Aspects on the Management of Patients with Eosinophilic Esophagitis

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“If food gets stuck in your throat you have to go
to the doctor and be vaccinated, or poke it away with a
small forceps, otherwise you will be small...
The body NEEDS food "

Rebecka, 4 years old.

“Om det är stopp i matstrupen måste man åka till doktorn och bli
vaccinerad, eller pilla bort det med en liten tång, annars blir man liten…
För kroppen MÅSTE ha mat”

Rebecka, 4 år.

Aspects on the Management of Patients with Eosinophilic Esophagitis

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ABSTRACT

Eosinophilic esophagitis (EoE) is an inflammatory disorder of the esophagus characterized by symptoms of esophageal dysfunction and eosinophilia in the esophageal mucosa. This condition may affect approximately 1% of the general population and is strongly associated with allergy/atopic diatheses.

Aims: The overall aim of this thesis was to examine the clinical aspects on the management of patients with EoE. The possibility of a seasonal variation of food bolus impaction in the esophagus, a common complication of EoE patients, was explored. The burden of symptoms and health-related quality of life (HRQL) of patients with EoE at diagnosis, after two months of treatment and at a long-term follow-up point were investigated. The association between the grade of mucosal eosinophilia and the symptoms was studied.

Methods & Results: Subjects with bolus impaction (n=314) were included in a retrospective study. A significantly higher incidence of bolus impaction was found in subjects with atopic disorders during the fall (n=90) than during any of the other three seasons (p=0.015). Untreated EoE patients were included in two prospective studies (n=31 and n=47, respectively). Symptoms and HRQL (Watson Dysphagia Scale, EORTC QLQ-OES18, SF-36) were evaluated at diagnosis, after two months of treatment with topical corticosteroids and at least one year after inclusion (median: 23 months after inclusion). The dysphagia-related scores improved after treatment and a partial remission was noted at the long-term follow-up point. The grade of mucosal eosinophilia in untreated patients with dysphagia and esophageal eosinophilia (n=65) was assessed using both hematoxylin-eosin staining and immunohistochemical technique. No correlation was found between the grade of eosinophilia and the symptoms/HRQL using the aforementioned questionnaires, however, a higher grade of eosinophilia was found among patients with concomitant bolus impaction as compared to those without.

Conclusions: A seasonal variation was found in the incidence of acute esophageal bolus impaction in patients with atopic disorders. EoE patients had a substantial burden of symptoms, which improved after treatment, and a partial remission was noted more than one year after diagnosis. A high grade of eosinophilia in the proximal part of the esophagus might serve as a marker for an increased risk of bolus impaction.

Keywords: eosinophilia, esophagitis, dysphagia, quality of life, bolus impaction.

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SAMMANFATTNING PÅ SVENSKA

Eosinofil esofagit (EoE), eller ”allergisk matstrupe” som det kallas i folkmun, är ett inflammatoriskt tillstånd i matstrupen som orsakar sväljningsbesvär och i många fall även totalstopp pga. att föda fastnar. För att ställa diagnosen krävs att patienten har associerade besvär och att man ser en ansamling av eosinofila celler i biopsier från matstrupsslemhinnan. Sjukdomen är starkt kopplad till andra allergiska sjukdomar såsom luftvägs- och födoämnesallergier samt astma. Prevalensen i den svenska normalbefolkningen är sannolikt ca 1% och såväl barn som vuxna kan drabbas. Flera olika behandlingsalternativ har prövats och idag rekommenderas i första hand lokal kortisonbehandling alternativt modifierad kost.

Syftet med denna avhandling och dess ingående studier är att belysa olika aspekter som berör det kliniska handläggandet av patienter med EoE. Vi ville undersöka en eventuell förekomst av säsongsvariation av patienter som sökt sjukvård pga. totalstopp i esofagus, en vanlig komplikation till EoE. Vidare önskade vi utvärdera symptom och hälsorelaterad livskvalitet hos patienter med EoE vid diagnos, efter två månaders lokal kortisonbehandling samt vid uppföljning minst ett år senare. Slutligen ville vi utvärdera eventuella samband mellan symptom och grad av eosinofili i matstrupsslemhinnan.

I en retrospektiv studie inkluderades under en 6-årsperiod, patienter (n=314) som sökt pga. totalstopp i matstrupen. Patienter med samtidig atopisk sjukdom (n=90) hade en större incidens under hösten jämfört med de övriga årstiderna. I två prospektiva studier (n=31 resp. n=47) inkluderades obehandlade EoE patienter. Symtom och livskvalitet mättes med hjälp av frågeformulär vid diagnos, efter två månaders lokalbehandling med kortison och vid en långtidsuppföljning minst ett år senare. De sväljningsrelaterade symtomen minskade efter behandlingen och vid uppföljning minst ett år senare (medeltid två år) kvarstod en lägre grad av symtombelastning jämfört med före behandling. I den sista studien fann vi att graden av eosinofili i matstrupsslemhinnan hos patienter med samtidiga sväljningssvårigheter (n=65) inte korrelerar med symtomgrad eller livskvalitet mätt med frågeformulär. Däremot fann vi en ökad grad av eosinofili i övre delen av matstrupsslemhinnan hos patienter med samtidig förekomst av totalstopp i matstrupen jämfört med de som inte hade detta.

Sammanfattningsvis var den observerade säsongsvariationen i incidens av främmande kropp i matstrupen accentuerad vid samtidig förekomst av atopisk sjukdom. Obehandlade patienter med EoE hade en hög symtombörda

vilken minskade efter en 2-månaders kur med lokal kortisonbehandling och en viss kvarstående effekt av behandlingen sågs mer än ett år senare. Slutligen skulle en ökad förekomst av eosinofiler i slemhinnan i den övre delen av matstrupen kunna ha ett samband med en ökad risk för att drabbas av främmande kropp i matstrupen.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by Roman numerals.

I. Larsson H, Bergquist H, Bove M.

The Incidence of Esophageal Bolus Impaction: Is There a Seasonal Variation?

Otolaryngology- Head and Neck Surgery. 2010; Nov 11: 186-190.

II. Bergquist H, Larsson H, Johansson L, Bove M.

Dysphagia and Quality of Life May Improve with Mometasone Treatment in Patients with Eosinophilic Esophagitis: A Pilot Study.

Otolaryngology- Head and Neck Surgery. 2011; April 145(4): 551-556.

III. Larsson H, Bergman K, Finizia C, Johansson L, Bove M, Bergquist H.

Dysphagia and Health-Related Quality of Life in Patients with Eosinophilic Esophagitis: A Long-Term Follow-Up.

Submitted. European Archives of Oto-Rhino-Laryngology.

IV. Larsson H, Norder Grusell E, Tegtmeyer B, Ruth M, Bergquist H, Bove M.

Grade of Eosinophilia versus Symptoms in Patients with Dysphagia and Esophageal Eosinophilia.

Submitted. Diseases of the Esophagus.

CONTENTS

ABBREVIATIONS

EMBP	Eosinophil Major Basic Protein
ENT	Ear, Nose and Throat
EoE	Eosinophilic esophagitis
EORTC	European Organization for Research and Treatment of Cancer
GERD	Gastro-Esophageal Reflux Disease
HE	Hematoxylin and Eosin
HPF	High-Power Field
HRQL	Health-Related Quality of Life
IHC	Immunohistochemical
IL	Interleukin
LES	Lower Esophageal Sphincter
NÄL	Norra Älvsborgs Länssjukhus
PPI	Proton-Pump Inhibitor
PPI-REE	Proton-Pump Inhibitor-Responsive Esophageal Eosinophilia
PRO	Patient-Reported Outcomes
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-OES18	Quality of Life Questionnaire Oesophageal Module 18
QoL	Quality of Life
SF-36	Short Form-36
Th2	T helper-2 cell
UES	Upper Esophageal Sphincter

1 INTRODUCTION

This thesis concerns the management of adult patients with eosinophilic esophagitis (EoE), an allergic, inflammatory disease affecting the esophagus and one of the leading causes of esophageal dysphagia.[1]

1.1 The Esophagus

The esophagus develops from the foregut at the fifth gestational week when the early foregut differentiates into the respiratory tract and the intestinal tract. The two organ systems share their early developmental background, although some details regarding the development are controversial.[2] The esophagus represents the first part of the alimentary tract linking the pharynx to the stomach. It passes through the thorax, behind the heart and trachea and between the lungs (Figure 1). It is a muscular tube of 20-22 cm, the wall is composed of four layers; the mucosa, the submucosa, the muscularis propria and the adventitia.[3] The mucosa consists of a nonkeratinized squamous epithelium with a thin layer of connective tissue, glands and lymphatic vessels (the lamina propria). Between the mucosa and the submucosa, there is a thin layer of smooth muscle fibers (the muscularis mucosa). The submucosa consists mainly of connective tissue and includes blood vessels and mucosal glands. The muscularis propria has a circular inner and an outer, longitudinal muscular layer. The adventitia is the external fibrous layer, which connects the esophagus to the surrounding structures. It is composed of loose connective tissue containing small blood vessels, lymphatic vessels and nerve fibers (Figure 2).[3, 4]

The most proximal border of the esophagus is the upper esophageal sphincter (UES), also called the cricopharyngeal sphincter. The UES as well as the proximal part of the esophagus contains striated muscle fibers. The transition to smooth muscle fibers occurs in the mid-portion of the esophagus, and the distal part contains only smooth muscle. The innervation changes from central innervation in the proximal part to mainly autonomic innervation in the distal part, including in the lower esophageal sphincter (LES). The LES is the gastro-esophageal junction and is a closed 3-4 cm high-pressure zone that protects the acid-sensitive mucosa of the esophagus from reflux of the stomach contents.[3]

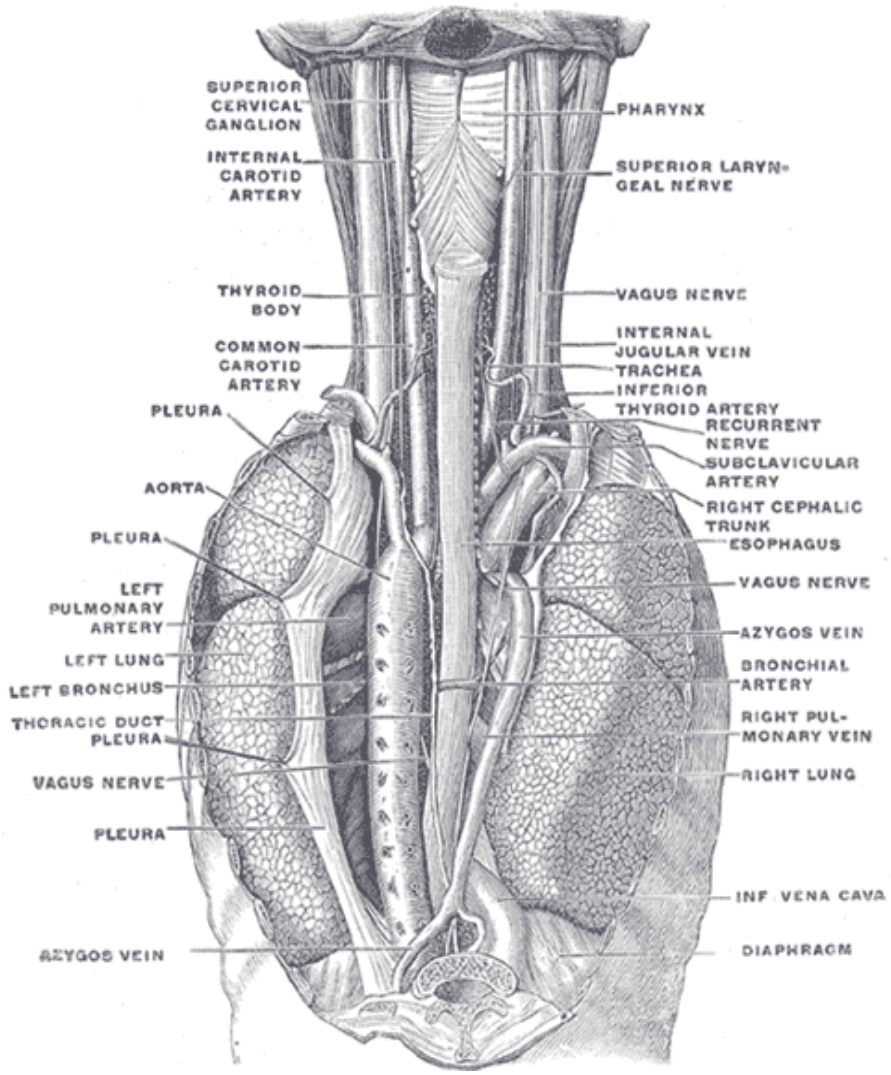

Figure 1. The position and relationships of the esophagus in the cervical region and posterior mediastinum. Seen from behind. (Source: Henry Gray, Anatomy of the human body, Plate 1032)

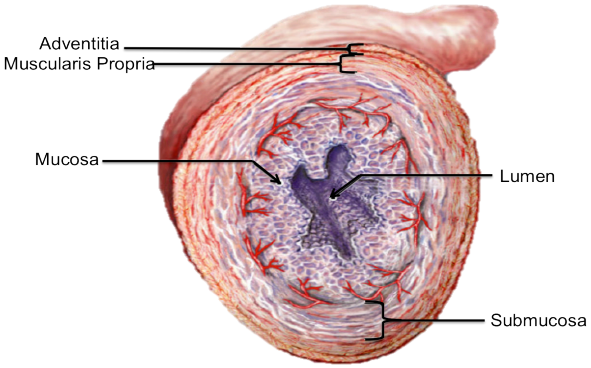

Figure 2. Cross-section of the esophagus. Printed with permission from Primal Pictures.

The swallowing act is a complex process comprising three different phases, the oral, pharyngeal and esophageal phases. The oral phase is voluntary and includes masticating and moistening the food and transforming it into a bolus using the teeth, tongue and salivary glands. The bolus is pushed backward toward the pharynx using the lingual muscles and the tongue. The pharyngeal phase is involuntary and is the most critical phase of swallowing because the food and airway cross in the pharynx, demanding smooth neuromuscular cooperation involving the 5th, 7th, 9th, 10th and 12th cranial nerves. In less than two seconds, as the bolus is pushed into the pharynx, the soft palate is elevated, blocking the passage upward to the nasopharynx, the larynx and the hyoid bone are elevated, causing a passive tilt of the epiglottis to cover the glottis, the vocal cords are strongly approximated to protect the trachea, and the UES relaxes, allowing the bolus to pass into the esophagus.

The esophageal passage of the bolus is involuntary, and under optimal conditions, when a person is in the upright position, gravity in combination with the movement of the bolus from the pharyngeal phase is generally sufficient. Even so, to facilitate this passage and to clear the esophagus of the bolus, contractions of the circular muscle layer narrows the lumen and contractions of the longitudinal muscle layer shortens the esophageal tube, creating a peristaltic movement. Activation of the contractions is both a continuation of the peristaltic wave that begins during the pharyngeal swallowing phase and a neurological response to the distension of the esophagus by the passing bolus. The peristaltic waves continue until the bolus has passed the esophagus and moved into the stomach.[3-5]

1.2 Dysphagia

Difficulty in performing the swallowing act is called dysphagia. The prevalence of this symptom in the general population ranges from 1.7% to 11.3%.[6, 7] Several underlying diseases that cause dysphagia occur at various ages. In the elderly population, neurological diseases are the main causes, e.g., dementia and Parkinson's disease. In the middle-aged population, other neurological diseases, immunological disorders and diseases associated with the local dysfunction of the esophagus, including achalasia, nut-cracker esophagus and EoE are common causes of dysphagia. In children, infections, EoE, prematurity or cerebral palsy may be responsible for this dysfunction.[7] Dysphagia can be divided into two categories depending on anatomic location: *oropharyngeal* and *esophageal.*

Oropharyngeal dysphagia is generally characterized by coughing and drooling during the early onset of eating. It is a common symptom of neuromuscular diseases, including stroke, amyotrophic lateral sclerosis, Parkinson's diseases and multiple sclerosis, and of diseases that affect the function of the salivary glands and thereby reduce the moisturizing of the bolus, e.g., Sjögren's syndrome.[3]

Patients with *esophageal* dysphagia often complain about the feeling that food becomes stuck or only slowly slips down to the stomach or that they need to vomit. It can be caused by a mechanical obstruction or by a neuromuscular disorder affecting the esophageal motility. Diseases causing motility disorders are generally associated with dysphagia for both liquids and solid food, whereas obstructive disorders generally present with dysphagia for solids. Obstruction may be caused by strictures (e.g., those due to peptic reflux, caustic damage or radiation), rings or webs, benign or malignant tumors, congenital anomalies or EoE. Patients with peptic strictures frequently have a long history of heartburn and other symptoms related to gastro-esophageal reflux disease (GERD). A rapidly progressing dysphagia in combination with weight loss and a poor general condition should raise a strong suspicion of malignant tumor as the underlying cause, and prompt urgent investigation.[3, 4]

1.3 Esophageal Bolus Impaction

Esophageal bolus impaction occurs in both children and adults and has a multifaceted etiology. Children may accidentally swallow toys, coins, and other sharp or hard items while playing, whereas adolescents and adults with a psychiatric background may intentionally swallow sharp items. In geriatric patients, esophageal dysphagia due to neuromotor disturbances or bad dentures may be the cause of esophageal obstruction. In addition to prior surgery to treat esophageal atresia or fundoplication, EoE is the most common underlying condition of esophageal bolus obstruction, particularly among young and middle-aged patients.[8] Studies have shown that as many as 30-50% of patients with esophageal bolus impaction have concomitant EoE.[9-11] The estimated annual incidence of bolus impaction is 11-19 episodes per 100.000 inhabitants, with a male preponderance (1.4-2.3:1). Most patients (86-99%) admitted to hospital due to esophageal bolus impaction require bolus retrieval, a procedure generally performed using flexible endoscopy.[9, 12-14] In Sweden, the ENT-surgeon is generally consulted and often performs rigid and flexible techniques under general anesthesia. In the majority of other countries, however, gastroenterologists and/or gastrointestinal surgeons more commonly treat these patients.

1.4 The Eosinophil

The eosinophil granulocyte is a fascinating cell that was first described in the mid-1800s (Figure 3). It was named in 1879 based on its strong avidity to the acidic dye, eosin, by the German physician Paul Ehrlich, who won the Nobel Prize in 1908 for his contributions to the field of immunology. Eosinophil granulocytes comprise 1–4% of the leukocytes in the bloodstream and are associated with T helper-2 (Th2) cells in allergic and anti-parasitic host immune responses.[1, 15]

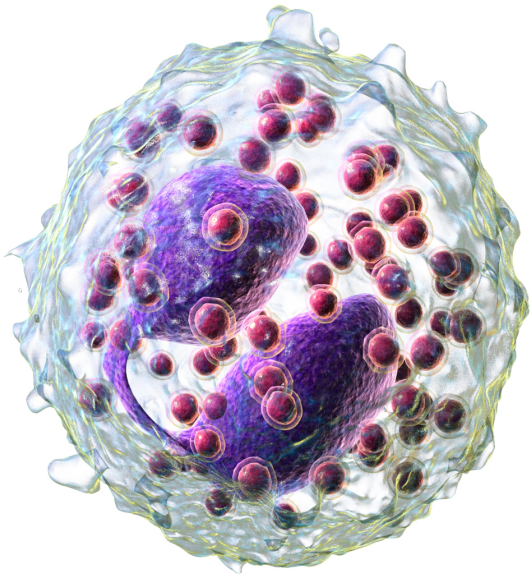

Figure 3. The Eosinophil (Source: Blausen gallery 2014. Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014.010. ISSN: 20018762.)

Eosinophils develop from myeloid precursor cells within the bone marrow, where they mature for 2–6 days before migrating into the bloodstream. They remain in the bloodstream for hours before migrating, which in healthy individuals is primarily to tissues and organs exposed to the external environment, such as the submucosa and loose connective tissue of the skin, the gastrointestinal tract (except for the healthy esophagus), the genital tract and the lungs.[1, 15, 16] The development, maturation and migration of eosinophils is governed by cytokines, particularly interleukin-5 (IL-5), that are produced mainly by the Th2 cells. The release of cytokines is part of the immunological process and is a response to an infectious agent, e.g., a parasite, or an allergic response to an antigen. An antigen-presenting cell (e.g., dendritic cells, macrophages or B-cells) activates a Th2 cell to produce and release the eosinophil-activating cytokines.[1] An eosinophil itself may act as an antigen-presenting cell, and it has been shown that circulating eosinophils display a distinctive disease-specific cytokine pattern.[17, 18]

Vesicles in the cytoplasm of eosinophils contain pro-inflammatory granules including basic proteins; interleukins, lipid mediators, cytokines, chemokines, growth factors and autocrine survival factors. When eosinophils are activated, the eosinophilic granules are released into the target tissue, causing local inflammation. The released granulae are cytotoxic, neurotoxic and tissue damaging. The airway and lung tissues of patients with eosinophilic asthma display epithelial cell damage, fibrosis and angiogenesis.[1, 19]

1.5 Eosinophilic Esophagitis

EoE is an allergic, inflammatory disorder of the esophagus that causes swallowing difficulties and the potentiality for severe complications.[1]

1.5.1 History

EoE has a fairly short history as a clinical entity. The knowledge of and interest in this disease has increased greatly over the last two decades. The first publication concerning EoE, in the late 1970s, was a case-report of a patient with eosinophilic esophagitis in combination with severe achalasia.[20] In the 1980s, an eosinophilic inflammation of the esophageal mucosa was associated with GERD, and it was not until 1993 that the British Professor of Surgery Stephen Attwood described the combination of dysphagia and eosinophilia and recognized EoE as a separate disease entity.[21, 22] In 2007, a systematic review of the literature was conducted by an international group of experts, followed by the publication of consensus recommendations regarding the diagnosis and treatment of EoE..[23] Updated recommendations were published in 2011 and 2013, and the first textbook concerning EoE was printed in 2012.[1, 24, 25]

1.5.2 Prevalence, Etiology and Pathogenesis

EoE is a chronic immune/antigen-mediated disease of the esophagus affecting people of all ages, with a male to female ratio of approximately 3:1.[1, 25] The reported prevalence varies considerably, with fewer registered cases in medical care units than in samples from the general population.[26-28] A Swedish population study (n=1000) reported a 0.7% prevalence of probable EoE, but the prevalence figures range from 10-59/100 000 in different studies.[26, 29-31] Similar to other allergic ailment, both the prevalence and incidence of EoE appear to be increasing. [27, 28]

The true etiology of EoE is not yet known. However, studies in both children and adults have verified that EoE is an antigen-driven allergic condition.[1, 24] There is marked over-representation (approximately 70%) of a personal history of allergy, atopic conditions and/or asthma among patients with EoE, and it has been shown that eliminating food allergen in pediatric patients has both histological and clinical beneficial effects; recently, similar results have been observed also in adults.[24, 32-35]

The role of eosinophils in the pathogenesis of EoE is also not yet entirely understood. These cells are thought to contribute to angiogenesis, which increases the supply of inflammatory blood cells, adding more eosinophils to the target tissue. Furthermore, eosinophils induce the proliferation of the esophageal epithelial cells, causing basal-zone hyperplasia and esophageal thickening. Myofibroblasts are also activated by eosinophils, proliferating and eventually causing subepithelial fibrosis, which contributes to the luminal narrowing and stricture formation observed in these patients.[36, 37] A delayed diagnosis, and thereby a prolonged eosinophilic inflammation, has been shown to increase the risk of esophageal stricture formation.[38] Other features contributing to the rigidity of the esophageal wall are the proliferation and hyperplasia of the smooth muscle cells. Altogether, these processes are believed to cause the symptoms, morphological changes and complications observed in patients with EoE.[1, 36]

1.5.3 Symptoms and Diagnosis

The typical adult EoE-patient is a middle-aged atopic man with a long history of solid-food dysphagia who commonly presents with a history of total esophageal obstruction by food that must be retrieved. Heartburn or upper abdominal pain are less commonly reported but may occur.[1] In small children, symptoms related to EoE are failure to thrive, feeding difficulties, vomiting and pain.[25] The average duration of symptoms before diagnosis may be as long as 4-5 years.[1]

EoE is a clinicopathological disease, the diagnosis of which should be established according to current guidelines. These criteria include; i. at least one biopsy from the esophageal mucosa showing eosinophilic inflammation with >15 eosinophils/high-power field (HPF) (peak value), ii. symptoms related to esophageal dysfunction and iii. exclusion of other causes of esophageal eosinophilia, such as proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE).[24, 25] Endoscopy should be performed and 2–4 biopsy samples from the distal and proximal esophagus should be collected. The eosinophilic infiltration of the esophageal mucosa is known to be patchy, and two and three biopsies have been shown to have a diagnostic sensitivity of 84% and 97.[24] Complementary biopsies from the ventricle and duodenum should always be obtained from children and adults if other diseases that might be associated with esophageal eosinophilia are suspected. The latter diseases include GERD, celiac or Crohn's disease, parasitic infections, vasculitis or drug hypersensitivity.[24, 25]

The association between GERD and EoE has not yet been fully explored. The two diseases overlap both histologically and symptomatically, although dysphagia is not as commonly observed in GERD patients as in EoE patients. While the number of eosinophils is often higher in EoE patients, histological signs of their effects, such as eosinophilic microabscesses, basal cell hyperplasia and dilated intercellular spaces are more commonly observed in EoE patients than in GERD-patients.[39]

Endoscopic findings

The typical endoscopic findings in EoE patients are esophageal rings (trachealization), strictures and a narrow-caliber esophagus (prevalence: 44%, 21% and 9%, respectively). Findings more prevalent in children are linear furrows, white plaques, and decreased vascularization (prevalence: 48%, 27% and 41%, respectively) (Figure 4).[40] None of these endoscopic features are, however, pathognomonic for EoE because they may occur in those with other esophageal disorders.[25] Furthermore, endoscopic examination have been reported to be normal in approximately 17% of EoE patients. [40]

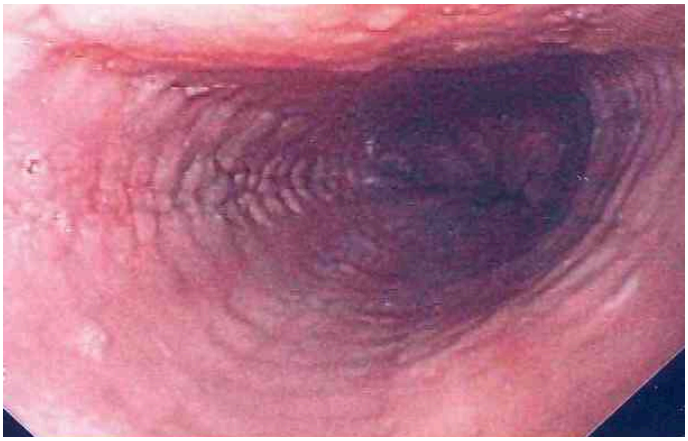

Figure 4. Endoscopic findings of EoE, including trachealization, linear furrows and white plaques. Photo: Dr. Mogens Bove.

Histological findings

Over the years, the peak number of eosinophils/HPF necessary to fulfill the diagnostic criteria of EoE has varied. However the consensus recommendation of 2007 of >15 eosinophils/HPF has become the established cut-off value.[23] A HPF is the area visible in a microscope under the maximum magnification, generally x400. Unfortunately, the area of a HPF has not been stringently defined and it might differ according to the objective lens used. In a review article published in 2007, the area of a HPF was found to range from 0,12 to 0,44 mm^2 in the few publications in which it was specified. Consequently, the possibility of specifying the area of a HPF in mm^2 is being discussed.[41]

In addition to the elevated number of eosinophils per HPF, several other characteristic histological signs are commonly found in biopsies of the esophageal mucosa of EoE patients. These findings include clusters of four or more eosinophils (eosinophilic microabscesses), eosinophilic degranulation, superficial layering, dilated intercellular spaces, basal cell hyperplasia and fibrosis of the lamina propria (Figures 5 and 6). Although the latter histological signs strongly indicate EoE, none of them are pathognomonic.[39]

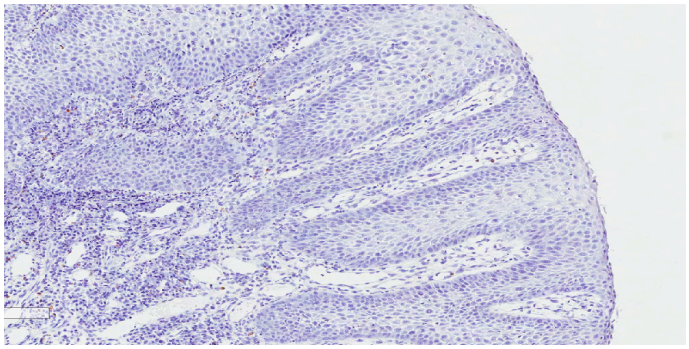

Figure 5. Histological image of a biopsy obtained from the esophageal mucosa of an EoE patient. Signs of inflammation with pronounced prolongation of the papillae nearly reaching the epithelial surface.

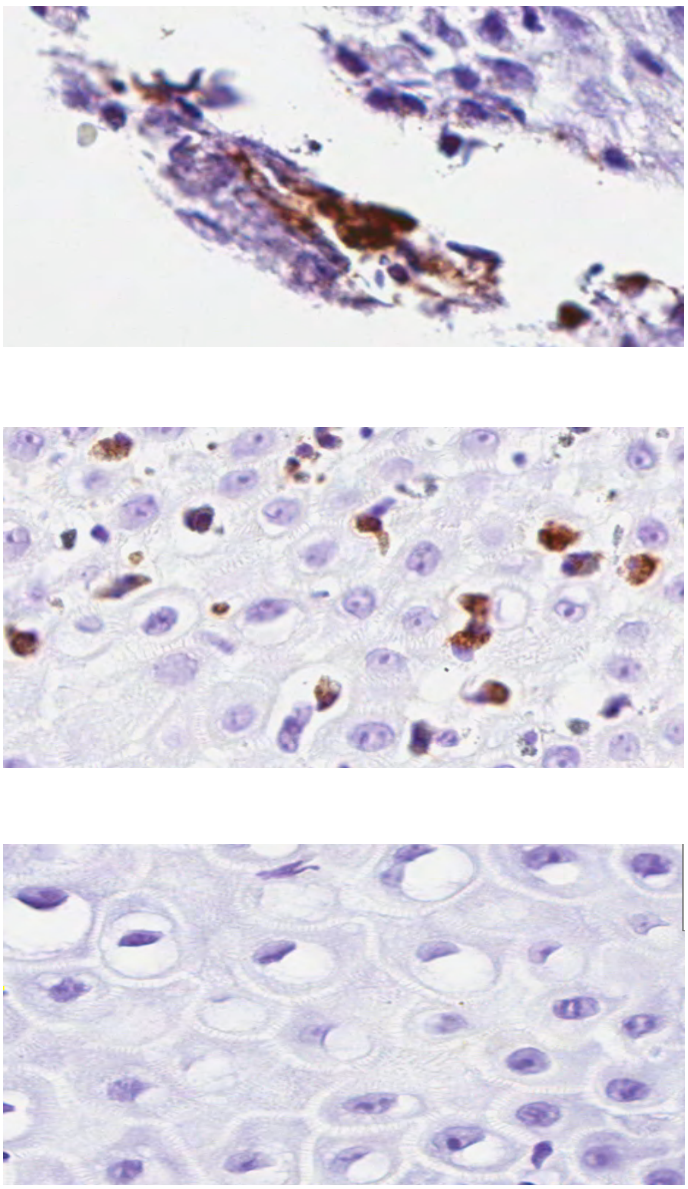

Figure 6. Histological images of biopsies obtained from the esophageal mucosa of an EoE patient. At the top: eosinophilic microabscesses In the middle: eosinophilic degranulation. At the bottom: dilated intercellular spaces.

1.5.4 Treatment

Several treatment strategies for EoE have been implemented including anti-allergic medication; allergen elimination diet, esophageal dilatation and proton-pump inhibitors (PPI) (Table 1).[23-25] The current first-choice therapy for adults are topical corticosteroids which, administered as an aerosol or viscous suspension, have beneficial effects both histologically, with a reduced eosinophilic load observed, and in terms of clinical improvement.[24, 25, 42] The length of the treatment described in different studies has ranged from two weeks to two months, and the corticosteroids most commonly used are fluticasone and budesonide.[42-44] Side-effects appear to be mild and are reasonably rare and include oral mucositis. According to current recommendations, topical corticosteroid therapy for EoE patients should be individually selected, and therefore the type of steroid and duration of treatment have not been specified.[24] A few longitudinal studies have been conducted, but the potential need for long-term treatment with steroids has not yet been fully evaluated.[24, 25] EoE patients who achieved histological remission and relief of symptoms after a high-dose short-term (15 days) course of budesonide treatment have been found to maintain long-term remission by continuing with a lower dose.[45] In a three-year follow-up study, repetitive treatment was required to suppress recurrent symptoms after an initial 6-week course of high-dose fluticasone treatment.[46] Moreover, in a five-year follow-up study, treatment with oral topical corticosteroids reduced the risk of esophageal food impaction and the requirement for endoscopic food retrieval.[47]

Because food allergies have been estimated to affect approximately 6% of the European population and EoE is known to be an immune-mediated disorder that can be triggered by food antigens, dietary allergen elimination would, at least theoretically, be expected to have a high impact on the disease.[1, 48] Allergen-elimination diets have been successfully used in children and recently, studies have reported beneficial effects in adults.[34, 35, 49] The most frequent EoE triggers in both adults and children appear to be cow's milk, soy, wheat, seafood and peanuts. After reintroducing each food, an evaluation of the clinical effect as well as endoscopic and histological evaluations may be warranted to identify specific food triggers.[34, 35] However, a dietary elimination treatment requires a major effort from the patient and is not always feasible.

According to some studies, approximately one-fifth of adult EoE patients develop esophageal strictures.[40] Esophageal dilatation may offer symptom relief but it does not affect the underlying inflammatory process. This

procedure is associated with rare but severe side effects, including esophageal perforation and bleeding, which occurs in less than 1% of the cases. Therefore, the procedure should be performed with caution and in well-selected patients.[50-52]

Because EoE is known to be an allergen-driven Th2-type inflammatory disease, several methods to specifically affect eosinophilic activity have been studied. Treatment using antibodies directed against IL-5 would, given the strong effect of IL-5 on both the development and activation of eosinophils, be expected to have a large impact on the disease.[1, 36] However, the few placebo-controlled studies performed to date showed only limited effects on either the symptoms and the grade of eosinophilia.[24, 25, 53, 54] Another cytokine that is mainly produced by Th2 cells, interleukin-13 (IL-13), affects eosinophils in a manner similar to IL-5 and recently, a placebo-controlled study in 25 EoE patients incorporating treatment with a specific inhibitor of IL-13 activity was carried out. A decrease in the eosinophilic load and a trend toward improved clinical symptoms was noted at the 6-month follow-up.[55] Another method for inhibiting the activity of the eosinophils was studied in a placebo-controlled trial in which EoE patients were given a course of treatment with an antagonist of the chemoattractant receptor-homologous molecule on Th2 cells. An anti-eosinophilic effect was found, with reduction of the eosinophilic load, but only modest beneficial clinical effects were seen.[56]

1.5.5 Proton-Pump Inhibitor-Responsive Esophageal Eosinophilia

Recently, a new ailment called proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE) has been described. PPI-REE patients, like EoE patients, exhibit eosinophil peak values that exceed 15/HPF but respond well histologically and/or symptomatically to PPI-treatment.[25, 57] It has been suggested that the epithelial damage caused by acidic gastric reflux may facilitate antigen exposure and thereby the activation of the Th2-immune defense and the development of EoE in individuals with an atopic predisposition. It may also be the other way around; the inflammation caused by EoE might make the epithelium more sensitive to reflux. However, whether PPI-REE is truly a separate disease entity or merely the condition of a subset of patients with EoE who respond well to PPI treatment is not yet known.[57, 58] Recently, studies have shown that, in addition to their anti-acidic effect, PPIs have anti-inflammatory and cell-stabilizing effects on the esophageal mucosa. In vitro experiments have also shown that PPIs affect the

Th2 cytokine and eotaxin-3 (an eosinophil chemoattractant) expression levels and thus, they may affect the potential mechanism limiting the immune-driven responses in the target organ.[16, 59, 60] To rule out PPI-REE in patients suspected of having EoE, a 2- month course of PPI treatment followed by endoscopic re-examination including biopsies are recommended.[24, 25] To date, no other diagnostic tests have been found to distinguish PPI-REE from EoE, and the controversy regarding the optimal management of these patients persists.

Table 1. Overview of randomized controlled trials of treatment for adult EoE patients. **= Ages 3-30 years. **Ages >14 years.*

Title	**Author /Year**	**Treatment**	**Design**	**Results**
Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE	Clayton *et al*. 2014 [54]	Omalizumab (n=16) /placebo (n=14)	Rand. double-blind.	No reduction in the eosinophil count or symptoms in the treatment group compared with the placebo group.
Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis	Butz *et al*. 2014 [43]	Fluticasone propionate 1760 mcg/d (n=28) /placebo (n=14)	Rand. double-blind. *	Reduced eosinophil count in 65% of the treated group and 0% of the placebo group.
Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia	Moawad *et al*. 2013 [61]	Fluticasone 880 mcg/d (n=21) /Esomeprazole 40 mg/d (n=21)	Rand. single-blind.	No change in the eosinophil count in any of the treatment groups. Symptoms improved in the esomeprazol but not in the fluticasone group. Similar improvement of the endoscopic findings in both groups.
Anti-eosinophil activity and clinical efficacy of the CRTH2 antagonist OC000459 in eosinophilic esophagitis	Straumann *et al*. 2013 [56]	OC000459 200 mg/d (n=14) /placebo (n=12)	Rand. double-blind.	Decreased eosinophil count and reduction in physician-reported disease activity in the treatment group.

Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis	Dellon *et al*. 2012 [62]	Budesonide 2mg/d nebulized (n=11) /viscous slurry (n=11)	Rand.	Decreased eosinophil count in the viscous-slurry group. Dysphagia was relieved in both groups
Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis	Alexander *et al*. 2012 [44]	Fluticasone 1760 µg/d (n=21) /placebo (n=15)	Rand. double-blind.	Decreased eosinophil count in the treatment group. No change in dysphagia between the groups.
Budesonide Is Effective in Adolescent and Adult Patients With Active Eosinophilic Esophagitis	Straumann *et al*. 2010 [42]	Budesonide 2 mg/d (n=18) /placebo (n=18)	Rand. double-blind. **	Decreased eosinophil count and reduced dysphagia in the treatment group.
Long-Term Budesonide Maintenance Treatment Is Partially Effective for Patients With Eosinophilic Esophagitis	Straumann *et al*. 2011 [45]	Budesonide 0,5 mg/d (n=14) /placebo (n=14)	Rand. double-blind. **	Eosinophil count increased more in the placebo group than in the treatment group. Dysphagia increased in the placebo group.
Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis	Peterson *et al*. 2010 [63]	Esomeprazole 40 mg/d (n=15) /Fluticasone 880 mcg/day (n=15)	Rand.	Decreased eosinophil count in the esomeprazole group and decreased count in the fluticasone group (although not statistically significant). No difference in dysphagia between the groups.
Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial	Straumann *et al*. 2010 [53]	Mepolizumab 750 mg/week (n=5) /placebo (n=6)	Rand. double-blind	Decreased eosinophil count in the treatment group.

1.6 Health-Related Quality of Life

Quality of Life (QoL) is a term with many interpretations. The World Health Organization has defined the concept of QoL as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns."[64] Health-Related Quality of Life (HRQL) is an important aspect of clinical research. HRQL concerns factors that affect the individual, not only the occurrence or absence of disease but also the impact of the disease on mental and social health.[65] Several methods for measuring HRQL have been developed, including various interviewing techniques and the use of specific questionnaires. Patient-Reported Outcomes (PRO) is a collective expression of information regarding a patient's health that is provided by the patient her- or himself without the interference of anyone else. PRO can be used to evaluate symptoms and HRQL through structured interviews or questionnaires. The use of questionnaires reduces the risk that the observer might under- or over-estimate the actual HRQL status. This method also reduces the possibility of biased answers, which might occur during interviews, for instance. There are numerous instruments available today for measuring HRQL. These are commonly divided into *generic* or *disease-specific* categories.[65]

Generic HRQL-evaluation instruments have been developed for general use and provide an overall picture, independent of the patient's condition or symptoms. Examples of a widely used generic HRQL questionnaire are the EuroQol-5D and the Short-Form-36 (SF-36).[66, 67] In contrast, *disease*- and/or symptom-specific instruments have been developed to focus on issues relevant to a specific disease or condition. There are several such questionnaires available today, such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), which was designed to evaluate important detailed aspects specifically for cancer patients, and the EORTC QLQ Oesophageal 18 module (EORTC QLQ-OES18), which focus on issues specifically relevant for patients with esophageal cancer, including their grade of dysphagia.[68-70] In the two latter questionnaires, the questions are organized into different domains and the answers are transformed to scales with scores ranging from 0 to 100.[71] When interpreting the outcome of the scoring, and as a complement to statistically significant differences, clinically significant differences in the scores are also commonly evaluated, which allows individual changes of importance to be indentified.[72, 73]

2 AIMS

The overall aim of this thesis was to investigate clinical issues relevant to the management of adult patients with EoE.

Study I

To evaluate a potential seasonal variation in the incidence of esophageal bolus impaction leading to hospital admittance. In addition, by excluding cases that involved sharp objects, atresia, cancer and the lack of coexisting allergic or other atopic disorders, verify whether such a variation could be traced to a subgroup with a high probability of having concurrent EoE.

Study II

To establish the baseline characteristics regarding dysphagia and HRQL in patients newly diagnosed with EoE and to survey the outcome after a 2-month course of treatment with topical corticosteroids.

Study III

To survey the outcome including symptoms and HRQL at least one year after diagnosis in a cohort of EoE patients who were treated with a 2-month course of topical corticosteroids.

Study IV

To evaluate potential correlations between the symptoms/HRQL and the grade of mucosal eosinophilia in the proximal and distal part of the esophagus of patients with dysphagia and esophageal eosinophilia. Additionally, to compare the standard hematoxylin-eosin (HE) staining method with an immunohistochemical (IHC) technique detecting Eosinophil Major Basic Protein (EMBP) for assessing eosinophil peak count.

3 PATIENTS AND METHODS

The patients included in the four studies described in this thesis were admitted to hospital due to esophageal bolus impaction (Study I) and/or were diagnosed with EoE according to the consensus-recommendations of 2007 (Study II-IV) (Table 2).[23] PPI-testing in order to exclude PPI-REE according to the recommendations of 2013 was not used as a criterion for inclusion.[25] Patients were recruited for the studies between January 2004 and the end of December 2012. The vast majority of patients was recruited in the Ear, Nose and Throat (ENT) Department at NÄL Medical Center Hospital, Trollhättan, Sweden (a secondary referral center that serves approximately 275 000 inhabitants), and a few patients were recruited in the ENT-department at Sahlgrenska University Hospital, Gothenburg, Sweden.

Table 2. Demographic data for the participants in studies I-IV.
**Presence of allergies in cases with soft food bolus impaction (n=223)*

	I	II	III	IV
No. of patients	314	31	47	65
Mean age, range (years)	57, 1-104	45, 18-89	49, 18-90	45, 19-88
Gender (males)	200 (65%)	23 (74%)	37 (79%)	48 (74%)
Concurrent allergic diatheses	90 (40%)*	21 (68%)	32 (68%)	47 (72%)
Events of esophageal bolus impaction	314 (100%)	14 (45%)	23 (49%)	26 (40%)

Study I included all of the patients with esophageal bolus impaction who were admitted to NÄL Medical Center Hospital during a 6-year period (January 1st 2004 to December 31st 2009). The case records were reviewed for demographic data, type of foreign body, medical history, including the presence of allergies or other atopic disorders and the time of the year of the incident (month and season).

The seasonal incidence of the event was calculated for all of the patients, and was recalculated after exclusion of the cases involving swallowed sharp items, cancer and atresia. Cases with and without an atopic diathesis were also analyzed separately (Figure 7).

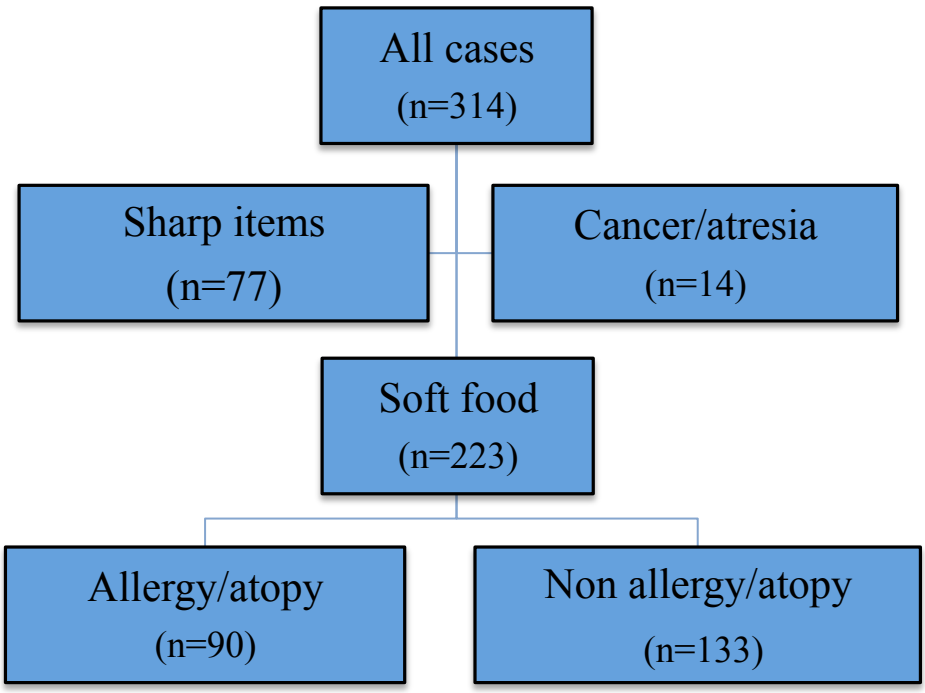

Figure 7. Flow-chart of the exclusion procedure of Study I.

Studies II, III and IV included a total of 83 individual, untreated patients who were diagnosed with EoE. Dysphagia-related symptoms and the HRQL were evaluated using the WDS scale and the EORTC QLQ OES-18 and SF-36 questionnaires. In addition, a thorough review of the medical records was conducted and each patient's data regarding the presence of allergies, type of allergy testing performed, history of esophageal bolus impaction events and endoscopic findings were recorded.

In **Studies II and III,** the EoE patients included were asked to complete the three questionnaires before and after treatment with a 2-month course of aerosolized mometasone furoate, 50 μg per spray, 4 sprays per dose taken 4 times daily. Patients were instructed to administer the doses orally after each meal (breakfast, lunch, and dinner) and before bedtime, and the patients were not allowed to eat or drink for 30 minutes after drug intake. The administration and duration of the treatment followed the recommendations of the American Gastroenterology Association (AGA) Institute, with the exception that mometasone furoate was used instead of fluticasone or budesonide, although at an equivalent dosage.[23] At the follow-up directly after the 2-month treatment course, the patients completed the questionnaires and were interviewed regarding their compliance and the effects of the treatment, including possible side-effects and adverse events. In **Study III**, a third evaluation was performed at least one year after the diagnosis. At this long-term follow-up, the formerly mentioned questionnaires were administered again, and in addition, a non-validated questionnaire comprising questions focusing on medication and hospital visits was administered. The patients were able to answer the latter questions in free text, but the answers were categorized for analytical purposes.

In **Study IV,** untreated patients with dysphagia and esophageal eosinophilia were asked to complete the questionnaires in connection with diagnostic endoscopy that included 3-4 biopsies from both the distal and the proximal part of the esophagus. The biopsies were processed routinely by fixation using 4% formaldehyde, embedded in paraffin wax and cut into 3-5 μm tissue sections that were HE stained. New tissue sections were later cut from the original frozen paraffin blocks. Prior to IHC staining, which involved antigen-antibody interactions and visualization using a marker, the tissue sections were pretreated with Proteinase K for epitope retrieval, thereby facilitating the interaction of the antibody with the antigen. A peroxidase-blocking step was performed to prevent nonspecific binding. The EnVisionTM Detection System, a two-step visualization system, was used to perform IHC staining. First, the sections were treated with the primary antibody, a mouse monoclonal antibody directed against human eosinophil

major basic protein (EMBP) (Santa Cruz Biotechnology Inc. Tex. USA; clone BMK13, ref. K5007). Next, to allow visualization of the antibody, a polymeric system with a dextran backbone that was conjugated to various enzymes and to antibody molecules directed against rabbit and mouse immunoglobulin was applied. Using a substrate solution of concentrated diaminobenzidine and chromogen and a hydrogen peroxide-containing buffer, the sites containing the target antigen were stained brown, and the nuclei were stained blue by HE counterstain. The IHC staining was conducted using a positive control. The stained slides were scanned and were anonymously viewed using the computer program Aperio ImageScope (Aperio Technologies, Vista, CA, USA), and the eosinophils in a high-power field were counted to determine the peak values.

3.1 Questionnaires

Currently, there are several scales and questionnaires with the potential to determine the grade of dysphagia and/or the HRQL of EoE patients (Table 3). The following scales and questionnaires were used in the research described in this thesis:

The *Watson Dysphagia Scale (WDS)* is an instrument for evaluating the grade of esophageal dysphagia. The WDS scale provides a score ranging from 0 (no dysphagia) to 45 (severe dysphagia) based on a 9-item assessment (ranging from liquids to solid food). The occurrence of dysphagia for each liquid or solid substance is determined by the patient and scored on a 3-point Likert scale (1=always, 0.5=sometimes, and 0=never); see *Appendix 1.* This score is then multiplied by a factor for each substance, and the scores for all of the substances are summed.[74, 75]

Although the WDS scale has not been properly validated according to the current recommendations, objective evaluations of it have been performed.[75] In a clinical study, patients with dysphagia were asked to eat various food items within 20 minutes. The outcome was scored according to the results of the WDS evaluations, which showed a high correlation of dysphagia and the ability to ingest the food items. The WDS scale has also been used in several studies involving patients with various etiology of esophageal dysphagia.[74-78]

The *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Oesophageal Module 18* (*EORTC QLQ-OES18)* was originally designed to investigate problems due to the location of esophageal cancer and its treatment.[69, 70] However, because the majority of the questions are not cancer specific, this questionnaire has been used in various HRQL studies, and its cross-cultural validity and psychometric properties are considered satisfactory. The questionnaire comprises the following: the dysphagia-, eating-, reflux-, and local-pain scales and six single questions concerning the related symptoms, and the scores are calculated according to the EORTC scoring manual.[71] The questions are scored by the patient on a 4-point Likert scale (not at all, sometimes, most of the time, and always), and the 4 points are transformed into a score ranging from 0 to 100, in which a high score represents a high level of symptoms/problems; see *Appendix 2*. A one-week time frame is used.

The *Short Form-36 (SF-36*) questionnaire is a multipurpose general-health survey consisting of 36 questions, which yields an 8-scale profile of functional health and well-being scores as well as psychometrically based physical and mental health summary values. This questionnaire has been used

in numerous studies, and its validity is well documented.[79-81] The patient answers the questions using a 2-, 3-, 5-, or 6-grade Likert scale, respectively, and a 4-week time frame is used. The scores are transformed into a score ranging from 0 to 100, in which a high score represents a high level of functioning/well-being; see *Appendix 3*.

Table 3. A selection of questionnaires potentially relevant for evaluating dysphagia in adult EoE patients.

Instrument	**Author / Year**	**Contents**	**Original population**
Adult Eosinophilic Esophagitis Activity Index (EEsAI)	Schoepfer *et al*. 2014 [82]	45 items, 5 domains: general-, 2symptom-, comorbidities and medication.	Adults with EoE
Adult eosinophilic oesophagitis quality of life questionnaire (EoO-QOL-A)	Taft *et al*. 2011 [83]	37 items, 5 subscales: eating/dietary-, social-, emotional-impact, disease and choking anxiety.	Adults with EoE
Esophageal Symptoms Questionnaire (ESQ)	Kwiatek *et al*. 2011 [84]	30 items, 3 subscales: dysphagia, globus sensation, and reflux symptoms.	Patients with esophageal and throat complaints including but not requiring globus sensation
Mayo Dysphagia Questionnaire-30 (MDQ-30)	McElhiney *et al*. 2009 [85]	28 items, 3 domains: dysphagia, heartburn and regurgitation.	Adult with esophageal diseases
Eating assessment tool (EAT-10)	Belafsky *et al*. 2008 [86]	10 items measuring different aspects of dysphagia.	Patients with a wide variety of causes of dysphagia
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Oesophageal Module 18 (EORTC QLQ-OES 18)	Blazeby *et al*. 2003 [70]	18 items, 4 subscales: dysphagia, eating, reflux, and local-pain scales and 6 single questions.	Patients with esophageal cancer
Watson Dysphagia Scale (WDS)	Dakkak *et al*. 1992 [75]	Occurence of dysphagia for 9 substances (ranging from liquids to solid food).	Patients with benign esophageal strictures

3.2 Statistics and Ethics

Non-parametric statistical tests were used in the studies described in this thesis (with the exception of Study I) for non-normally distributed variables, such as symptom scores and cell counts. All of the significance tests were two-tailed and were conducted using the 5% significance level. The mean, median, standard deviation, and range values were used for descriptive purposes.

Study I The binomial test was used to analyze dichotomous data. The χ^2 test with 3 degrees of freedom was used to analyze discrete data that were distributed into four categories.

Study II & III The mean, median, standard deviation, and range were used for descriptive purposes, and the Wilcoxon matched-pairs signed-rank test was used to compare the questionnaire scores obtained at each time point.

Study IV Spearman's correlation coefficients were used to analyze correlations. For comparison between groups, the Mann-Whitney U-test was used in the case of continuous variables. The statistical analyses were performed using Statistiska Konsultgruppen, Göteborg (www.stat-grp.se).

The studies were performed in accordance with the Declaration of Helsinki and were approved by the Regional Ethical Committee of the University of Gothenburg (D Nr 388-12). Informed consent was obtained from each participant before inclusion (studies II-IV).

4 STUDY DESIGNS

Study I:

Case series with chart review. A retrospective cohort analysis was performed, including patients with esophageal bolus impaction who were admitted to NÄL, Medical Center Hospital, Trollhättan, Sweden during a 6-year period (2004-2009). Step-by-step analysis regarding the seasonal variation of incidence was performed for the entire cohort, for cases with soft bolus impaction and then after subdividing the patients according to the presence or absence of coexisting atopic disorders.

Study II:

Case series with planned data collection. A prospective study of consecutively included EoE patients, with assessment of dysphagia-related symptoms and the HRQL before and after a 2-month course of treatment using topically administered mometasone furoate.

Study III:

Cross-sectional cohort study. EoE patients treated with a 2-month course of topically administered mometasone furoate were evaluated regarding dysphagia-related symptoms and the HRQL, medication and complications at least one year after diagnosis.

Study IV:

A retrospective correlation analysis. Dysphagia-related symptoms and HRQL of untreated patients with dysphagia and esophageal eosinophilia were evaluated in conjunction with esophageal biopsy findings, and the results were correlated with the grade of mucosal eosinophilia.

5 RESULTS

Study I

During the 6-year inclusion period, 314 cases (302 individual patients) were admitted to NÄL Medical Center Hospital due to esophageal bolus impaction. A significantly higher incidence of this event was found during the summer and fall than during the winter or spring (p=0.048). After excluding cases involving accidental or structural causes as well as those without coexisting atopic disorders, leaving a group with soft food bolus impaction and a coexisting atopic disorder (n=90), an even stronger seasonal variability appeared (p=0.004), including an unprejudiced general variation among the four seasons (p=0.015). A corresponding variation was found among the 24 cases (22 individuals) in which EoE was diagnosed (p=0.04). In contrast to these findings, no seasonal variation was found in the group of patients with soft-food bolus impaction but without a coexisting atopic disorder (n=133) (Figure 8).

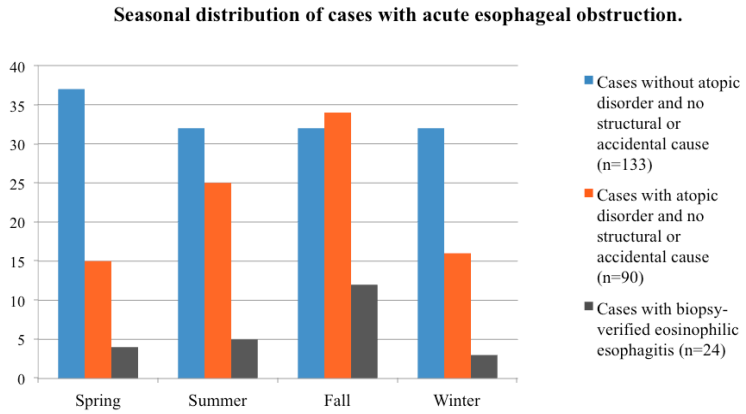

Figure 8. The seasonal variation in cases with soft food bolus impaction with (n=90) or without (n=133) a coexisting atopic disorder and in cases with coexisting EoE (n=24).

Study II

Thirty-one consecutive, newly diagnosed, untreated EoE patients were recruited to the study during a one-year period. None of the patients declined participation. The aforementioned questionnaires were completed both at inclusion and after treatment. Significant improvements were found for several of the dysphagia-related scales and items, including the overall WDS score (Figure 9), the EORTC QLQ-OES18 dysphagia and eating scores, and the score for the problems-with-choking item. In addition, improvements were found in the SF-36 item scores for bodily pain, general health, social functioning and mental health, whereas the EORTC QLQ-OES18 item score for trouble-with-coughing worsened. The information collected through the interviews indicated that the treatment was well accepted and that the level of compliance was high. One patient experienced side effects and developed oral candidiasis two weeks after the initiation of the treatment. The condition was successfully treated with topical antifungal medication (amphotericin B), and the patient continued the corticosteroid treatment throughout the study period. No other adverse events were reported during the trial or during the follow-up visits.

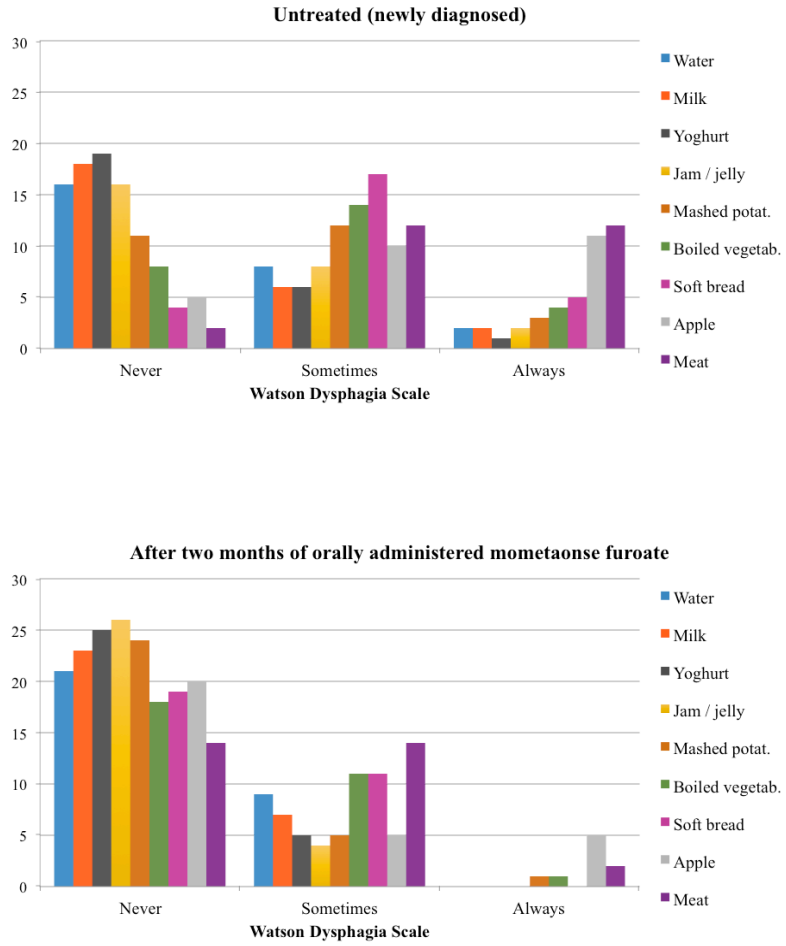

Figure 9. Results of the assessment of the dysphagia of patients prior to treatment and after a 2-month course of mometasone furoate treatment, performed using the Watson dysphagia scale.

Study III

Of 51 eligible EoE patients, 48 completed the questionnaires. One patient declined participation, two did not answer despite several reminders, and one patient was excluded due to the existence of a concomitant esophageal disease (scleroderma). Consequently, 47 patients (92%) were included (January, 2009 to March, 2011) in the study, and the median time from diagnosis to the long-term follow-up was 23 months (range, 13-34). Consistent with the results of Study II, the WDS scores as well as the EORTC QLQ-OES18 dysphagia, eating and choking scores were all significantly improved after the 2-month course of treatment compared with those observed at the time of diagnosis. In the case of the WDS and EORTC QLQ-OES18 dysphagia-and eating scores, the improvements persisted at the time of the long-time follow-up, a finding that was not observed for the choking-item score. However, the WDS-based scores declined significantly from directly after treatment began to the time of the long-term follow-up (Figure 10). According to the results obtained using the supplementary questionnaire that was provided at the long-term follow-up, the majority of the patients reported having experienced episodes of aggravated swallowing difficulties and esophageal bolus impaction during the study period. Even so, according to the medical records, none of these patients was referred to a hospital for the retrieval of an impacted bolus, none of the patients underwent endoscopic dilatation, and most of the patients received only the initial 2-month course of topical corticosteroid treatment after the diagnosis.

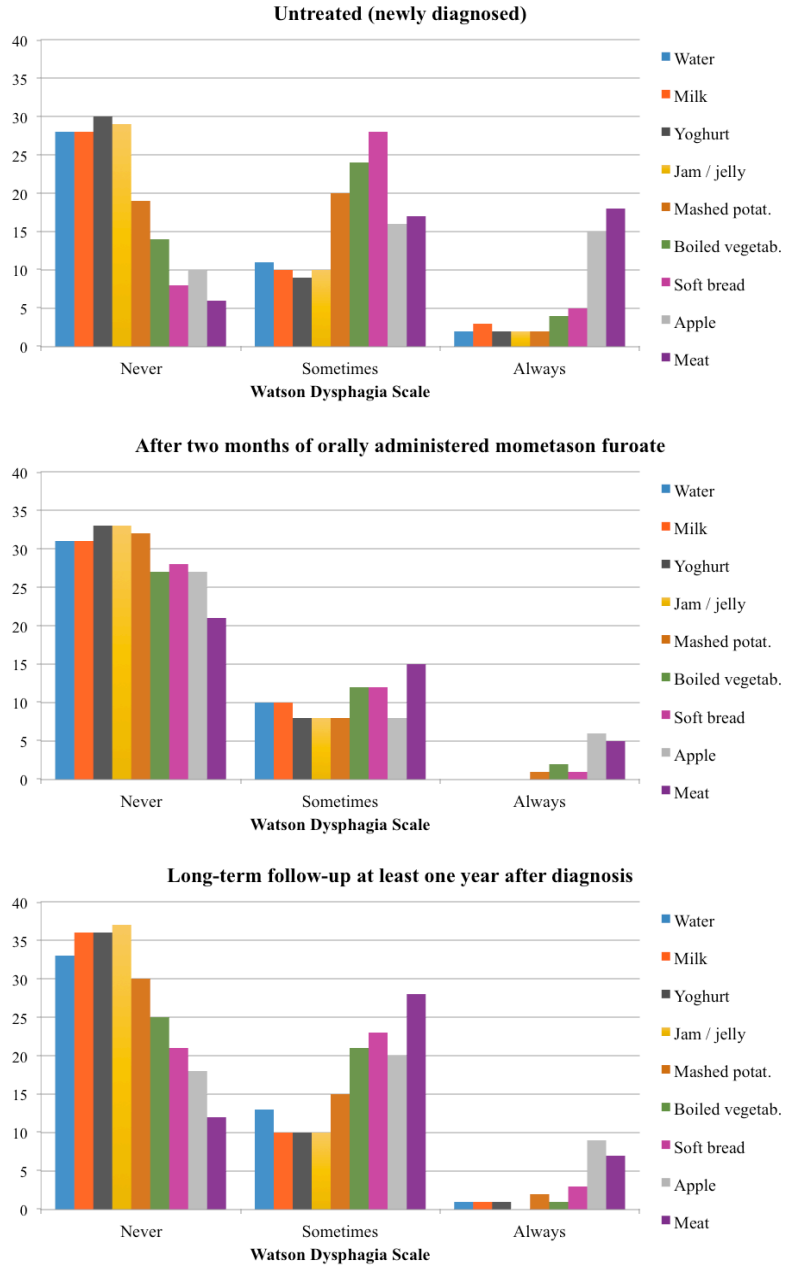

Figure 10. Results of the assessment of the dysphagia of patients prior to treatment, after a 2-month course of mometasone furoate treatment and at the long-term follow-up at least one year after diagnosis performed using the Watson Dysphagia Scale.

Study IV

Of 83 eligible, untreated patients with dysphagia and esophageal eosinophilia (September 2007 to December 2012), four patients declined to participate in the study, and 12 were excluded from analysis due to missing questionnaires. Furthermore, two of the histopathology slides could not be examined due to unsuccessful staining, why 65 patients were considered in the final analysis. Regardless of the staining method (HE or IHC) used (Figure 11 and 12), no significant correlation was found between the grade of eosinophilia and the symptom or HRQL scores.

The average number of eosinophils detected using the IHC technique was twice as high as that detected using the HE staining technique (mean value: 70.9 vs. 34.5). Patients diagnosed in conjunction with an event of acute bolus impaction had an increased grade of eosinophilia in biopsy samples taken from the proximal part of the esophagus compared to that of subjects without concomitant bolus impaction.

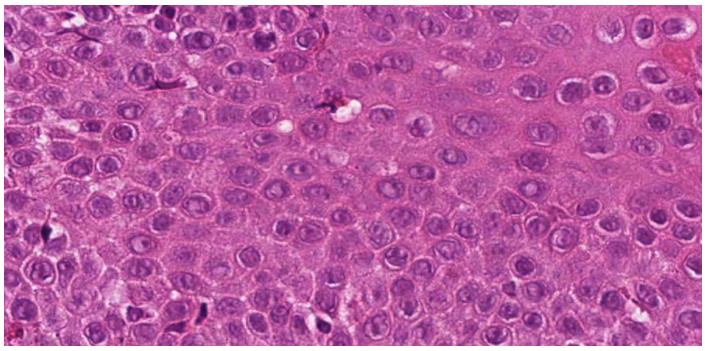

Figure 11. HE stained esophageal mucosal biopsy sample taken from an EoE patient.

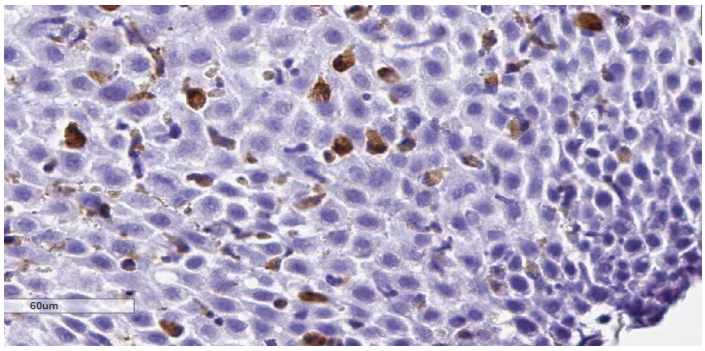

Figure 12. IHC stained esophageal mucosal biopsy sample taken from an EoE patient.

6 DISCUSSION AND FUTURE PERSPECTIVES

The research described in this thesis confirmed that there is a seasonal variation in the incidence of acute esophageal bolus impaction in patients in which a causative effect of diagnosed or undiagnosed EoE might be suspected, that untreated EoE patients may have a high burden of symptoms that respond well to a 2-month course of topical corticosteroid treatment and that this response may persist for a more than a year. Furthermore, it was found that the vast majority of EoE patients have had symptoms for many years before diagnosis and that a high proportion of them experienced at least one episode of an acute bolus impaction that required retrieval before the diagnose was established.

Study I was designed with the knowledge that a seasonal variation in the incidence of EoE was previously demonstrated and that patients with an impacted esophageal bolus requiring endoscopic removal have been shown, in approximately 30 to 50% of cases, to have concomitant EoE.[10, 11, 87, 88] At the time of patient inclusion (2004 to 2009), the awareness of the importance of obtaining biopsies from patients admitted to the hospital due to esophageal bolus impaction was still low in the ENT department of NÄL Hospital Medical Center. The clinical signs and conceivable complications of EoE had not reached out to every single doctor on call. Therefore, only a limited fraction of the patients in this study were properly biopsied during the acute endoscopic removal of the foreign body, a procedure that currently has become routine or at least much more common in our department. We found a seasonal variation in the incidence of acute esophageal bolus impaction, with the highest incidence observed during the summer and fall. Furthermore, this variation was traced to a subgroup with symptoms or signs of a coexisting atopic disorder and therefore a higher likelihood of underlying EoE. Knowing this, one must be careful to not over-interpret these results because the existence of an atopic diathesis is not a very firm criterion and there may be other explanations for the observed variance. To prove such causation would demand a prospective study with firm criteria regarding the allergic status of the patients and adequate biopsy collection in all cases of bolus impaction. Furthermore, to evaluate a potential seasonal variation in symptom severity and/or the HRQL, a prospective study in which the appropriate instruments for this assessment were applied repeatedly throughout the year is needed. Nevertheless, the clinical consequence of the

first study is that henceforth EoE should be suspected in all cases of esophageal bolus impaction warranting proper biopsies and the investigation of allergies.

In Studies II and III, surveys of the baseline characteristics regarding the dysphagia and HRQL of untreated patients with EoE were performed using the WDS scale and the EORTC QLQ-OES18 and SF-36 questionnaires. A substantial burden of symptoms was found, with a significant improvement observed after a 2-month course of treatment using orally administered mometasone furoate. Our results support the previous demonstrations of the favorable effects of topical corticosteroid treatment in EoE patients.[42, 61, 62, 89] The reasons for selecting mometasone furoate as the "drug of choice" for our patients included our previous experience with the substance and its low systemic availability. However, although we used the equivalent dosage and administration technique described in the consensus document, the optimal duration and need for repeated courses of topical mometasone furoate treatment have not been fully evaluated. A randomized, placebo-controlled trial with repetitive follow-ups, including assessments of complications such as the development of fibrosis is warranted to assess causality and evaluate the long-term effects.

In the long-term follow-up evaluations performed in Study III, the improvement in the dysphagia-related symptoms was found to persist, at least to a certain degree, at more than one year after the diagnosis. Whether the reason for this long-lasting improvement was pharmacological or merely the consequence of an increased awareness of the disease among the patients, resulting in the modification of eating habits, should also be subjected to further investigation. Interestingly, according to the medical records, none of the patients required the retrieval of an impacted bolus during the follow-up period, indicating that the incidents reported in the supplementary questionnaire were most likely transient and self-resolving. Consistent with this hypothesis, Kuchen *et al*. found in a study of 206 EoE patients (with a median follow-up period of five years) that oral topical corticosteroids resulted in a reduced risk (OR 0.41) of the occurrence of future esophageal bolus impaction.[47] In addition, the results of Study III showed that more than half of the patients required only one 2-month course of corticosteroid treatment after diagnosis, and that among the patients who reported repeated treatment, the majority had undergone only one, or less commonly, two extra courses of treatment. These findings, together with the improved scores obtained using the WDS scale and the EORTC QLQ OES-18 questionnaire, further supported the prolonged effect on dysphagia obtained after the initiation of treatment. The outcome of the WDS evaluation at the long-term

follow-up, not only showed a significant improvement compared with the conditions at the time of inclusion, but also demonstrated a deteriorated outcome compared with that after the 2-month course corticosteroid treatment. This finding indicated, quite reasonably, a slow but declining effect of the initial treatment over time and highlighted the superior ability of the WDS scale for detecting minor changes in dysphagia compared with that of the other scales used in this study. In other words, the WDS scoring of dysphagia for the nine ranked food items performed by the patients resulted in a higher sensitivity compared with that observed when the patients answered the three questions on the EORTC QLQ-OES18 Dysphagia questionnaire. Altogether, the WDS scale and the EORTC QLQ- OES18 questionnaire appear to be clinically useful instruments for surveillance over time and the detection of changes in dysphagia-related symptoms and the HRQL of EoE patients. However, using questionnaires that were specifically designed and therefore properly validated for EoE patients would unquestionably yield more reliable results in future studies. Taft *et al.* recently developed a quality of life questionnaire for evaluating adult EoE patients.[83] The validation analysis demonstrated reliable results for patients without a confirmed diagnosis, and according to the author, this questionnaire should be re-validated with patients who have been diagnosed according to the EoE-consensus recommendations. Just recently, Schoepfer *et al* developed and validated a symptom-based activity index instrument specifically for use in adults with EoE. [82]

EoE is defined as a clinicopathological disease and therefore both its symptoms and eosinophilia in the esophageal mucosa are required to meet the diagnostic criteria. In Study IV, we evaluated any potential correlation between the symptoms/HRQL and the histological findings of untreated patients with dysphagia and esophageal eosinophilia. An association would, at least theoretically, add credibility to the diagnostic criteria, particularly because eosinophils are likely to contribute to esophageal dysfunction.[81] Contrary to our initial hypothesis, no such correlation could be found regardless of level of the biopsies or the questionnaire used. Our findings were also somewhat contradictory to the results of Pentiuk *et al.*, who found a modest correlation between the symptoms and the peak distal eosinophil count (r^2=0.37) of a group of 15 untreated children and adolescents with EoE.[90] However, in that study, in which 49 subjects were evaluated using the pediatric EoE symptom score (PEESS), histological remission after treatment was associated with symptomatic improvement. In a placebo-controlled trial, Alexander *et al.* also demonstrated a similar inconsistent correlation between the effect of treatment on the symptoms and the eosinophil counts.[44]

The observed lack of correlation between the number of eosinophils observed and the severity of symptoms may be due to several factors, and a discrepancy was previously observed.[91] Although the diagnostic criteria of >15 eosinophils/HPF and the presence of symptoms of esophageal dysfunction has high sensitivity and specificity, EoE is known to be a patchy disease.[24, 92, 93] Straumann *et al.* reported that biopsy samples taken from regions of the mucosa with white exudates had a higher density of eosinophils compared with that in biopsy samples taken from the regions of mucosa with a normal endoscopic appearance. They also noted that a higher symptom score, as assessed through an interview, was associated with a higher occurrence of whitish exudates.[92] A future prospective study designed to evaluate this correlation through the use of disease-specific questionnaires and biopsy forceps that allow the collection of biopsy material not only from the superficial part of the mucosa but also from the underlying lamina propria, allowing an assessment of fibrosis development, would be desirable. The results of such a study would be likely to facilitate the evaluation of various treatment strategies and to increase the possibility of individualizing the management of EoE patients.

Although no correlation was found between symptom severity and the grade of eosinophilia in our study, subjects with concomitant bolus impaction were found to have a significantly higher number of eosinophils in the proximal part of the esophagus ($p<0.05$ based on HE staining and $p<0.05$ based on IHC staining), a finding that, to the best of our knowledge, has not been previously described. Whereas a possible explanation for this result might be the temporary irritation caused by the food bolus, followed by the recruitment of eosinophils from the blood supply, an increased peak value of eosinophils in the proximal part of the esophagus was previously suggested to have a greater diagnostic impact than the corresponding value in the distal part of this organ.[94, 95] Our findings thus could support greater attention being given to the proximal part of the esophagus of EoE patients.

The second aim of Study IV was to compare the eosinophil counts obtained using the standard HE staining method with those obtained using an IHC technique for detecting EMBP in the mucosa. Significantly higher eosinophil counts were obtained using IHC staining than were obtained using HE staining, a finding that is basically uncontroversial.[96, 97] Mueller *et al*. found a significantly higher number of intraepithelial eosinophils using (using antibodies directed against Major Basic Protein) IHC staining than with HE staining, in a study of 30 EoE patients.[96] This result was confirmed by the same authors in a study comparing the histological parameters of EoE and GERD.[97] Dellon *et al.* found that IHC staining distinguished EoE patients

from controls (patients examined endoscopically due to dysphagia or GERD symptoms), although using this method did not distinguish EoE patients from patients with PPI-REE.[98] Nevertheless, today HE staining is a well-established method, and more evidence is definitely needed before changing current practice. Prospective studies with firm diagnostic criteria comparing various mucosal staining techniques combined with inter-observer analyses could be fruitful steps in this direction.

7 CONCLUSIONS

The following conclusions could be drawn from the results of the studies described in this thesis:

- A seasonal variation in the incidence of esophageal bolus impaction was confirmed.
- The seasonal variation was pronounced in patients with a coexisting atopic diathesis.
- A causative effect of diagnosed or undiagnosed EoE on this seasonal variation might be suspected.
- Dysphagia-related symptoms and the HRQL improved significantly in EoE patients after a 2-month course of topical mometasone furoate treatment.
- A randomized placebo-controlled trial is warranted to assess the causality.
- A partial remission persisted more than one year after diagnosis and the discontinuation of medication.
- The WDS scale and the EORTC QLQ-OES18 questionnaire appeared to be sensitive instruments appropriate for the surveillance of EoE patients. However, proper validation studies are warranted.
- A lack of correlation between the symptoms/HRQL and the grade of mucosal eosinophilia was found in patients with dysphagia and esophageal eosinophilia.
- Acute bolus impaction was associated with an elevated grade of mucosal eosinophilia in the proximal part of the esophagus.

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APPENDIX

Appendix 1
Watson Dysphagia Scale

Watson Dysphagia Score

1	Water
2	Milk (or thin soup)
3	Custard (or yoghurt or pureed fruit)
4	Jelly
5	Scrambled egg (or baked beans or mashed potato)
6	Baked fish (or steamed potato or cooked carrot)
7	Bread (or pastries)
8	Apple (or raw carrot)
9	Steak (or pork or lamb chop)

The presence of any dysphagia for each liquid or solid substance is first deter- mined and scored; dysphagia always = 1 point, sometimes = 1/2 point, never = 0 points. A score from 0 (no dysphagia) to 45 (severe dysphagia) is then determined by multiplying the score for each substance by the adjacent line number, and then summing all nine lines.

Originally published:
Watson DI, Pike GK, Baigrie RJ, et al.
Prospective double-blind randomized trial of laparoscopic Nissen fundoplication with division and without division of short gastric vessels.
Ann Surg 1997; 226(5): 642-52.

Appendix 2
EORTC QLQ-OES18

EORTC QLQ – OES18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Could you eat solid food?	1	2	3	4
32.	Could you eat liquidised or soft food?	1	2	3	4
33.	Could you drink liquids?	1	2	3	4
34.	Have you had trouble with swallowing your saliva?	1	2	3	4
35.	Have you choked when swallowing?	1	2	3	4
36.	Have you had trouble enjoying your meals?	1	2	3	4
37.	Have you felt full up too quickly?	1	2	3	4
38.	Have you had trouble with eating?	1	2	3	4
39.	Have you had trouble with eating in front of other people?	1	2	3	4
40.	Have you had a dry mouth?	1	2	3	4
41.	Did food and drink taste different from usual?	1	2	3	4
42	Have you had trouble with coughing?	1	2	3	4
43.	Have you had trouble with talking?	1	2	3	4
44.	Have you had acid indigestion or heartburn?	1	2	3	4
45.	Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
46.	Have you had pain when you eat?	1	2	3	4
47.	Have you had pain in your chest?	1	2	3	4
48.	Have you had pain in your stomach?	1	2	3	4

Appendix 3
SF-36

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)

- Excellent ☐
- Very Good ☐
- Good ☐
- Fair ☐
- Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)

- Much better than one year ago ☐
- Somewhat better now than one year ago ☐
- About the same as one year ago ☐
- Somewhat worse now than one year ago ☐
- Much worse now than one year ago ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	**Yes, Limited A Lot**	**Yes, Limited A Little**	**Not Limited At All**
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Waling **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	(Please circle one number on each line.)	**Yes**	**No**
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?

	(Please circle one number on each line.)	**Yes**	**No**
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please circle one number on each line.)	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

	(Please circle one number on each line.)	**Definitely True**	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

Thank You!