Eosinophilic esophagitis: studies on an emerging disease
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Chapter 1

General introduction & outline of the thesis

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Bram D. van Rhijn & A.J. (Arjan) Bredenoord
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Eosinofiele oesofagitis: een vaak gemiste oorzaak van dysfagie
Bram D. van Rhijn, Andreas J.P.M. Smout & A.J.(Arjan) Bredenoord
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General introduction

Eosinophilic esophagitis (EoE) was first described as a distinct disease entity in 1993. It is a relatively recently discovered disease, for which the first consensus guidelines were published in 2007. In these guidelines, EoE was defined as “a primary clinicopathologic disorder of the esophagus, characterized by esophageal and/or upper gastrointestinal (GI) tract symptoms in association with esophageal mucosal biopsy specimens containing 15 intraepithelial eosinophils per high-power field in 1 or more biopsy specimens and absence of pathologic gastroesophageal reflux as evidenced by a normal pH monitoring study of the distal esophagus or lack of response to high-dose PPI medication”. Most of the patients with EoE have atopic co-morbidity. EoE has a male predilection (approximately 70%), and the disease can occur at any age. Key symptoms include food refusal, regurgitation, and failure to thrive in children, and dysphagia and food impaction in adults. Disease symptoms and treatments can have profound effects on the quality of life of affected patients and their families.

Epidemiology

At the start of this PhD project in the AMC, few studies had been published about the epidemiology of EoE in adults. In pediatric patients with esophageal eosinophilia in the USA, the incidence and prevalence of EoE significantly increased from 2000 to 2003, with an incidence/prevalence (per 100,000) of 9.09/9.91 in 2000, 9.91/19.83 in 2001, 10.33/30.16 in 2002, and 12.81/42.96 in 2003. This increase of EoE was also observed in other studies performed in the USA, Sweden and Switzerland, and may reflect a “true” (environmentally-driven) increase but also augmented awareness of the disease. So far, no data have been published on the incidence or prevalence of EoE in the Netherlands. Considering the previously mentioned increase of EoE in western countries, we hypothesized that the incidence of EoE in the Netherlands increased as well. In Chapter 2 we describe an epidemiological study on the incidence of EoE in the Netherlands.

Studies on the natural history of patients with EoE indicate that EoE is a chronic, relapsing disease. As the disease is relatively novel and not always recognized, the delay between the onset of symptoms and the diagnosis of EoE is long, approximately 4.5 years. Some patients with longer disease duration report increasing symptoms of dysphagia, suggesting that EoE is a progressive disease. In Chapter 3, we describe the influence of disease duration on the quality of life, and in Chapter 4 we report the effect of disease duration on manometric characteristics in EoE patients.

Pathophysiology

The pathophysiological mechanisms underlying EoE are not completely known. The observations that many patients have an atopic constitution and that food elimination diets are effective, suggest that food allergens trigger EoE. This hypothesis is supported by multiple studies demonstrating that most food elimination diets are effective in EoE. Studies demonstrating seasonal variation in disease activity, together with an experimental study in mice in which intranasal antigen administration caused esophageal eosinophilia, suggest...
that also aero allergens may play a role in EoE.\textsuperscript{17-19} In Chapter 8 we describe the sensitization patterns in patients with EoE using a new allergy test and in Chapter 9 we describe the effect of an elimination diet based at the sensitizations found using this allergy test.

There is evidence that EoE has a strong familial association, suggesting a genetic component as well.\textsuperscript{6,20,21} The estimated sibling recurrence risk ratio for EoE is approximately 80, which is high compared with asthma in which it is approximately 2.\textsuperscript{22,23} This relatively high sibling recurrence risk ratio for EoE indicates that EoE is likely to have a relatively large genetic component.\textsuperscript{21} EoE patients express unique EoE transcriptome which can be used to distinguish EoE from gastroesophageal reflux disease (GERD): in EoE, eotaxin-3, a molecule attracting and activating eosinophilic granulocytes is overexpressed.\textsuperscript{22,24}

IL-13 seems to be an important factor in the pathophysiology of EoE. Intratracheal exposure to IL-13 induces experimental EoE in mice, whereas mice with a deletion of STAT6 are protected from IL-13-induced experimental EoE.\textsuperscript{25} In addition, IL-13-deficient mice have reduced levels of allergen-induced experimental EoE.\textsuperscript{26} IL-13 is overexpressed in the esophagus of patients with EoE and induces eotaxin-3, which attracts and activates eosinophils.\textsuperscript{27} IL-13 also induces periostin, which is overexpressed in the esophageal epithelium of EoE patients.\textsuperscript{28} Periostin is expressed in collagen-rich connective tissues, plays a role in tissue remodeling and is also induced by TGF-β.\textsuperscript{28-30} It regulates eosinophil adhesion and promotes eosinophil recruitment.\textsuperscript{28} Furthermore, IL-13 downregulates filaggrin, which is decreased in the esophageal epithelium of EoE patients.\textsuperscript{22} Filaggrin is a protein that is important for maintaining epithelial barrier integrity in the skin; loss of function is associated with increased skin permeability and susceptibility to atopic dermatitis.\textsuperscript{31}

A role for acid gastroesophageal reflux in the pathophysiology of EoE has also been suggested. In theory, acid reflux could promote the development of EoE via the following mechanisms: 1) acid reflux increases the longevity of eosinophils; 2) acid reflux induces mast cell degranulation and endothelial expression of adhesion molecules which are recognized by eosinophils; 3) GERD is associated with dilated intercellular spaces in the esophageal epithelium and increased transepithelial permeability in the esophagus, possibly enabling permeation of antigens which cause an immune reaction.\textsuperscript{32-34} In support of an etiological role for gastroesophageal reflux, reports exist of patients with typical symptoms and signs of EoE who reached complete remission after proton pump inhibitor treatment.\textsuperscript{35,36} In Chapter 6 we describe the results of a study on the effect of proton pump inhibition on the esophageal inflammation and barrier integrity in patients with suspected EoE. In EoE patients not responding to proton pump inhibition, we also investigated the effect of anti-inflammatory treatment on the esophageal inflammation and barrier integrity, which is described in Chapter 7.

Figure 1 displays a simplified summary of the things we know and do not know about the pathophysiology of EoE.
Pathophysiology of EoE

![Diagram](image)

**Figure 1.** The pathophysiology of EoE is incompletely known. In this thesis, we present several studies in which we have investigated the pathophysiology of EoE.

**Diagnosis**

EoE is a clinicopathological diagnosis.² Currently, no diagnostic peripheral biomarker for EoE exists. Furthermore, manometric abnormalities are not specific for EoE, and the role of 24h pH-impedance monitoring is unknown. In Chapter 5, we describe acid exposure and baseline impedance values using pH-impedance monitoring in EoE patients.

The diagnosis of EoE is based on the presence of esophageal eosinophilia in patients with symptoms of esophageal dysfunction. Therefore, in patients with symptoms suggestive of EoE, endoscopy with esophageal biopsy sampling should be performed to enable histopathological analysis.

Endoscopic signs of EoE include concentric rings, longitudinal furrows, white exudates, edema, strictures, a crepe paper aspect, and diffuse narrowing (Figure 1).² In prospective studies, ≥1 endoscopic sign of EoE was found to be present in 93% of the patients.³⁷ Although none of these signs are pathognomonic for EoE, their presence should alert the endoscopist for the possibility of EoE, and esophageal biopsy samples should be taken. In 2013, a novel classification system for the scoring of endoscopic signs of EoE (called “EREFS”) was introduced, with reasonable interobserver agreement (Table 1).³⁸ In Chapter 11 we report on the intraobserver agreement of this classification system, and in Chapter 12 we
compared the endoscopic signs found using this classification with histopathological signs of EoE.

Histopathologically, EoE is characterized by the intraepithelial presence of ≥15 eosinophils per high-power field (eos/HPF), which is required for diagnosis (Figure 2). Other abnormalities include eosinophilic microabscesses, eosinophilic degranulation, mast cell infiltration, hyperplasia of the basal cell layer, spongiosis (dilation of intercellular spaces) and increased lamina propria fibrosis. Since eosinophils have a patchy distribution throughout the esophagus, several biopsy specimens should be obtained at different levels of the esophagus in order to be able to diagnose EoE. The sensitivity for finding at least 15 eos/HPF is 100% when taking 6 biopsy specimens.

Figure 1. At least one endoscopic sign of EoE is present in 93% of the patients: A) concentric rings, B) white exudates, C) linear furrows, D) edema, E) stricture, F) crepe paper esophagus.

Figure 2. Histopathology in EoE patients shows A) the abnormal infiltration of eosinophils, in this case also clustered into eosinophilic microabscesses, B) widespread spongiosis, or dilation of intercellular spaces, and C) increased mast cell infiltration, in the esophageal epithelium.
Table 1. Classification of the esophageal signs of eosinophilic esophagitis

<table>
<thead>
<tr>
<th>Major features</th>
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<tbody>
<tr>
<td>Concentric rings</td>
<td></td>
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<tr>
<td>- Grade 0: none</td>
<td></td>
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<tr>
<td>- Grade 1: mild (subtle circumferential ridges)</td>
<td></td>
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<tr>
<td>- Grade 2: moderate (distinct rings that do not impair passage of a standard diagnostic adult endoscope)</td>
<td></td>
</tr>
<tr>
<td>- Grade 3: severe (distinct rings that do not permit passage of a diagnostic endoscope)</td>
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<tr>
<td>White exudates</td>
<td></td>
</tr>
<tr>
<td>- Grade 0: none</td>
<td></td>
</tr>
<tr>
<td>- Grade 1: mild (lesions involving &lt;10% of the oesophageal surface area)</td>
<td></td>
</tr>
<tr>
<td>- Grade 2: severe (lesions involving &gt;10% of the oesophageal surface area)</td>
<td></td>
</tr>
<tr>
<td>Linear furrows</td>
<td></td>
</tr>
<tr>
<td>- Grade 0: absent</td>
<td></td>
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<tr>
<td>- Grade 1: present</td>
<td></td>
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<tr>
<td>Edema</td>
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<tr>
<td>- Grade 0: absent (distinct vascularity present)</td>
<td></td>
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<tr>
<td>- Grade 1: loss of clarity or absence of vascular markings</td>
<td></td>
</tr>
<tr>
<td>Stricture</td>
<td></td>
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<tr>
<td>- Grade 0: absent</td>
<td></td>
</tr>
<tr>
<td>- Grade 1: present</td>
<td></td>
</tr>
<tr>
<td>Minor features</td>
<td></td>
</tr>
<tr>
<td>Crepe paper esophagus</td>
<td></td>
</tr>
<tr>
<td>- Grade 0: absent</td>
<td></td>
</tr>
<tr>
<td>- Grade 1: present</td>
<td></td>
</tr>
</tbody>
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Treatment

Treatment options for EoE can be divided into three categories: drugs, diets, and (endoscopic) dilation. So far, few randomized controlled trials have been conducted in EoE, comparing the efficacy of different drugs. The efficacy of diets and dilation has not been investigated using randomized controlled trials.

Drugs

**Glucocorticoids.** Glucocorticoid induction therapy decreases symptoms and esophageal eosinophilia in children and adults with EoE. Some studies also show that glucocorticoids improve endoscopic signs of EoE. However, symptoms almost always recur after discontinuation of glucocorticoid treatment. Nevertheless, long-term use of oral glucocorticoids is not recommended because of potential side effects. A randomized trial has shown that topical glucocorticoids are as effective as oral (systemic) glucocorticoids in reaching clinicopathological remission. Maintenance treatment using low-dose topical glucocorticoids has been shown effective in preventing clinicopathological recurrence.
Proton pump inhibitors. According to international guidelines, EoE can be diagnosed only when patients show clinicopathological non-response to high-dose proton pump inhibition treatment for 8 weeks.\textsuperscript{2} However, one randomized study has demonstrated that proton pump inhibitors and topical glucocorticoids have similar clinicopathological efficacy.\textsuperscript{45} Considering its diagnostic value and the potential side effects of long-term use of glucocorticoids, a proton pump inhibitor trial is recommended as initial treatment for patients with suspected eosinophilic esophagitis.\textsuperscript{2}

Anti-interleukin-5. Two randomized trials have shown that anti-interleukin-5 reduces esophageal eosinophilia.\textsuperscript{49,50} However, in these studies no effect was seen on symptoms, and the available evidence therefore does not support the clinical use of these medications currently.

Diets
Three different approaches for food allergen elimination diets have been described for the treatment of EoE: 1) a diet in which food elimination is based on allergy testing (skin prick testing or atopy patch testing), 2) a diet in which the six groups of most common food allergens are eliminated ("six food elimination diet", or "SFED"), and 3) a hypoallergenic diet consisting of an amino acid formula. Most food elimination diets have reasonable efficacy in patients with EoE, although evidence in adults is limited.\textsuperscript{51} The potential advantage of all types of dietary treatment options is that they prevent the development of EoE, without the side effects related to glucocorticoid use. A drawback of allergy test-based diets is that positive and negative predicting values are highly variable and these tests can only identify a small set of allergens each time.\textsuperscript{52,53} Compliance to SFED is difficult due to the long-term, broad food elimination of staple foods, together with the need for multiple endoscopies.\textsuperscript{54-56} An elemental diet is highly effective, but expensive and unpalatable to many.\textsuperscript{57} Dietary treatment options for EoE thus need optimization.

Dilation
Endoscopic dilation is very effective in reducing symptoms, relieving dysphagia in 92% of the patients.\textsuperscript{58} The risk for perforation was initially thought to be relatively high (5%), however seems to have been overestimated.\textsuperscript{58} A disadvantage of endoscopic dilation is that it merely treats symptoms and not the underlying disease. For this reason, guidelines advise that endoscopic dilation can be considered in case of drug treatment failure, or in case of severe esophageal structuring/narrowing.\textsuperscript{2}

No data are available on stent placement for perforation in patients with EoE. In Chapter 10, we describe a case report of stent placement following esophageal perforation in an EoE patient.
Outline of the thesis

In **Part 1**, we present epidemiological studies in EoE patients.

- In **Chapter 2**, we describe a retrospective study in which we used the nationwide histopathology database PALGA to determine the incidence of EoE in a large cohort.
- The influence of disease duration on the quality of life is unknown, and will be described in **Chapter 3**.
- It is also unknown whether disease duration affects manometric abnormalities in EoE patients. In **Chapter 4**, we present a study describing manometric abnormalities in EoE patients with varying disease duration.

In **Part 2**, we present studies investigating the pathophysiology and treatment of EoE. We describe a number of studies in which we evaluated the esophageal barrier integrity in patients with EoE, and investigated the effect of commonly used drugs on their esophageal mucosal integrity. We also investigated allergic sensitization patterns and a diet based on these sensitizations in these patients. Furthermore, as esophageal stent placement for perforation had not been described in patients with EoE, we report such a case.

- In **Chapter 5**, we describe baseline esophageal impedance values in EoE patients measured with ambulatory 24-h pH-impedance monitoring.
- In **Chapter 6**, we evaluate the baseline esophageal barrier integrity using several techniques in patients with suspected EoE, and we describe the effect of proton pump inhibitors on the esophageal barrier integrity in these patients.
- In **Chapter 7**, we present a study in which we evaluated the effect of topical fluticasone propionate on the esophageal barrier integrity.
- In **Chapter 8**, we describe sensitization patterns in patients with EoE found using a novel microarray allergy assay.
- In **Chapter 9**, we present a study in which we evaluated the effect of dietary therapy based on these sensitizations.
- In **Chapter 10**, we report a case of esophageal perforation after endoscopic removal of an impacted food bolus in an EoE patient, for which a stent was placed.

In **Part 3**, we describe the value of endoscopic and histopathological signs for the diagnosis of EoE.

- In **Chapter 11**, we present the inter- and intraobserver agreement of the novel endoscopic reference score (EREFS) for the assessment of esophageal signs of EoE.
- In **Chapter 12**, we describe a study in which we compared esophageal signs of EoE, scored according to the endoscopic reference score (EREFS), with histopathological signs of EoE.
References


