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Management of eosinophilic esophagitis in daily clinical practice

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SUMMARY. **In recent years, new guidelines and recommendations have been published regarding the diagnostic criteria and therapeutic management of eosinophilic esophagitis (EoE). The aim of this study is to assess the diagnostic and therapeutic management of patients diagnosed with EoE in daily clinical practice and whether this was performed according to current guidelines and recommendations. A population-based, multicenter retrospective cohort study was conducted using data from the national pathology registry (PALGA), medical records, and telephone interviews of patients diagnosed with EoE in two academic and two nonacademic hospitals in the period 2004 to 2014. The study was approved by all involved ethical committees. Data regarding demographics, clinical manifestations, endoscopic results, histologic samples, and therapeutic strategies were collected. Standard statistical analyses were performed to summarize patient characteristics. We included 119 patients diagnosed with EoE in this study. The median age at onset of symptoms was 29 years (IQR: 15–42) and the median age at diagnosis was 38 years (IQR: 23–51 years), leading to a median diagnostic patients' delay of 6.5 years (IQR: 2–14 years). The median physicians' delay in diagnosis between first contact in the hospital and diagnosis was 1.0 year (IQR: 1–7 years). The incidence of newly diagnosed patients with EoE increased steadily over a period of 11 years. Criteria for the microscopic diagnosis of EoE varied between pathologists in each hospital. Initial treatment included topical corticosteroids (TCS) (30.3%), proton pump inhibitors (PPI) (29.4%), or a combination (10.1%). A follow-up endoscopy was performed in 40.3% of patients. During follow-up, treatment included PPIs (76.0%), TCS (59.6%), a combination of PPIs and TCS (45.4%), and endoscopic dilations (6.7%). Diagnostic and therapeutic discrepancies between daily clinical practice and recommendations from current and past guidelines were observed. Apart from developing guidelines, efforts should be undertaken to implement these in daily clinical practice.**

KEY WORDS: **cohort study, daily clinical practice, decision-making, eosinophilic esophagitis, guidelines.**

ABBREVIATIONS: EoE: eosinophilic esophagitis; GERD: gastro esophageal reflux disease; IQR: interquartile range; PALGA: national pathology registry; PPI: proton pump inhibitor; PPI-REE: proton pump inhibitor responsive esophageal eosinophilia; SD: standard deviation; TCS: topical corticosteroids

INTRODUCTION

Eosinophilic esophagitis (EoE) is a relatively novel disease, discovered and recognized just two decades ago.[1,2] Clinicians found that some patients with supposedly gastroesophageal reflux disease (GERD) did not respond to acid suppression, but did respond to an elimination diet to decrease their symptoms of dysphagia and esophageal eosinophilia.

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EoE is currently defined as a chronic, immune-mediated or antigen-mediated esophageal disease characterized by symptoms related to esophageal dysfunction and eosinophil-predominant inflammation.[3] Epidemiologic data from two studies in the Netherlands[4] and Switzerland[5] show a rising incidence of 1.31/100.000 in 2010 in the Netherlands and respectively 6.3/100.000 in 2013 in Switzerland. Most patients are males, with a male to female ratio of 2.8 to 1[5] and a peak incidence in the age group of 30 to 39 years.[4]

Since the discovery of EoE three consecutive guidelines[6–8] on diagnostic and therapeutic management have been developed. The most recent guideline was published by Dellon *et al.*[8] in 2013. Recently, the diagnostic and therapeutic management has changed to some extent through the recognition of the subentity proton pump inhibitor responsive esophageal eosinophilia (PPI-REE).[9] To diagnose PPI-REE, an eight week PPI trial and a follow-up endoscopy after the trial is recommended to evaluate PPI responsiveness and thus therapeutic consequences.[8]

Until now limited data are available on clinical management of adult patients with EoE in the daily clinical practice of the Netherlands. We wondered whether the management of EoE has been in line with the development of international guidelines and recommendations since a delay in diagnosis may have considerable consequences for the patient if no appropriate timely treatment is provided. It is known that an increased risk of benign stricture formation is correlated with the duration of untreated disease.[10] Therefore, the aim of this study is to assess the diagnostic and therapeutic management of patients diagnosed with EoE in daily clinical practice and whether this was performed according to guidelines and recommendations.

METHODS

Study design, patient population, and data collection

A multicenter retrospective cohort analysis was performed in patients from two academic hospitals and two nonacademic hospitals. All patients diagnosed with EoE in the participating hospitals between January 2004 and December 2014 were identified from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA).[15] The registry was scrutinized for the diagnostic code 'eosinophilic esophagitis' and synonyms, or one of the search terms including 'eosinophi'. If the pathologist considered microscopic EoE in the differential diagnosis, the patient was evaluated more thoroughly with use of the medical records. Subsequently, the identified patients were selected for inclusion in the analysis if they met the inclusion criteria: (1) symptoms related to esophageal dysfunction at the time of histologic diagnosis EoE; and (2) diagnosis of EoE in biopsies of esophageal mucosa according to the evaluating pathologist in the particular hospital; and (3) no other cause of esophageal eosinophilia (eosinophilic gastrointestinal disease, Celiac disease, Crohn's disease, infection, hypereosinophilic syndrome, achalasia, drug hypersensitivity, vasculitis, pemphigus, connective tissue disease, graft vs. host disease);[3] and (4) current age $\geq$18 years. After inclusion, data were collected regarding demographic characteristics: clinical manifestations, endoscopic characteristics, histologic characteristics, and therapeutic characteristics.

Additional information regarding patient characteristics was obtained via a telephone interview. In addition, patients' informed consent was obtained for the telephone interview. The aim of the telephone interview was to obtain information on current clinical manifestations and additional information on patients' natural history, severity of symptoms, treatment and missing data.

Primary outcomes and definitions

We used the following endpoints: (1) initial treatment after diagnosis of EoE; and (2) all treatment modalities regarding treatment of EoE during follow-up of patients; and (3) delay in diagnosis from onset of symptoms related to esophageal dysfunction (patients' delay) and from the first visit to any physician to evaluate symptoms related to esophageal dysfunction (physicians' delay).

EoE was defined as a clinicopathologic diagnosis. At the time of diagnosis, the patient was required to have clinical manifestations related to esophageal dysfunction (dysphagia, food impaction, chest-pain, or regurgitation) and to have a microscopic diagnosis of EoE. Each participating pathologist diagnosed microscopic EoE according to their local criteria. Patients diagnosed with PPI-REE were defined as EoE patients. Dysphagia was defined as the difficulty of swallowing solid or liquid foods passing the esophagus into the stomach. Food impaction was defined as the sensation of food bolus obstruction in the esophagus. Chest pain was defined as pain located central or retrosternal on the chest following on consuming food. Regurgitation was defined as reflux of swallowed foods in the oropharyngeal cavity. Heartburn, also known as pyrosis, was defined as a retrosternal or epigastric burning sensation in the chest or upper abdomen. Atopic constitution was defined as a history of clinical manifestations related to atopic asthma, allergic rhinoconjunctivitis, food allergy, and atopic dermatitis.

The diagnostic delay was defined as the time interval between symptom onset related to esophageal dysfunction and the moment of EoE diagnosis made. The delay in diagnosis in the medical circuit (physicians' delay) was defined as the time interval between

the moment of first visit to any physician by the patient for symptoms of esophageal dysfunction and the moment of EoE diagnosis made. Follow-up time was defined as the time interval between date of diagnosis and date of the telephone interview.

An overview of the diagnostic and therapeutic recommendations from the three consecutive EoE guidelines is listed in Supplementary Table S1.

Statistical analysis

Data from the medical records and telephone interviews were analyzed with the SPSS 21.0 statistical analysis package (SPSS Inc., Chicago, Illinois, USA) for Windows. The analysis of results consisted of standard descriptive statistics: (1) categorical data are expressed as frequency and percentage; and (2) continuous data as mean and standard deviation (SD) or median and interquartile range (IQR). The Pearson Chi-Square and the one-way analysis of variance (ANOVA) test are used to determine differences in treatment modalities between academic and nonacademic centers. The McNemar test is used to determine differences in a nominal dependent dichotomous variable between two paired outcome measures. Differences were considered statistically significant when p was less than 0.05.

Ethical considerations

The study was approved by the local ethics committees in all participating hospitals. Patient consent was required for each telephone interview. Informed consent was obtained at the beginning of the telephone interview or written with a signed form returned by mail prior to the telephone interview.

RESULTS

The search in PALGA identified a total of 214 patients with a possible diagnosis of EoE. After selection, a total of 119 patients diagnosed with EoE in the four participating hospitals were enrolled in the analysis. We excluded patients without microscopic EoE ($n = 45$), pediatric patients ($n = 38$), and patients with reflux esophagitis ($n = 12$). In one academic hospital, patients were diagnosed with the subentity PPI-REE. Figure 1 shows the flowchart with the distribution per hospital. Figure 2 shows the total annually incidence of newly diagnosed patients with EoE in the participating hospitals between 2004 and 2014. The incidence steadily increased with one case in 2004 and 18 cases in 2014.

Patient and disease characteristics are listed in Table 1. The majority of patients were male (79.8%) and the median age at diagnosis was 38 years (IQR: 23–51 years) with a median age at onset of symptoms of 29 years (IQR: 15–42 years). The median patients' delay was 6.5 years (IQR: 2–14 years). The median doctor delay was 1.0 year (IQR: 1–7 years). The most frequent symptoms of esophageal dysfunction at the time of diagnosis were dysphagia for solid foods (95.0%) and food impactions (72.6%). Atopic constitution was present in more than half of

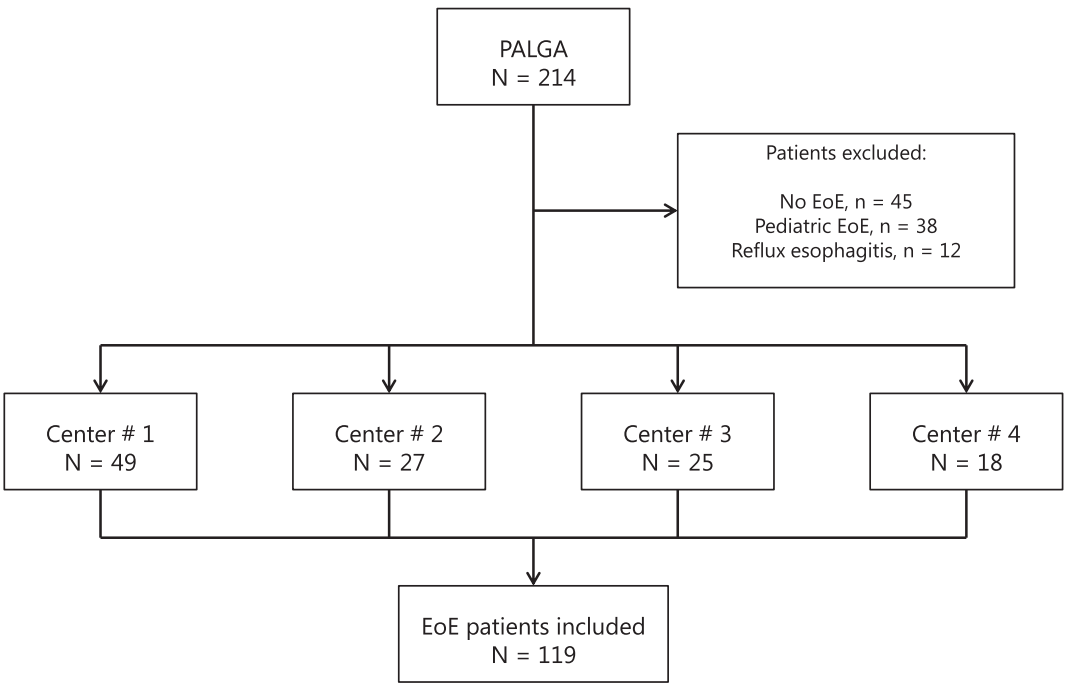

Fig. 1 Flowchart of EoE patient selection in four centers. EoE, eosinophilic esophagitis; PALGA, national pathology registry.

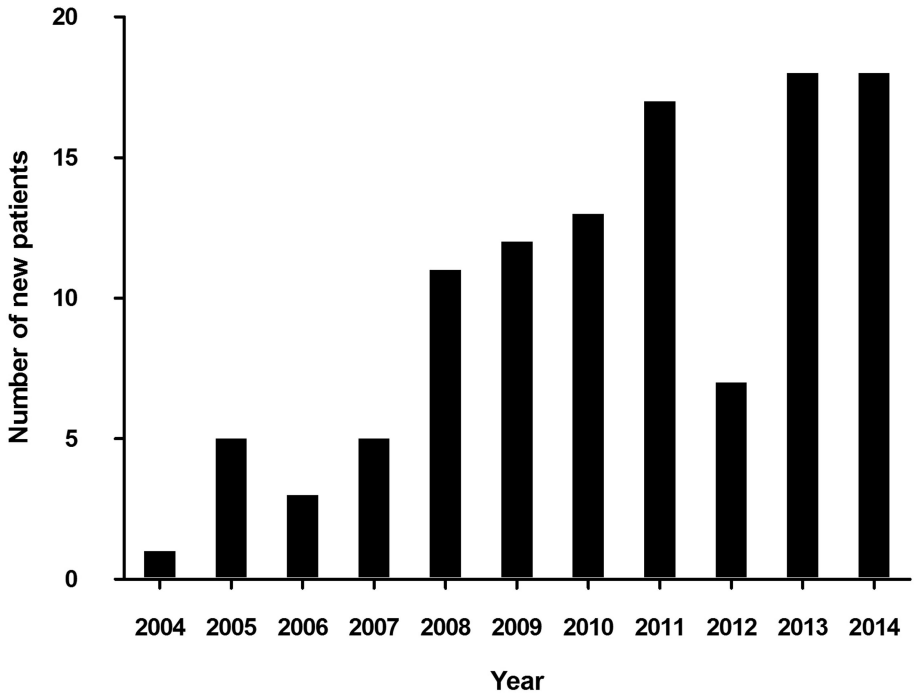

Fig. 2 Incidence of eosinophilic esophagitis over time, with years (2004–2014) on the x-axis and number of new EoE patients on the y-axis.

Table 1 Patient and disease characteristics of patients with EoE

Number of patients, *n*	119
Male gender (*n*, %)	95 (79.8)
Age (years) at diagnosis, median (IQR, range)	38 (23–51, 7–88)
Age (years) at symptom onset, median (IQR, range)	29 (15–42, 0–71)
BMI, mean ± SD, [range]	25.0 ± 4,4 [14.6–43.3]
Smoking, *n* (%)	14 (14.0)
Alcohol, *n* (%)	48 (48.0)
Symptoms at diagnosis (*n*, %)	
Dysphagia solids	113 (95.0)
Food impaction	85 (72.6)
Heartburn	48 (41.0)
Chest pain	44 (37.6)
Regurgitation	41 (35.0)
Dysphagia liquids	27 (23.1)
Dyspeptic symptoms	10 (8.5)
Weight loss	8 (6.8)
Atopic constitution (*n*, %)	
Asthma	68 (61.3)
Allergic rhinoconjunctivitis	45 (40.9)
Atopic dermatitis	27 (24.8)
Food allergy	29 (26.1)

BMI, body mass index; EoE, eosinophilic esophagitis; IQR, interquartile range; *n*, number of patients; %, percentage; SD, standard deviation.

patients (61.3%). At the time of diagnosis, inflammatory and fibrotic findings at endoscopy typical for EoE were present in the majority of patients (87.4%). The most frequent findings were esophageal corrugated rings (69.7%). An esophageal stricture or stenosis was observed in 30.3% of patients.

The pathologists of the participating hospitals were requested to state their diagnostic criteria for microscopic EoE prior to analysis of the study results. The results per hospital are listed in Table 2. As can be seen, there is heterogeneity in criteria utilized by each pathologist. One pathology group used the currently recommended diagnostic criteria for microscopic EoE. The other groups did not use the diagnostic criteria for microscopic EoE that are currently recommended by the most recent guidelines.[8]

Endoscopic and therapeutic results during follow-up

The initial treatment modalities after EoE diagnosis are shown in Table 3. In 6 patients (5.0%), treatment

Table 2 Criteria for microscopic EoE diagnosis per center

Center	Criteria
Center #1	≥15 eos in ≥1 HPF 20–25 eos in 1 HPF Biopsy taken at random location
Center #2	≥15 eos in 1 HPF ≥1 biopsies taken at random location Combination with degranulation
Center #3	≥15 eos in 1 HPF Biopsy taken at random location
Center #4	≥15 eos in ≥2 HPFs ≥1 HPF proximal, ≥1 HPF distal esophagus 1 HPF ≥15 eos in distal esophagus: GERD in DDx

DDx, differential diagnosis; EoE, eosinophilic esophagitis; eos, eosinophils; HPF, high power field.

Table 3 Initial treatment modality of patients after EoE diagnosis

Treatment modality	Total, *n* (%) (*n* = 119)	Center #1, *n* (%) (*n* = 49)	Center #2, *n* (%) (*n* = 27)	Center #3, *n* (%) (*n* = 25)	Center #4, *n* (%) (*n* = 18)	*P*-value*
TCS	36 (30.3)	17 (34.7)	5 (18.5)	11 (44.0)	3 (16.7)	0.17
PPI	35 (29.4)	16 (32.7)	8 (29.6)	4 (16.0)	7 (38.9)	0.31
PPI + TCS	12 (10.1)	5 (10.2)	1 (3.7)	4 (16.0)	2 (11.1)	0.49
Dilation	3 (2.5)	0	2 (7.4)	0	1 (5.6)	NS
Prednisone	2 (1.7)	0	1 (3.7)	1 (4.0)	0	NS
TCS + dilation	1 (0.8)	1 (2.0)	0	0	0	NS
Diet	0	0	0	0	0	NS
None	24 (20.2)	9 (18.4)	8 (29.6)	4 (16.0)	3 (16.7)	NS
Missing	6 (5.0)	1 (2.0)	2 (7.4)	1 (4.0)	2 (11.1)	NS

PPI, proton pump inhibitor; *n*, number of patients; %, percentage; NS, not significant; TCS, topical corticosteroids.
*One-way analysis of variance (ANOVA) test.

data were not available. A total of 36 patients (30.3%) was initially treated with TCS, 35 patients (29.4%) with PPIs, 12 patients (10.1%) with a combination of TCS and PPIs, 3 patients (2.5%) underwent an endoscopic dilation, 1 patient (0.8%) underwent an endoscopic dilation of the esophagus and treatment with TCS, and no patients were put on a therapeutic diet. A total of 24 patients (20.2%) did not receive any treatment at the time of the EoE diagnosis. The differences between the participating hospitals are further specified in Table 3. No significant differences in initial treatment modalities between the participating hospitals were observed.

Endoscopic findings at diagnostic and follow-up endoscopy are listed in Table 4. Less than half of patients (39.5%) underwent a follow-up endoscopy. During follow-up endoscopy, inflammatory and fibrotic findings typical for EoE were observed in most patients (75.0%). The most frequently observed finding was esophageal corrugated rings (61.7%). A stricture or stenosis of the esophagus was seen in 27.7% of patients. Data on localization of biopsies were not reported in 55.0% of diagnostic endoscopies and 44.7% of follow-up endoscopies.

All cumulative treatment modalities during follow-up in total and per participating hospital are listed in Table 5. A total of 90 patients (76.0%) were treated with PPIs during follow-up, 71 patients (59.6%) with TCS, 9 patients (7.6%) were put on any therapeutic diet, 8 patients (6.7%) underwent an endoscopic dilation, 8 patients (6.7%) received systemic prednisone, and 3 patients (2.5%) received no treatment during follow-up. Moreover, a total of 54 patients (45.4%) were treated with a combination of PPIs and TCS, 41 patients (34.5%) were treated with PPIs only and 17 patients (14.3%) with TCS only. The differences in treatment modalities between the participating hospitals are further specified in Table 5. Significant differences between the participating hospitals were observed in PPI treatment ($P < 0.001$), TCS treatment ($P = 0.03$), only PPI treatment ($P = 0.01$) and only TCS treatment ($P < 0.001$). Significant differences between the academic and nonacademic hospitals were observed in PPI treatment ($P = 0.02$), dietary treatment ($P = 0.02$) and only TCS treatment ($P = 0.01$) (Table 5).

Telephone interview

A telephone interview was conducted in a total of 86 patients (72%), while 33 patients (28%) did not respond or refused a telephone interview. The median follow-up was 56 months (IQR: 27–83 months). Symptoms and behavioral adaptations related to

Table 4 Endoscopic characteristics of EoE patients at diagnostic and second endoscopy

	Diagnostic endoscopy, *n* (%) 119 (100)	Second endoscopy, *n* (%) 47 (39.5)
Endoscopic findings (%)		
Normal	12.6	25.0
Rings	69.7	61.7
Whitish exudates or papulae	42.9	38.3
Linear furrows	46.2	39.6
Crepe paper mucosa	11.8	10.6
Narrowing	6.7	8.5
Stenosis or stricture	30.3	27.7
Location biopsies (%)		
Proximal + distal	36.1	42.6
Proximal only	7.6	4.3
Distal only	3.3	8.5
Not reported	55.0	44.7

n, number of patients; %, percentage.

Table 5 Cumulative treatment modalities in EoE patients during follow-up

Treatment modality	Total, *n* (%) (*n* = 119)	Center #1, *n* (%) (*n* = 49)	Center #2, *n* (%) (*n* = 27)	Center #3, *n* (%) (*n* = 25)	Center #4, *n* (%) (*n* = 18)	*P*-value*
Follow-up (months), median (IQR, range): 56 (27–83, 3–252)						
PPI	90 (76.0)	42 (86.0)	20 (74.0)	13 (52.0)	15 (83.0)	<0.001
TCS	71 (59.6)	32 (65.1)	11 (41.0)	22 (88.0)	6 (33.3)	0.03
Diet	9 (7.6)	7 (14.3)	2 (7.4)	0 (0.0)	0 (0.0)	0.55
Dilation	8 (6.7)	2 (4.1)	3 (11.1)	1 (4.0)	2 (11.1)	0.13
Prednisone	8 (6.7)	1 (2.0)	5 (18.5)	2 (8.0)	0 (0.0)	0.84
None	3 (2.5)	2 (4.1)	1 (3.7)	0 (0.0)	0 (0.0)	0.74
Combination or monotherapy with TCS and PPI						
PPI + TCS	54 (45.4)	28 (57.1)	9 (33.3)	11 (44.0)	6 (33.3)	0.15
PPI only	41 (34.5)	14 (28.6)	14 (51.9)	4 (16.0)	9 (50.0)	0.01
TCS only	17 (14.3)	4 (8.2)	2 (7.4)	11 (44.0)	0 (0.0)	<0.001

Treatment modality	Total, *n* (%) (*n* = 119)	AC, *n* (%) (*n* = 76)	Non-AC, *n* (%) (*n* = 43)	*P*-value**
Follow-up (months), median (IQR, range): 56 (27–83, 3–252)				
PPI	90 (76.0)	62 (81.6)	28 (65.1)	0.02
TCS	71 (59.6)	43 (56.6)	28 (65.1)	0.28
Diet	9 (7.6)	9 (11.8)	0 (0.0)	0.02
Dilation	8 (6.7)	5 (6.6)	3 (7.0)	0.93
Prednisone	8 (6.7)	6 (7.9)	2 (4.7)	0.47
None	3 (2.5)	3 (3.9)	0 (0.0)	0.19
Combination or monotherapy with TCS and PPI				
PPI + TCS	54 (45.4)	37 (48.7)	17 (39.5)	0.28
PPI only	41 (34.5)	28 (36.8)	13 (30.2)	0.51
TCS only	17 (14.3)	6 (7.9)	11 (25.6)	0.01

AC, academic centers; *n*, number of patients; NS, not significant; %, percentage; PPI, proton pump inhibitor; TCS, topical corticosteroids.
*One-way analysis of variance (ANOVA) test.
**Pearson Chi-Square test.

esophageal dysfunction at the time of the telephone interview were present in 76.0% of patients and are listed in Table 6. The severity of symptoms related to esophageal dysfunction at the time of the telephone interview is listed in Table 7. The most frequently mentioned symptom was dysphagia in 61.8%, while 23.3% of patients had no symptoms of esophageal dysfunction. When compared to symptoms at the time of EoE diagnosis (Table 6), dysphagia for solid foods ($P < 0.001$), food impaction ($P < 0.001$), heartburn ($P = 0.04$), and dyspepsia ($P = 0.04$) showed significant difference. However, symptoms at diagnosis were doctor-reported outcomes from the medical records and symptoms at follow-up are patient-reported outcomes.

DISCUSSION

This multicenter retrospective cohort study demonstrates heterogeneity in diagnostic and therapeutic management of patients with EoE in two academic and two nonacademic hospitals in the Netherlands in the period between 2004 and 2014.

Table 6 Symptoms and behavioral adaptations related to esophageal disfunction in EoE patients at diagnosis and follow-up (telephone interview)

Total patients	Diagnosis, *n* (%)	Follow-up, *n* (%)	*P*-value
Symptoms	119 (100%)	86 (72%)	
Dysphagia solids	113 (95.0)	47 (61.8)	<0.001
Food impaction	85 (72.6)	28 (36.8)	<0.001
Heartburn	48 (41.0)	26 (34.2)	0.04
Chest pain	44 (37.6)	28 (36.8)	0.54
Regurgitation	41 (35.0)	36 (47.3)	0.74
Dysphagia liquids	27 (23.1)	12 (15.7)	0.06
Dyspeptic symptoms	10 (8.5)	14 (18.4)	0.04
No symptoms	0 (0.0)	20 (23.3)	<0.001
Behavioral adaptations			
Washing food down	NR	50 (58.1)	
Eating slowly	NR	37 (43.0)	
Choke/cough/vomit	NR	12 (14.0)	
None	NR	24 (28.0)	

n, number of patients; NR, not reported; %, percentage.

Table 7 Severity of symptoms related to esophageal dysfunction in EoE patients at follow-up (telephone interview)

	Severity of symptoms in EoE patients ($n = 86$), *n* (%)			
Symptom	Every meal	Daily	Sometimes	Never
Dysphagia solids	6 (7.0)	9 (10.5)	36 (41.9)	35 (40.7)
Dysphagia liquids	0 (0.0)	4 (4.7)	9 (10.5)	73 (84.9)
Food impaction	1 (1.2)	7 (8.1)	21 (24.4)	57 (66.3)
Regurgitation	1 (1.2)	5 (5.8)	33 (38.3)	47 (54.7)
Chest pain	0 (0.0)	7 (8.1)	24 (27.9)	55 (64.0)

EoE, eosinophilic esophagitis; *n*, number of patients; %, percentage.

Figure 2 displays a rising annual incidence of newly diagnosed patients with EoE during the last decade. Three other Western European studies that investigated the incidence of EoE came to comparable results.[4,5,11] Other cohort studies describe similar results on demographic, clinical, endoscopic, and histologic characteristics compared to our patient population.[5,10,12–16] A noteworthy difference in our cohort as compared to other cohorts[5,13,16] is the number of patients suffering from heartburn at diagnosis (48 patients, 41%).

A median patients' delay of 6.5 years (IQR: 2–14 years) was observed from onset symptoms related to esophageal dysfunction to time of diagnosis. This finding is consistent with other studies that investigated patients' delay[10,16] and can likely be explained by the patients' ability to adapt their eating behavior in order to alleviate the symptoms of esophageal dysfunction.[17] All patients that reported any symptoms of esophageal dysfunction (76.0%) also reported to have developed behavioral adaptations to their symptoms (Table 6).The median delay in diagnosis between first contact in the hospital and diagnosis was 1.0 year (IQR: 1–7 years). This type of diagnostic delay has not been described in previous studies and is suggestive of a doctors' delay in recognizing and diagnosing EoE, mainly general practitioners and gastroenterologists.

Considerable differences in diagnostic management were observed in daily clinical practice between the participating centers. Only one hospital considered PPI-REE in their diagnostic work-up and 11 patients were diagnosed with PPI-REE. The other participating hospitals never mentioned PPI-REE in the patients' medical charts. To put this in perspective, the third guideline by Dellon *et al.*[8] of April 2013 recommends diagnosing PPI-REE in patients that clinically and histologically respond to PPIs. This guideline recommends PPI-REE to be considered in each patient suspected of EoE. To diagnose PPI-REE, an 8-week PPI trial and a second endoscopy to evaluate the effect of PPI treatment on symptoms and histology is recommended.[8] Furthermore, Molina-Infante *et al.*[18] recently advised to start a trial of PPIs in every patient because of the similar endoscopic and inflammatory effects of PPI treatment in PPI-REE patients compared with steroids in patients with EoE.

Another difference in the diagnostic management is observed in the criteria for microscopic EoE. As listed in Table 2, a considerable heterogeneity existed between the pathologists of the participating hospitals. Only one pathology group used the recommended criteria for microscopic EoE. The other pathology groups used criteria that partly contradicted the currently recommended criteria. Interestingly, most differences were observed in the localization of the

esophageal biopsies (Table 2). This diagnostic discrepancy on biopsy location was observed in the practice of endoscopists. Data on localization of the diagnostic esophageal biopsies in the endoscopic report were not reported in more than half of patients (55.0%). To put this in perspective once more, the two latest guidelines from 2011[7] and 2013[8] recommend that esophageal biopsies should be taken from the proximal and distal esophagus. This suggests the unawareness of the recommended criteria for the microscopic diagnosis EoE at the level of both the pathologist and the gastroenterologist.

Considerable differences in therapeutic management were observed in daily clinical practice between the participating centers. When the clinicopathologic diagnosis EoE is confirmed, a wide variety of therapies was initiated (Table 3). This variety in therapy continues during follow-up (Table 5). However, the observed heterogeneity in the initial therapeutic approach is not surprising since three consecutive guidelines, that recommend significantly different diagnostic and therapeutic strategies (Supplementary Table S1), were published over the course of the studied period. Overall, TCS and PPIs were the most commonly used treatment modalities for EoE. At the time of EoE diagnosis, 12 of 47 (25.5%) patients that received PPIs as initial therapy were already on PPIs before EoE diagnosis. Remarkably, in the nonacademic setting, no dietary treatment modalities were prescribed, in contrast to the academic setting where 11.8% of patients were put on an elimination diet.

This study has various strengths. In contrast to other studies, our study is the first to assess the daily clinical practice of EoE management over an extensive 11-year period. Additionally, the patient population was selected in both the academic and nonacademic setting. Using telephone interviews in nearly three-quarter of patients (72%), certain incomplete data from the patients' medical charts were obtained and an accurate collection of data such as time at symptom onset, first contact with a doctor for esophageal dysfunction, current symptoms, and behavioral adaptations was achieved.

The main limitation of this study is the retrospective design. In most cases, this resulted in missing data concerning treatment characteristics (e.g. dosage and duration) and treatment outcome. Due to this, we were not able to assess factors associated with treatment decisions and treatment outcomes.

The observations from this study present an overview of the diagnostic and therapeutic management in daily clinical practice. Our results demonstrate trends that are suggestive of still limited awareness of the current guidelines and recommendations among gastroenterologists and pathologists. To increase the awareness of EoE among gastroenterologists, appropriate education on the most recent guidelines and recommendations is desired. Furthermore, a standardized protocol to diagnose microscopic EoE should be implemented in daily practice of pathologists.

In conclusion, our multicenter retrospective cohort study shows that various diagnostic and therapeutic strategies were utilized in EoE, and that these strategies were often not consistent with the current guidelines and recommendations. Our results indicate that, apart from developing clear guidelines, efforts should be undertaken to implement them in daily clinical practice.

SUPPLEMENTARY DATA

Supplementary data are available at *DOTESO* online.

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