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Alimentary Tract

Diagnostic and therapeutic management of eosinophilic oesophagitis in children and adults: Results from a Spanish registry of clinical practice

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ABSTRACT

Background: Eosinophilic oesophagitis has emerged as a common cause of oesophageal symptoms.
Aims: To document practice variation in care provided to eosinophilic oesophagitis patients in Spain and to assess adherence to available guidelines.
Methods: A prospective survey-based registry including data from all patients receiving care from gastroenterologists and allergists throughout Spain was developed.
Results: Data from 705 patients (82% adults, male:female ratio 4.1:1) were collected from 26 Spanish hospitals. 42.7% received care in teaching hospitals. Adults presented dysphagia and food impaction more frequently; vomiting and weight loss predominated in children ($p < 0.01$). A mean diagnostic delay of 54.7 and 28.04 months was documented for adults and children, respectively. Normal endoscopic exams were reported in 27.6% and directly related to the experience in managing the disease ($p < 0.05$). Paediatric patients, non-teaching hospitals and greater experience in managing eosinophilic oesophagitis were associated with increased frequency in eosinophil count reports and with taking gastric and duodenal biopsies ($p < 0.001$).

Initial therapy consisted of topical steroids (61.7% of patients), proton pump inhibitors (52.4%), dietary modifications (51.26%) and endoscopic dilation (7.2%). Referrals to allergy units occurred more frequently in teaching hospitals ($p = 0.003$) where food restrictions generally followed allergy test results ($p < 0.001$).
Conclusions: Availability of facilities and the physician's experience constituted the most important factors in explaining differences in patient management.

1. Introduction

Eosinophilic oesophagitis (EoE) is a chronic, food allergy-associated, inflammatory disease characterized clinically by symptoms related to oesophageal dysfunction and histologically by an eosinophil-predominant inflammation [1]. EoE persists from childhood into adulthood [2] and has exhibited a rapidly increasing epidemiology, with the prevalence for EoE in Europe and the USA ranging from 43 to 55 affected patients per 100,000 inhabitants [3–5]. Today, EoE is the second leading cause of chronic oesophagitis after gastro-oesophageal reflux disease (GORD) [6] and the most frequent cause of dysphagia in young patients. Cases of EoE have been reported throughout the world, including in Europe [4,7–13], Canada [14], the United States [3,15], Brazil [16], Japan [17], Australia [18], and China [19]. EoE also has a great impact on several psychological and social domains [20], with three quarters of patients expressing a significantly worse health-related quality of life (QoL) than control subjects [2].

Up until five years ago, the diagnosis of EoE depended upon demonstrating oesophageal eosinophilic infiltration in endoscopic biopsy samples taken of patients with upper digestive tract-related

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symptoms. However, diagnostic criteria have evolved with the publication of consensus recommendations in 2007 [21] and their recent update in 2011 [1], calling for a multidisciplinary approach to EoE patients. Currently, the diagnostic criteria for EoE include symptoms of oesophageal dysfunction, ≥15 eos/hpf and either a lack of histological response to PPI therapy or normal pH monitoring. Nevertheless, the majority of research conducted on EoE to date has not confirmed the validity of these criteria [22].

No studies have compared the different therapeutic strategies used to manage the disease [23] and there is limited information on the sustained effect of different treatment modalities in terms of disease remission, health-related QoL and costs for health systems. These limitations may partly account for the wide variability in current clinical practice [24,25], as neither the way in which different diagnostic and therapeutic options are used in clinical practice nor their results have been extensively assessed.

In fact, no study has assessed the practice patterns of medical care providers for EoE patients in Europe in general or Spain in particular.

In order to document and understand the clinical presentation of EoE in Spain as well as practice variability in its diagnosis, management and treatment, and to compare these practices with the available guidelines, we conducted a nation-wide survey targeted at adult and paediatric gastroenterologists and allergists. As the first multicentre case registry in Europe, we hope that this research will publicize the need for additional clinical trials, consensus and guideline development and education about the disease so that we can better understand the real situation of patients suffering from EoE in our country.

2. Patients and methods

2.1. Study design

This was a prospective survey-based study promoted by the Castilian Association of Digestive Diseases *(Asociación Castellana de Aparato Digestivo* or *ACAD)* and conducted between December 2010 and June 2012 with the help of gastroenterologists and allergists. The self-administered forms were sent via e-mail and by regular post to all member physicians of the ACAD. Additional mailings were sent to physicians from all the regions of Spain, including those working in paediatric and adult gastroenterology and allergy departments involved in EoE care, with and without published experience or presentations in managing this disease. The form was also available on-line on the ACAD web page (www.acad.es). One form per patient was filled out with the help of clinical record data. In order to avoid bias, researchers were asked to include all EoE patients whom they had attended in their respective practices. The information provided on the returned forms was introduced into a database by the study coordinators, avoiding duplicated information.

In order to assess findings across a spectrum of practice patterns, both university/academic/teaching and non-university/non-academic/non-teaching hospitals were included. The degree of expertise in managing EoE patients was arbitrarily classified into 3 stages according to the number of patients receiving care from each reporting physician (regardless of his/her medical speciality): (1) 0–10 patients, (2) 11–20 patients and (3) >20 patients.

2.2. Form design

The form was composed of 71 questions which assessed nine categories for each individual patient: (1) demographic data, reporting physician, department and hospital data; (2) family and (3) personal allergy background; (4) clinical characteristics of EoE (symptoms and duration), endoscopic findings at diagnosis and previous endoscopic exams; (5) histopathologic evaluation; (6) manometry and pH-metry; (7) initial treatment for EoE; (8) laboratory and allergy test results; (9) EoE evolution and follow-up.

2.3. Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Research Committee at Tomelloso General Hospital and the Scientific Society sponsoring it.

2.4. Data analysis

Means and standard deviations were reported for continuous variables. Proportions were reported for categorical data. Comparisons between groups were performed with the chi square test for nominal variables and the Student's *t*-test for quantitative variables.

All significance tests were two-tailed, with alpha values < 0.05 considered significant. Analyses were performed with PASW v18.0 software (SPSS, Inc., Chicago, IL).

3. Results

3.1. Demographic and clinical data

At the moment of result analysis (July 31, 2012), data had been collected from 705 EoE patients, 578 of whom were adults (82%), and from 26 different Spanish hospitals (Table S1, Figure S1). Overall, 301 patients (42.7%) received care at teaching hospitals. Most recruited patients (608 or 86.2%) came from highly experienced physicians (degree 3) who had attended ≥ 20 EoE patients. A minority of patients were reported by physicians either with a low (44 patients, 6.2%) or a medium degree of experience (53 patients, 7.5%) in managing EoE.

A progressive increase in diagnosed cases was documented from 2004 to 2011 (Figure S2), with no age-related differences. Thus, 85% of all patients were diagnosed with EoE within the last 5 years. The male/female ratio was 4.1:1, with no differences between age groups. Age at diagnosis was 36 years (SD: 12.2; range: 16–84) for adult patients and 9 years (SD: 3.8; range 0–15) for paediatric patients. Table 1 provides the most relevant clinical characteristics of the registered patients.

The symptoms reported by patients showed significant differences between age groups, with dysphagia and pyrosis being significantly more frequent in adults ($p < 0.001$) while vomiting and weight loss were observed mainly in children ($p < 0.01$) (Table 2). The mean time of evolution of symptoms before reaching a diagnosis of EoE was longer for adults (54.7 ± 62 months) than for children (28.04 ± 30 months) ($p < 0.001$).

3.2. Endoscopic, histopathological and motility/pH monitoring evaluation

A total of 35.1% of patients (33.8% of children and 35.4% of adults) had already undergone an endoscopic exam because of their symptoms before a diagnosis of EoE was reached: these patients underwent a mean of 1.63 (range 1–12) endoscopies before a final diagnostic exam was conducted.

With regard to the endoscopic examination which led to a diagnosis of EoE, 23.2% of patients showed some degree of narrowing in oesophageal calibre, with oesophageal rings present in 50.6% of patients. Regarding alterations in the appearance of the mucosal surface, some type of abnormality was noted in 72.1% of patients. Most interestingly, 22.6% of endoscopic exams revealed no alterations in either the oesophageal calibre or the appearance of the

Table 1
Clinical characteristics of eosinophilic oesophagitis patients included in the Spanish registry.

Characteristics	No. (%)
Age (years) mean (SD) [rank]	31.2 (15.2) [0–84]
Gender, M/F	567 (80.4)/138 (19.6)
Personal background of allergy	
Rhinoconjunctivitis	307 (47.4)
Drug allergy	33 (5.1)
Bronchial asthma	212 (32.8)
Dermatitis	39 (6)
Food allergy/sensitization	166 (25.7)
Family background of atopy	166 (23.2)
Symptom evolution time (months) mean (SD) [rank]	50.72 (59.54) [0–360]
Symptoms	
Dysphagia	530 (76.1)
Food impaction	437 (62.8)
Heartburn	183 (26.3)
Chest pain	110 (15.8)
Vomiting	62 (8.8)
Weight loss	19 (2.7)
Endoscopy	
Oesophageal rings	351 (50.6)
Normal mucosal appearance	192 (27.9)
Hiatus hernia	191 (27.6)
Reduced oesophageal calibre	160 (23.2)
Peak eosinophil count/hpf, mean (SD) [rank]	36.5 (30.2) [12–350]

SD, standard deviation; M/F, male/female ratio.

mucosal surface. Both an altered calibre and mucosal abnormalities were more frequently reported by medium- or highly-experienced doctors compared to those with a lesser degree of experience in managing EoE patients ($p < 0.05$) (Table 3).

The current EoE consensus recommends that peak eosinophil counts be obtained from the most densely populated hpf, and that some additional histological features be evaluated and noted in pathology reports. Although all registered patients fulfilled the currently recommended 15 eos/hpf as a cut-off point for a diagnosis of EoE, only 51.1% of the pathology reports displayed exact peak eosinophil counts (documenting 51.97 ± 33.5 eosinophils/hpf), which were more frequently provided for children than for adults ($p = 0.001$), and came more often from non-teaching hospitals (67.3% compared to 29.9%; $p < 0.001$) and from highly-experienced physicians (54.7% compared to <30% for specialists with a medium or low degree of experience; $p < 0.001$) (Table 3). Additional EoE-associated histological features were hardly ever reported.

The consensus guidelines also recommend that gastric antrum and duodenal biopsies be obtained at least once in children to rule out eosinophilic gastroenteritis. While it is also reasonable to perform these biopsies on adults, there is little data to support routine sampling in the absence of symptoms or endoscopic abnormalities [1]. Gastric biopsies were taken in 47.8% of registered patients (with no differences between children and adults), with 53.9% of them presenting a normal histology, 18.1% showing different types of gastritis with no *Helicobacter pylori*, 26.5% exhibiting *H. pylori*-associated chronic gastritis, and 0.5% showing unspecific chronic inflammation. Pathological eosinophilic infiltration concordant with eosinophilic gastroenteritis was reported in 1% of gastric samples. Duodenal biopsy samples were taken in 40.8% of cases; most were normal (88%), with the remaining cases corresponding to lymphocytic duodenitis (4.9%), chronic inflammation (2.8%), gastric metaplasia (1.1%) and Marsh III stage villous atrophy (1.1%). This last group was diagnosed with celiac disease-associated EoE. Eosinophilic infiltration was present in 2.1% of duodenal biopsy samples. Gastric and duodenal biopsies were obtained more frequently in non-teaching hospitals ($p < 0.001$) and in centres with highly-experienced physicians ($p < 0.001$).

In order to exclude GORD as a cause of oesophageal eosinophilia, 20% of the subjects underwent 24 h of pH-metry monitoring, while 44.1% of patients received antisecretory PPI therapy before undergoing a diagnostic endoscopy. Thus, in one out of 3 patients, neither a response to PPIs nor a negative pH study was needed to make a diagnosis of EoE. Differences were observed depending on the type of hospital, with GORD excluded in 68% of patients from academic

Table 2
Comparative differential characteristics between adult and paediatric eosinophilic oesophagitis (EoE) patients.

Characteristics	Children ($n = 127$)	Adults ($n = 578$)	p^*
Symptoms			
Dysphagia, no. (%)	67 (54.9)	461 (80.6)	<0.001
Vomiting, no. (%)	30 (24.6)	31 (5.4)	<0.001
Heartburn, no. (%)	9 (7.4)	174 (30.4)	<0.001
Weight loss, no. (%)	9 (7.4)	10 (1.7)	0.002
Symptom evolution time months, mean (SD)	28.04 (29.93)	54.07 (62)	<0.001[$]
Allergic background			
Dermatitis, no. (%)	19 (24.7)	20 (3.5)	<0.001
Previous food allergy/sensitization, no. (%)	38 (49.4)	127 (22.4)	<0.001
Endoscopy aspects			
PPI treatment before endoscopy, no. (%)	41 (34.5)	262 (46)	0.021
Mucosal rings, no. (%)	34 (28.6)	315 (55.2)	<0.001
Hiatus hernia, no. (%)	7 (5.9)	183 (32)	<0.001
Additional studies			
Manometry, no. (%)	9 (7.2)	143 (25)	<0.001
pH-monitoring, no. (%)	17 (13.6)	123 (21.5)	0.045
EoE treatment			
PPIs, no. (%)	31 (27)	282 (59)	<0.001
Swallowed topical steroids, no. (%)	56 (48.7)	310 (65)	0.001
Anti-allergic drugs, no. (%)	28 (24.3)	48 (10)	<0.001
Food removal, no. (%)	73 (63.5)	230 (48.2)	0.003
Maintained in follow-up			
Patients, no. (%)	115 (92)	478 (83.6)	0.017

SD, standard deviation.
[*] Chi-square test.
[$] Student's *t*-test.

Table 3
Comparative differential characteristics of eosinophilic oesophagitis (EoE) patients, distributed by level of experience of the attending physician and type of hospital.

Characteristics	Experience in EoE			
	Low ($n=44$)	Medium ($n=53$)	High ($n=608$)	p^*
Abnormal oesophageal mucosal appearance, no. (%)	22 (50)	36 (67.9)	440 (74.3)	0.002
Abnormal endoscopy, no. (%)	24 (54.5)	41 (77.4)	464 (78.4)	0.001
Peak eosinophil count/HPF, no. (%)	13 (29.5)	15 (28.3)	329 (54.7)	<0.001
Gastric biopsies available, no. (%)	17 (38.6)	12 (23.1)	303 (50.6)	<0.001
Duodenal biopsies available no. (%)	7 (15.9)	6 (11.5)	271 (45.2)	<0.001
Manometry, no. (%)	2 (4.5)	21 (39.6)	130 (21.6)	<0.001
pH-monitoring, no. (%)	0	23 (43.4)	119 (19.7)	<0.001
Referred to allergy study, no. (%)	38 (86.4)	47 (88.7)	390 (64.6)	<0.001
Follow-up, no. (%)	42 (95.5)	52 (98.1)	503 (83.1)	0.002
EoE therapy				
Systemic steroids, no. (%)	0	6 (11.5)	11 (2.2)	<0.001
PPI treatment, no. (%)	31 (73.8)	29 (55.8)	253 (50.3)	0.012
Antiallergic drugs, no. (%)	6 (14.3)	14 (26.9)	57 (11.3)	0.006
Food restriction diet according to allergy test results, no. (%)	22 (78.6)	18 (72)	90 (36)	<0.001
Food restriction diet according to food-induced symptoms, no. (%)	2 (7.1)	3 (12)	111 (44.4)	<0.001

HFP, high power field; PPI, proton pump inhibitors.
* Chi-square test.

and 41.2% of patients from non-academic hospitals ($p<0.001$). With regard to age, GORD was ruled out more frequently in adult patients than in children, either through PPI pre-treatment ($p<0.021$) or pH-metry ($p=0.045$).

21.9% of patients underwent oesophageal manometry to document EoE-associated motor disturbances, being most of them adult patients ($p=0.045$).

Patients who received care at teaching hospitals or from highly experienced physicians more frequently underwent pH-monitoring or manometry, respectively, in comparison with patients receiving care at non-academic centres and from physicians with a low degree of experience ($p<0.001$).

3.3. Laboratory and allergy tests

Although the role of allergy testing in patients with EoE remains controversial, evaluation by an allergist is recommended as part of the diagnostic workup, especially for the treatment of coexisting allergic disorders [1]. That being said, only 478 (67.8%) of registered patients were studied in an allergy department. Significant differences ($p=0.003$) were observed in favour of academic hospitals, but not when comparing children with adults. Among the patients studied, the following characteristics were reported:

A first-degree family background of allergies was present in 228 (33.4%) patients; the most relevant was bronchial asthma (25.23%).

A personal background of atopy was present in 61.8% of the subjects referred to allergy departments; highlighting rhinoconjunctivitis (47.4%), bronchial asthma (32.8%), allergic skin diseases (6%), and food allergies and/or food sensitization (25%). Children showed both allergic skin diseases ($p<0.001$) and food allergies ($p<0.001$) with a significantly higher frequency (Table 2).

Among those patients studied in allergy departments, 77.3% underwent skin prick testing (SPT), with some kind of positive result being found in 88.2%, while only 12.8% of patients underwent atopic patch testing (APT), which gave positive results in 54.1%. Of all patients who underwent to allergy testing, 42.5% were sensitized to inhalant antigens (mainly olive and grass pollen) and 25.7% presented food sensitization. Drug allergies were present in only 5.1% of patients, with NSAIDs and penicillin being the most common allergens.

Most of the biochemical and haematimetric parameters gave normal values (Table 5), with the exception of eosinophil counts, which were >350 cells/μL in 57.2% of patients. Patients with blood eosinophilia showed a mean of 648.8 (SD 277.27) eosinophils/mm^3 compared with 222.5 (SD 81.04) in patients without blood eosinophilia. No signs of malnutrition or iron deficiency were documented. No additional differences were observed in any of the analysed parameters between patients with or without blood eosinophilia, except for serum total IgE levels, which were 259.4 and 425.5 KU/L, respectively. Serum specific IgE to food and airborne allergens were documented in 43.6% of cases (Table 5).

3.4. Initial EoE therapy

Pharmacological therapies for EoE include topical corticosteroids for both children and adults and PPI to treat GORD as a comorbid disease. Treatment with sodium cromolyn, leukotriene receptor antagonists, and immunosuppressive agents is not recommended [1].

Specific initial treatments for EoE in our series included various strategies; drug therapy predominated followed by different dietary approaches, with a low proportion of patients being managed with endoscopic dilations.

Of the drugs used, swallowed topical steroids were the most commonly administered (61.7%), being fluticasone propionate used in 98% of cases and budesonide in 2%. Systemic steroids were rarely used (2.9%). PPI was used in more than half the patients (52.4%), usually as a co-therapy (78.6% of them), but also as the sole treatment in 21.4% patients, usually adults ($p<0.001$). Remarkably, up to 12.9% of patients received anti-allergic drugs for EoE, especially montelukast, more frequently in paediatric patients ($p<0.001$).

EoE consensus guidelines recommend dietary therapy in all EoE children; preliminary observations suggest that dietary restrictions should also be considered for motivated adult patients [1]. Half of our registered patients (51.26%) were prescribed some kind of dietary restriction, although different approaches were used. Thus, in 27.45% of patients food restriction was based on allergy test results while for 68.63%, food restrictions were assigned on an empirical basis (i.e. six food-elimination diet or depending on food-related symptoms). The two strategies were combined in 3.92% of patients.

Forty-three patients (7.2%) underwent endoscopic dilation at some moment during the evolution of the disease. A mean of 2.3 dilation procedures per patient were carried out (range 1–30).

Finally, a solitary therapeutic intervention (i.e. an isolated drug or dietary intervention) was carried out in 39.7% patients while combined therapeutic modalities were used in 60.3% EoE patients.

Patients receiving care at teaching hospitals were given some drugs more frequently than patients at non-academic centres: swallowed steroids were used in 75.9% and 50.7% ($p<0.001$),

Table 4
Comparative characteristics of Spanish eosinophilic oesophagitis (EoE) patients according to whether care was received at a teaching or non-teaching hospital.

Characteristics	Teaching hospitals ($n=300$)	Non-teaching hospitals ($n=405$)	p^*
Previous endoscopic exams (patients), no. (%)	118 (39.3)	108 (31.5)	0.038
PPI treatment before endoscopy, no. (%)	173 (57.9)	132 (33.6)	<0.001
Peak eosinophil count, no. (%)/HPF	90 (29.9)	267 (67.3)	<0.001
Gastric mucosa biopsies available, no. (%)	121 (40.3)	211 (53.4)	0.001
Duodenal mucosa biopsies available, no. (%)	98 (32.7)	186 (47)	<0.001
Esophageal manometry, no. (%)	90 (29.9)	63 (15.8)	<0.001
pH-monitoring, no. (%)	87 (28.9)	53 (13.3)	<0.001
GORD exclusion (by PPI treatment or pH-monitoring), no. (%)	204 (68)	162 (41.2)	<0.001
Referred to allergy study, no. (%)	222 (73.8)	253 (63.3)	0.003
EoE therapy			
Swallowed steroids, no. (%)	198 (75.9)	170 (50.7)	<0.001
PPI treatment, no. (%)	164 (62.6)	149 (44.5)	<0.001
Anti-allergic drug treatment, no. (%)	58 (22.1)	19 (5.7)	0.001
Dietary treatment, no. (%)	119 (45.6)	187 (56)	0.012
Food restriction according to allergy test results, no. (%)	61 (51.3)	69 (36.9)	<0.001
Food restriction according to food-induced symptoms, no. (%)	35 (29.4)	81 (43.3)	<0.001

HPF, high power field; GORD, gastro-oesophageal reflux disease
* Chi-square test.

respectively, while PPI was used in 62.6% and 44.5% ($p<0.001$), respectively. Specific foods were more frequently excluded from the patients' diets following allergy test results in teaching hospitals ($p<0.001$) whereas in non-academic centres, this decision tended to be guided by symptoms ($p<0.001$) (Table 4). Allergy test results addressed dietary restrictions more frequently in centres with a medium or low degree of experience ($p<0.001$) while symptom-related guidance was predominately used by highly experienced doctors ($p<0.001$) (Table 3). The amount of experience in managing EoE was also associated with differences in drug prescriptions; physicians with a medium degree of experience prescribed antiallergic drugs more frequently ($p=0.006$) while physicians with a low degree of experience prescribed PPI more frequently ($p=0.012$) than the other two groups (Table 3).

3.5. EoE patient follow-up and outcomes

The follow-up of EoE patients and the frequency of endoscopic exams among them are major unresolved issues affecting their management. Most of our EoE patients underwent some kind of programmed medical care. In fact, only 105 patients (15%) either voluntarily interrupted medical care for EoE or were not given appointments by care providers. Among the remaining patients, gastroenterologists were the most frequently involved professionals, either alone (62.6%) or together with allergists (17.3%) (Table 6). Follow-up appointments were scheduled more frequently for paediatric patients (92%) than for adults (86.6%) ($p<0.017$).

Optimal end points of treatment (e.g., symptom relief or histological normalcy) remain unresolved in the consensus guidelines [1]. However, in 38.7% of our EoE patients who underwent regular follow-up, complete clinical and pathological remission was documented after treatment. In addition, reporting physicians found that 53.3% patients exhibited improved symptoms, albeit not complete disease remission, while in 5.2% patients the disease was reported as unchanged. A worsening in EoE was declared for 2 (0.4%) patients. Physicians' reported outcomes varied depending on the degree of experience in EoE management, with highly-experienced physicians reporting 15% more cases of disease remission than physicians with a low or medium degree of experience.

Table 5
Main analytical and allergy test results of our eosinophilic oesophagitis registry patients.

Biochemistry values	Mean (SD)
Glucose (mg/dL)	90.8 (11.7)
Fibrinogen (mg/dL)	320.8 (87.4)
Blood nitrogen urea (mg/dL)	32.7 (8.4)
PCR (mg/dL)	0.5 (0.6)
Creatinine (mg/dL)	0.9 (0.2)
Total cholesterol mg/dL)	188.7 (42.7)
Serum iron (μg/dL)	93.5 (32.8)
Transferrin (mg/dL)	266.8 (42.6)
Transferrin saturation index (%)	28.7 (11)
Ferritin (ng/mL)	150.7 (136.5)
Haematology values	**Mean (SD)**
Total blood eosinophil count (cells/mm^3)	478.4 (359.7)
Blood platelet count $\times 10^3$ (cells/mm^3)	244.7 (88.2)
Haemoglobin (g/dL)	14.9 (1.4)
Haematocrit (%)	43.7 (3.9)
VCM (fL)	87.8 (4.7)
Total leucocyte count $\times 10^3$ (cells/mm^3)	7.1 (1.9)
Granulocytes (%)	51.8 (10.6)
Lymphocytes (%)	33.7 (8.6)
LDH (UI/L)	266.7 (81.6)
Total serum IgE (KU/L)	373.6 (546.2)
Positive specific immunoglobulin E serum levels	**Number of patients (%)**
Food-directed specific serum immunoglobulin E	189 (43.6)
Wheat	79 (18.3)
Milk	56 (13)
Eggs	48 (11.1)
Fish	39 (9.0)
Corn	37 (8.6)
Pollens	145 (33.6)
Dust mites	69 (16)
Animal epithelia	63 (14.6)

Table 6
Departments and medical specialities involved in the follow-up of eosinophilic oesophagitis patients in Spain.

Departments	Number of patients (%)
Gastroenterology	374 (62.6%)
Gastroenterology + allergy	103 (17.3%)
Paediatrics	61 (10.2%)
Allergy	33 (5.5%)
Paediatric gastroenterology	11 (1.8%)
Gastroenterology + paediatrics	6 (1%)
Allergy + paediatrics	6 (1%)
Internal medicine	2 (0.3%)
Neumology + internal medicine	1 (0.2%)

4. Discussion

The present registry constitutes the first survey of medical management of EoE in children and adults in Europe and the largest Spanish survey focusing on EoE. As such, it has helped quantify practice variability and also shed light on the complexity of EoE in the clinics involved. As previously reported by the only two studies to evaluate the conformity of EoE diagnosis and therapy with available guidelines to date, both conducted in the US [3,25], our results demonstrate a wide heterogeneity in the medical management of EoE patients and a low adherence to consensus documents by the physicians caring for them.

Previous studies documented significant differences in EoE management between paediatric and adult gastroenterologists [26], as we corroborated in our study. In contrast, unlike previous studies, we found that the academic character of the hospital and the experience of the reporting physician were unrelated when analysing differences in EoE patient management. Thus, while a similar proportion of patients in our registry came from academic and non-academic hospitals, differences in access to allergy facilities may have determined the type of dietary management imposed on EoE patients. For example, patients receiving care at teaching hospitals were slightly but significantly more frequently attended in allergy clinics, with food restrictions more commonly based on allergy test results. On the other hand, for patients who were not referred to allergy departments, dietary changes were significantly more frequently prescribed depending on specific food-associated symptoms. Interestingly, the more experienced the centre was in managing EoE, the smaller the role of allergy studies in patient care. An absence of a relationship between the type of hospital and the team's experience in EoE arises as the only explanation for this finding.

Additionally, in academic hospitals significantly more patients received PPI, swallowed topical steroids and anti-allergic drugs. Paradoxically, however, clinicopathological remission was more frequently achieved at non-academic hospitals; the quality of data recording and the severity of case mix, together with a particular interests or specific professional dedication might underlie these findings.

We have documented that EoE diagnostic practice in Spain diverges from the proposed international guidelines in several aspects: First of all, physicians did not specifically exclude GORD as a cause of oesophageal eosinophilia in 1/3 of patients, a relevantly lower proportion than that reported for the US (75%). Remarkably, pH monitoring was used significantly more frequently in adult patients and within academic hospital environments, two differences that can be explained by both the acceptance and the availability of this technique under these circumstances. A higher level of professional education cannot be invoked to explain differences, since avoidance of non-recommended antiallergic drug therapies, histopathological evaluation (peak eosinophil count) and biopsy samplings in duodenal and gastric mucosa were all significantly more common in non-academic hospitals. One logical explanation for these inconsistencies is the lack of common protocols among pathologists, clinicians and endoscopists at highly complex hospitals, where endoscopic exams are probably not carried out by the same health professional in charge of EoE patients.

More interestingly, the degree of experience in managing EoE patients, was essential in understanding differences in adhesion to available protocols. Endoscopic exams from centres with the highest degree of experience more frequently presented altered features. In addition, a higher proportion of gastric and duodenal biopsy samples were obtained, pathology reports specifically displayed eosinophil counts, and esophageal manometry and pH-monitoring were performed less frequently when the attending physician had a higher degree of experience in managing EoE. All differences observed for these parameters were significant.

Several limitations of our study deserve mention. As we saw, 86.2% of patients were reported by physicians caring for $\geq$20 EoE patients; they may thus have a better knowledge of current guidelines. This may also explain certain differences with previously reported results from the US, in that GORD was more commonly excluded in Spanish reports.

Our results may also be influenced by the selection of the centres contributing to this registry and the fact that the study was promoted by a Gastroenterological Scientific Society. A particular interest in EoE could lead to voluntary submission of patient data to this registry by physicians linked to the disease. Thus, the possibility that we have only registered the clinical practice of centres with a better knowledge of current guidelines should be also be taken into account. We can speculate about whether this registry, had it been primarily promoted by paediatricians or allergists, would have given different results. We tried to minimize variability by including patient information from several sources, but doubts remain.

Furthermore, since data from patients reported by physicians caring for fewer than 20 EoE patients were very scarce, results derived from them may not be representative. Finally, we collected information from patients diagnosed both before and after the release of the consensus guidelines, but since the diagnostic criteria did not vary between the documents published in 2007 and 2011, and as most of our patients were diagnosed within the last 5 years, we believe the impact of this latter limitation is insignificant.

As a conclusion, we have documented a wide variability in the management of EoE patients in a representative sample of Spanish hospitals, demonstrating that the availability of facilities and the level of experience in caring for EoE patients are major factors in explaining these heterogeneous results. In order to offer our patients an uniform management according to available evidences, additional clinical trials, education and consensus development are needed.

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Potential interests

None of the authors have any conflict of interest or affiliation with any of the institutions, organizations, or companies mentioned in this manuscript.

Appendix A. The ACAD Group of Researchers

The following investigators participated in the present study as part of the ACAD group of researchers: Ávila Castellanos MR (H. Universitario Virgen del Rocío, Sevilla), Rodríguez-Téllez M, San Juan Acosta M (H. Universitario Virgen Macarena, Sevilla), Santander Vaquero C (H. Universitario de La Princesa, Madrid), Balbuena Garrido T (H. Universitario Infanta Sofía, Madrid), Delgado Pérez M, Eizaguirre Arocena FJ (H. Universitario de Donostia, Guipúzcoa), Rodrigo Sáez L, Pérez Martínez I (H. Universitario Central de Asturias, Oviedo), Hernández Alsina T (H. San Pedro, Logroño), Vila J (H. San Juan de Dios, Barcelona), Sancho del Val L, Barrio J, Alcaide Suárez N (H. Universitario Río Hortega, Valladolid), Alcalá Escriche MJ (H. Obispo Polanco, Teruel), Lucendo AJ (H. General de Tomelloso, Ciudad Real), Legido Gil J (Hospital General de Segovia, Segovia), Doménech Witek J (H. General de Elda, Alicante),

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Appendix B. Supplementary data

Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.dld.2013.01.013.

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