</table>
Complications

Subepithelial remodeling as a result of long-standing uncontrolled EE may lead to inflammatory strictures and diffuse narrowing of the esophagus. It is unclear if all patients with EE will progress to these complications [23]. Eosinophilic inflammation is associated with an increased risk of mucosal shearing. Esophageal perforation or rupture is the most severe complication of EE [24]. Perforation has been described following endoscopic food bolus removal or esophageal balloon dilatation. The perforation risk was highest after rigid esophagoscopy [25]. Rigid endoscopy should therefore be avoided in patients with known or suspected EE. Other complications of EE include *Herpes simplex* [26] and *Candida albicans* esophagitis [27], particularly after treatment with swallowed fluticasone aerosols. At this stage there is no evidence for an increased risk of Barrett’s metaplasia or esophageal adenocarcinoma in patients with EE [2]. However, long-term data are not available.

Investigations

The diagnosis of EE can only be confirmed after upper gastrointestinal endoscopy [2]. Endoscopic examination allows direct visualization of the mucosal appearance of the esophagus, as well as collection of biopsy specimens from different esophageal levels. White mucosal plaques in patients with EE may be mistaken for esophageal candidiasis. The presence of longitudinal furrowing, mucosal thickening, white plaques or rings (trachealization) of the esophagus are characteristic mucosal findings associated with EE. However, an unremarkable macroscopic appearance does not rule out significant tissue eosinophilia, and esophageal biopsies should always be obtained.

In view of the high prevalence of food and inhalant sensitization in patients with EE, skin prick testing (SPT) and atopy patch testing (APT) should be performed to assess underlying allergies [2]. If used in combination, SPT and APT have a high sensitivity and specificity for food allergy [28]. The interpretation of SPT and APT results with regard to implementation of specific elimination diets requires specialist expertise. Measurement of food-specific serum IgE levels (by Immuno-CAP) is not considered useful, as no positive predictive diagnostic values have been defined in EE [2]. In approximately one third of EE patients, SPT and APT are negative [2]. This may indicate non-atopic EE. However, some of these patients may be diet-responsive, despite negative skin tests [28].

Differential Diagnosis

The key to the differential diagnosis between EE and GORD lies in the histological features. Winter et al. [29] proposed in the early 1980s that the presence
of any eosinophils in the esophagus was a specific marker for reflux esophagitis. However, the finding of EE a decade later challenged this view [1, 2]. While low numbers of mucosal eosinophils in the distal esophagus are suggestive of acid-peptic reflux esophagitis, greater numbers (≥15 eosinophils per high power field) indicate a diagnosis of EE, particularly if present in mid or upper esophageal biopsies [2]. The presence of mucosal neutrophils or epithelial erosion indicates likely acid-peptic mucosal injury and favors a diagnosis of GERD [7].

Cheung et al. [21] found a bimodal distribution for esophageal eosinophil counts in children presenting with dysphagia. In that study, eosinophil counts were either clustered around 0–5 or above 20 eosinophils per high power field, suggesting that EE and GERD in children with dysphagia are distinct clinical entities. In clinical practice, however, there appears to be significant clinical overlap, and both conditions may coexist [7, 18]. Symptoms are often similar, and without endoscopic and histological examination both conditions may be indistinguishable (table 2). Both EE and GERD may present with dysphagia and strictures. However, GERD-induced peptic strictures are usually located in the distal esophagus, while strictures in EE may occur at any level of the esophagus.

**Natural History and Prognosis**

The natural history of untreated EE is largely unknown. As a rule, EE is a chronic relapsing disease. There are only a few documented cases of spontaneous clinical remission in children, most likely reflecting the resolution of underlying food allergies. Apparent resolution or clinical improvement may also be suggested by seasonal fluctuation in the severity of tissue eosinophilia [17]. It is not known if all patients will progress to adverse outcomes if left untreated. While infants present predominantly with reflux-like symptoms and feeding difficulties, dysphagia and swallowing difficulties appear to develop after a latency of 5–10 years [4]. This may suggest a gradual disease progression over years to decades. A longitudinal 10-year study in 30 adults with EE with dysphagia showed that 67–86% of patients had endoscopic or radiological evidence of esophageal remodeling [23]. However, there may be considerable variation in the duration of the asymptomatic interval between the onset of eosinophilic inflammation and the first manifestation of symptoms.

**Treatment**

The treatment of EE mainly relies on use of elemental or elimination diets, swallowed corticosteroid aerosols (fluticasone, budesonide), or systemic corticosteroids (prednisolone) [30]. In addition, endoscopic food disimpaction, dilatation of strictures and medical acid suppression are often required [25, 31]. Most therapeutic trials so far have been conducted in children, and
Table 2. Comparison of the clinical features of patients with gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EE)

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>GERD</th>
<th>EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age groups</td>
<td>Infants, children and adults</td>
<td>Infants, children and adults (strong male preponderance)</td>
</tr>
<tr>
<td>Associated atopic disorders</td>
<td>Associated with asthma, but not eczema or allergic rhinoconjunctivitis</td>
<td>Commonly associated with asthma, eczema and allergic rhinoconjunctivitis</td>
</tr>
<tr>
<td>Esophageal pH monitoring</td>
<td>Abnormal</td>
<td>Normal or borderline</td>
</tr>
<tr>
<td>Distribution of inflammatory changes</td>
<td>Lower esophagus</td>
<td>Pan-esophagitis</td>
</tr>
<tr>
<td>Eosinophil count (at 400x magnification)</td>
<td>0–15 per high power field</td>
<td>≥15 per high power field</td>
</tr>
<tr>
<td>Mucosal infiltrate</td>
<td>Neutrophils, some eosinophils</td>
<td>Eosinophils, mast cells, T-helper 2 lymphocytes</td>
</tr>
<tr>
<td>Epithelial erosion or ulceration</td>
<td>Common</td>
<td>Absent</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Uncommon, unless due to strictures</td>
<td>Common, particularly in adolescents and adults. Food bolus impaction</td>
</tr>
<tr>
<td>Seasonal variation in symptom severity (grass or tree pollen sensitization)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Complications</td>
<td>Hematemesis, peptic strictures, Barrett’s esophagus, adenocarcinoma</td>
<td>Persistent narrowing of esophageal lumen, strictures, perforation or rupture</td>
</tr>
<tr>
<td>Esophageal strictures</td>
<td>Yes (usually lower esophagus)</td>
<td>Yes (anywhere)</td>
</tr>
<tr>
<td>Responsive to elimination diets</td>
<td>No (except in subset of infants with food allergy)</td>
<td>Yes (better response in children compared to adults)</td>
</tr>
<tr>
<td>Responsive to acid-suppressive medications (proton pump inhibitors)</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Responsive to corticosteroids</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Natural history and prognosis</td>
<td>Infantile GORD commonly resolves around 12–18 months of age. Older children and adults follow similar course with persistent symptoms</td>
<td>May resolve in childhood if tolerance develops to offending food antigens Older children and adults usually follow a chronic, relapsing course</td>
</tr>
</tbody>
</table>
only a few randomized studies are currently available in adults. As the natural history of untreated EE is not known, there is ongoing debate as to the proportion of patients with EE who will develop clinical disease or complications. While some investigators have advocated complete remission of tissue eosinophilia as the treatment goal, others have suggested aiming for control of symptoms to reduce the need for repeated endoscopies and risk of cumulative steroid toxicity.

In childhood, most patients improve on an elemental [1, 32, 33] or multiple food elimination diet [34, 35]. Response rates to elemental formula are close to 100%, whereas specific elimination diets have resulted in clinical and histological improvement in 74–100% of children [2]. A dietician should be involved in monitoring the nutritional adequacy of elimination diets in children in order to prevent growth failure or micronutrient deficiencies. No data on the effectiveness of elimination diets in adults are currently available. In theory, due to the lower prevalence of food allergy in adults, elimination diets are less likely to be effective.

While systemic corticosteroids are effective in treating EE, their use is limited by cumulative steroid toxicity (e.g. growth failure in children or loss of bone mass). Swallowed fluticasone aerosols are well tolerated and provide effective short-term control of EE in children [36, 37]. However, the long-term efficacy is at this stage unclear. The clinical response to topical fluticasone aerosols was found to be lower in patients with allergic disease, compared to non-atopic EE [36]. The suggested daily dose of fluticasone aerosol is 440–880 µg in children and 880–1,760 µg in adolescents and adults for 6–8 weeks [30]. As an alternative, a budesonide gel has been successfully used in children [38]. The administration of the steroid in gel is thought to improve topical penetration into the esophageal mucosa.

Several other medications have been used in the treatment of EE. Montelukast, a leukotriene inhibitor used in asthma prevention, has been studied in one small adult trial [39]. The medication, when administered at a high dose of 100 mg daily, was effective in 7 of 8 patients but caused significant side effects. Montelukast is therefore not recommended in the treatment of EE [2]. Similarly, cromolyn sodium (dose 100 mg, 4 times daily for 1 month) was found to be ineffective in a small trial of children with EE [2, 33]. Mepolizumab, a monoclonal antibody against the T helper-2 cytokine IL-5, has been shown to transiently reduce peripheral blood eosinophil counts, as well as tissue eosinophilia [40]. However, data on the safety and long-term efficacy of mepolizumab in EE are not yet available. The significant costs may limit its use in EE.

**Conclusion and Suggestions for Future Research**

Recent population-based studies have demonstrated that EE is a common condition that may affect over 1% of adults. The morbidity associated with
EE is significant and at times severe. The natural history of EE deserves further study. It is currently unclear what proportion of patients with untreated disease will develop long-term complications, and asymptomatic patients may not always require treatment. Further randomized head-to-head clinical trials are required to define the most effective, and least invasive, long-term treatment of EE in children and adults. Future studies need to take into account the possible seasonal variation in the severity of EE. Finally, as the monitoring of EE currently relies on repeated endoscopic examination, noninvasive markers of the disease activity are needed.

References

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Discussion

Dr. Wiedermann: You said that one of the treatment possibilities would be to suppress acid. There is a group in Vienna that has shown that antacid treatment could promote the development of food allergy. Is there any evidence that antacid treatment promotes food allergy in these patients who also have an atopic background?

Dr. Heine: That’s a very good question. Many patients with eosinophilic esophagitis would have been on acid-suppressant medication long-term, and it’s really not clear whether eosinophilic esophagitis has developed as a result of acid suppression. Spechler et al. [1], for example, suggested that esophageal mucosal acid injury may facilitate sensitization to food antigens. The immune reaction to foods in eosinophilic esophagitis has features of both IgE-mediated and non-IgE-mediated food allergy. For example, you can have a negative skin prick test and a negative atopy patch test, but still react to that food. Alternatively, you may have a positive patch test and a positive skin prick test, but tolerate the food without problems. The mechanisms are unfortunately still poorly understood.

Dr. Prescott: You clearly showed that these patients also have inhalant disease, asthma, rhinitis, and many of them may be undergoing a sublingual immunotherapy, which I am quite interested in because obviously they follow the allergens. Is there any evidence that eosinophilic esophagitis improves or is exacerbated during this process? Regarding gender differences, do you have any idea about the mechanism of this, and I assume it is prepubertal as well?

Dr. Heine: We see two distinctive sensitization patterns in patients with eosinophilic esophagitis. The younger patients predominantly have food sensitization, but little inhalant sensitization. They are better candidates for dietary interventions. About 10–20% of adolescents are sensitized to grasses which may be of importance in the pathogenesis. I remember the case of a boy who developed acute esophageal obstruction after handling hay, probably due to a large load of swallowed or inhaled grass pollen. Anecdotally, desensitization to grasses for allergic rhinitis may also improve eosinophilic esophagitis, but at present no formal studies are available. The exact mechanisms explaining the male preponderance in eosinophilic esophagitis are unknown, but several studies on genetic factors are underway.

Dr. Belli: Regarding therapy, you talked about the elemental diet, but what do you think is important? Sugar and lipids are not involved; is it only extensive hydrolysate?

Dr. Heine: The diet is amino acid-based, not extensively hydrolyzed.

Dr. Belli: Yes, but the question is can we use normal glucides and lipids with the hydrolysate in this condition because I think the taste is better? There is a solution with saccharose, normal lipids and extensive hydrolysate. Do you think it is also a good attempt at therapy because the taste is better for the patients?

Dr. Heine: You raise an important point regarding the taste of elemental diets, as older children and adolescents often refuse the formula and would require tube feeding, which is usually too invasive.

Dr. Haschke: Is there enough evidence that elemental formulas are superior to extensively hydrolyzed formulas? Are there randomized controlled studies in the literature? Elemental formulas contain lipids such as MCT which are not necessary for treatment of cow’s milk allergy. In addition they contain carbohydrates which are non-bifidogenic. On the other hand, there are extensively hydrolyzed formulas on the market which contain protein-free lactose. Ingestion of these formulas would stimulate the growth of lactobacilli and bifidobacteria. Can you comment on this?

Dr. Heine: To my knowledge there are no studies comparing elemental and hydrolyzed formulas in patients with eosinophilic esophagitis.
Dr. Haschke: But there is a standardized testing procedure which indicates whether an extensively hydrolyzed formula can be used for the treatment of cow’s milk allergy.

Dr. Heine: I agree, but this has not been studied. You are right in saying that elemental formulas are not bifidogenic, and an adverse effect of these formulas on tolerance development and maturation of early immune functions appears possible.

Dr. Vaidya: My question is with regard to the age at presentation. The median age range was 7–8 years and there are some babies of 2 and 3 months of age. So how early can you suspect this, especially in infancy? In our country we are starting to look for this condition.

Dr. Heine: The majority of patients are older children and young adults. We have also seen eosinophilic esophagitis in infants with multiple food intolerance who presented with irritability, profuse vomiting, and failure to thrive. Eosinophilic esophagitis in infants may have a better prognosis and be outgrown, whereas the bulk of patients will have ongoing, relapsing disease.

Dr. Sartor: Why the esophagus? If this is a food allergy, why not a diffuse gastro-proximal enteritis as well as esophagus? For celiac disease, obviously a dietary component, you don’t have eosinophilic esophagitis; perhaps there is no tissue transglutaminase there. Is it exclusively in the esophagus; is this a manifestation of a more diffused eosinophilic process in the gut, and if it is localized, speculate as to why?

Dr. Heine: Eosinophilic esophagitis can occur as part of hyper-eosinophilic syndromes, such as eosinophilic gastroenteritis. But the condition is typically limited to the esophagus. This may be due to the common foregut origin of the lungs and esophagus, and immune responses in the esophagus may be initiated in the lung, or vice versa.

Dr. Sartor: Is asthma common?

Dr. Heine: It is.

Dr. Sartor: Is the issue the same as in celiac disease and IBD? If there is a genetic predisposition and a common stimulant, bacteria in your case and food in celiac disease, why do some people not develop manifestations until late in life?

Dr. Heine: This is unclear. People have looked at the link between celiac disease and eosinophilic esophagitis and proposed an association, but it’s probably a random association because both conditions are reasonably common. It is not understood why patients present at a certain age. The pathophysiology is still unclear, and we don’t know whether gut microbiota play a role.

Dr. Fox: It has been my experience that children in the UK with eosinophilic esophagitis got a bad deal with late diagnosis and often suboptimal management that goes on for years. One of the reasons for this is because it is a condition that straddles the specialties of allergology and gastroenterology. The allergists can’t do the necessary endoscopies whilst the gastroenterologists are not necessarily well equipped to perform atopy patch tests and skin prick tests. In your experience outside centers where both allergists and gastroenterologists work together, do you find this same problem or have you found that models of care have enabled children to get better management?

Dr. Heine: We have two specialists with training in both gastroenterology and allergy who manage many patients with eosinophilic gut disorders. In other centers the collaboration between specialties may not be as close. It is essential to develop a team of gastroenterologists, allergists and dieticians to successfully manage gastrointestinal food allergy and related conditions, such as eosinophilic esophagitis.

Dr. Du Toit: Parents are often reluctant to let their children undergo a biopsy, particularly re-biopsy, if the diet has worked. Are there any other surrogate markers? Surely these eosinophils need to be replenished from the marrow. Circulating
Heine

eosinophils or eosinophil cationic protein or other markers for eosinophilia, or anything else we can use?

**Dr. Heine:** I wish we had a good marker because gastroscopic examination after every dietary trial is quite invasive. We often need a series of up to 6 biopsies over 2 years to evaluate whether foods are tolerated or not. Unfortunately, there are no good surrogate markers of disease activity. Serum eotaxin-3 does not appear to be sensitive enough because it may also be elevated in patients with asthma.

**Dr. Berdel:** Do you have step-down and step-up therapy?

**Dr. Heine:** We have a step-down regimen, starting with a broad-based elimination diet, and reintroducing foods as tolerated. The difficult question is how many foods to reintroduce per challenge cycle and gastroscopy. If you want a clear-cut answer then you might only want to challenge one food at the time. Several low-risk foods could perhaps be challenged together.

**Dr. Berdel:** But how do you proceed with steroids?

**Dr. Heine:** The use of steroids is similar to asthma treatment. We aim to induce remission with a higher dose, and then reduce the dose to a maintenance level. Most studies have not clarified whether treatment should be given for a 6-week course or be ongoing. In children, there is of course concern regarding the long-term toxicity of steroids. Steroid-sparing drugs, such as montelukast or azathioprine, may improve disease control, but require further study.

**Dr. Stanley:** How certain are we about this lack of association with malignancy? This is a relatively new disease, and people have actually gone back and looked at biopsies taken 50 years ago from adults with malignancy.

**Dr. Heine:** To my knowledge there is still no evidence for an increased risk of esophageal carcinoma or Barrett’s esophagus in patients with eosinophilic esophagitis.

**Dr. Cerf-Bensussan:** I was just wondering whether these patients can be cured at some point, or is it a life-long disease? Are they relapsing all the time?

**Dr. Heine:** We don’t really know the natural history because the condition was only recognized 15–20 years ago. In food allergic disease, tolerance development may result in remission of eosinophilic esophagitis, although this may be the exception. In most children and adults eosinophilic esophagitis may persist life-long unless we find better immune-modulating therapies.

**Dr. Cerf-Bensussan:** Is it a familial disease?

**Dr. Heine:** There are reports of familial clusters of eosinophilic esophagitis, spanning 3 or 4 generations. The exact gene locus is not clear.

**Dr. Tobin:** Following up on the questions from London whether markers play a role in some of the patients who have very elevated IgE at diagnosis. Can you comment on that? Should we not have these children on a registry if we are to get the long-term analyses that we need?

**Dr. Heine:** The second question first, there is a web-based registry in Cincinnati. We don’t have a registry in Australia, but I think it would be worth pursuing.

**Dr. Tobin:** Our immunology colleagues have a registry for other immune diseases, so it might worth tacking on to them, at least in Australia.

**Dr. Heine:** That’s a good suggestion. Regarding your question about high IgE antibody levels: if you have high specific IgE levels to a food it is likely that you will react with an immediate reaction. These foods don’t cause diagnostic dilemmas as avoidance is required anyway. For foods with low or negative IgE antibody levels it is more difficult to know whether they are implicated in the pathogenesis or not.

**Dr. von Berg:** In allergic asthma exhaled NO is now used as a marker for inflammation. I wonder whether this could be used as a marker for activity in this disease?

**Dr. Heine:** It may work, but perhaps only if patients don’t have active asthma at the same time.
Dr. Motala: Do you know whether there are any comparative studies between the use of systemic steroids and swallowed steroids for this condition? What about the risk of *Candida* affecting the esophagus with swallowed steroids?

Dr. Heine: There is one randomized trial comparing prednisolone versus swallowed steroid aerosols. Systemic corticosteroids were more effective, but had more adverse effects. Mucosal candidiasis is a well-known complication, and we therefore ask patients to rinse their mouths after taking swallowed steroid aerosols. There are also case reports of Herpes esophagitis in patients with eosinophilic esophagitis.

Dr. Venter: Spergel and Brown-Whiteborn [2] seem to identify milk, egg and soy as the most important foods causing allergic esophagitis. When you do elimination diets, do you always go for the big 8 or do you sometimes go for a shorter list to increase patient compliance?

Dr. Heine: I think you have to individualize your diets and you can put children on restrictive diets only for a short period of time. If I can convince my patients to go onto a more broad-based elimination diet, that would be my preference. If parents fear that their children won’t tolerate a particular diet, I will make some compromises and allow certain foods and move to swallowed steroid aerosols if the diet fails.

Dr. Venter: I know there are no studies comparing the use of extensively hydrolyzed formulas to elemental formulas in this group of patients. Have you any practical experience with using extensively hydrolyzed formulas in these patients or do you always use elemental formulas?

Dr. Heine: We always use amino acid-based formulas. There are no studies using extensively hydrolyzed formulas. In addition, in Australia only amino acid-based formula is currently funded for the treatment of eosinophilic esophagitis.

Dr. Latour de Yunen: We know that food allergies in children tend to disappear by themselves, so we could assume that in adulthood the cause of eosinophilic esophagitis due to food allergens would tend to decrease in the same way. Do you see this trend in eosinophilic esophagitis in adulthood? Do you find less food allergy in the adults with this condition than in the children?

Dr. Heine: The proportion of food-allergic adults is much lower, 4% of the whole population, so food allergy may not play a major role in adults. That is perhaps the reason why there are no diet trials in adults.

Dr. Thornton: Do the non-allergic groups with eosinophilic esophagitis have circulating eosinophilia as well?

Dr. Heine: I am not sure what the exact percentage is in non-atopic individuals.

Dr. Thornton: In infants who have a diagnosis very early in the first few months of life, do you know if there is any effect of mode of delivery on diagnosis?

Dr. Heine: Not that I am aware of.

Dr. Micskey: In Hungary we have seen some food additives as etiological factors causing eosinophilic esophagitis and we eliminated them. So we don’t need the elemental diet, for example.

Dr. Heine: We have no experience with food additive restriction. We recommend using fresh foods and avoiding food additives or other unwanted ingredients. But I am not sure that food additives play a big role in this.

Dr. Swain: In those with no food allergy, do you find any difference in the food triggers? For children you are talking about the big 6 or the big 8 food allergens, when it comes to adults where there is less of an incidence of food allergy, is there a difference in the triggers that you find cause eosinophilic esophagitis?

Dr. Heine: When I say we are looking at the main 6 or 8, it’s actually hard to know which foods to choose. Currently, immunologists have chosen common IgE-mediated food allergens. To the gastroenterologist, other foods such as soy, corn, wheat or meats may also be important.
Dr. Swain: That leads to my next question. Apart from the immunological 6 or 8, what are the other triggers that you commonly find are a problem with eosinophilic esophagitis? Do you find meat to be another common one?

Dr. Heine: Meats, wheat, corn, are foods that are commonly implicated. By contrast, I am not sure whether restriction of peanut plays much of a role in non-sensitized patients with eosinophilic esophagitis.

References
