Clinical Gastroenterology and Hepatology 2020;18:2903–2911

ALIMENTARY TRACT

Efficacy of Therapy for Eosinophilic Esophagitis in Real-World Practice

Emilio J. Laserna-Mendieta,[*,‡] Sergio Casabona,[‡,§] Edoardo Savarino,[‖] Antonia Perelló,[¶] Isabel Pérez-Martínez,[#] Danila Guagnozzi,[**] Jesús Barrio,[‡‡] Antonio Guardiola,[§§,‖‖] Teresa Asensio,[¶¶] Susana de la Riva,[##] Miriam Ruiz-Ponce,[*] Juan Armando Rodríguez-Oballe,[***] Cecilio Santander,[‡,§,‡‡‡] Ángel Arias,[‡,‡‡‡,§§§] and Alfredo J. Lucendo,[*,‡,‡‡‡] on behalf of the EUREOS EoE CONNECT research group

*Department of Gastroenterology, Hospital General de Tomelloso, Tomelloso, Spain; ‡Instituto de Investigación Sanitaria Princesa, Madrid, Spain; §Department of Gastroenterology, Hospital Universitario La Princesa, Madrid, Spain; ‖Department of Surgery, Oncology and Gastroenterology, Università di Padova, Padova, Italy; ¶Department of Gastroenterology, Hospital de Villadecans, Barcelona, Spain; #Department of Gastroenterology, Hospital Universitario Central de Asturias, Oviedo, Spain; **Department of Gastroenterology, Hospital Universitario Vall d'Hebron, Barcelona, Spain; ‡‡Department of Gastroenterology, Hospital Universitario Río Hortega, Valladolid, Spain; §§Department of Gastroenterology, Hospital Universitario de Fuenlabrada, Fuenlabrada, Spain; ‖‖Instituto de Investigación Sanitaria La Paz, Madrid, Spain; ¶¶Department of Allergy, Complejo Hospitalario Universitario de Albacete, Albacete, Spain; ##Clínica Universitaria de Navarra, Pamplona, Spain; ***Department of Gastroenterology, University Hospital Santa María - University Hospital Arnau de Vilanova, Lerida, Spain; ‡‡‡Centro de Investigacion Biomedica en Red Enfermedades Hepáticas y Digestivas, Madrid, Spain; and §§§Research Unit, Hospital General Mancha Centro, Alcázar de San Juan, Spain

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e161. Learning Objective–Upon completion of this activity, successful learners will be able to list the main alternatives for the treatment of patients with eosinophilic esophagitis; list the expected response rates for each of these alternatives; and be able to select effectively the most suitable treatment option for patients with eosinophilic esophagitis based on their clinical characteristics.

BACKGROUND & AIMS: **Topical steroids, proton pump inhibitors (PPIs), and dietary interventions are recommended first- and second-line therapies for eosinophilic esophagitis (EoE). We investigated differences in their effectiveness in a real-world, clinical practice cohort of patients with EoE.**

METHODS: **We collected data on the efficacy of different therapies for EoE (ability to induce clinical and histologic remission) from the multicenter EoE CONNECT database—a database of patients with a confirmed diagnosis of EoE in Europe that began in 2016. We obtained data from 589 patients, treated at 11 centers, on sex, age, time of diagnosis, starting date of any therapy, response to therapy, treatment end dates, alternative treatments, and findings from endoscopy. The baseline endoscopy was used for diagnosis of EoE; second endoscopy was performed to evaluate response to first-line therapies. After changes in treatment, generally because lack of efficacy, a last endoscopy was performed. The time elapsed between endoscopies depended on the criteria of attending physicians. Clinical remission was defined by a decrease of more than 50% in Dysphagia Symptom Score; improvement in symptoms by less than 50% from baseline was considered as clinical response. Histologic remission was defined as a peak eosinophil count below 5 eosinophils/hpf. A peak eosinophil count between 5 and 14 eosinophils/hpf was considered histologic response. We identified factors associated with therapy selection and effectiveness using $\chi 2$ and multinomial logistic regression analyses**

RESULTS: **PPIs were the first-line treatment for 76.4% of patients, followed by topical steroids (for 10.5%) and elimination diets (for 7.8%). Topical steroids were most effective in inducing clinical and histologic remission or response (in 67.7% of patients), followed by empiric elimination diets (in 52.0%), and PPIs (in 50.2%). Among the 344 patients who switched to a second-line therapy,**

Abbreviations used in this paper: DSS, Dysphagia Symptoms Score; EED, empiric elimination diets; eos/hpf, eosinophils per high power field; EoE, eosinophilic esophagitis; PPI, proton pump inhibitor; SFED, 6-food elimination diet.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2020.01.024

dietary interventions were selected for 47.1% of patients, followed by PPIs (for 29.1%) and topical steroids (for 18.6%). Clinical and histologic remission or response was achieved by 80.7% of patients treated with topical steroids, 69.2% of patients given PPIs, and 41.7% of patients on empiric elimination diets. Multivariate analyses found the stricturing phenotype of EoE to be associated with selection of topical steroids over PPIs as the first-line therapy; lack of fibrotic features at initial endoscopy was associated with selection of elimination diets over topical steroids as a second-line therapy. The recruiting center was significantly associated with therapy choice; second-line treatment with topical steroids or PPIs were the only variables associated with clinical and histologic remission.

CONCLUSIONS: **In an analysis of data from a large cohort of patients with EoE in Europe, we found topical steroids to be the most effective at inducing clinical and histologic remission, but PPIs to be the most frequently prescribed. Treatment approaches vary with institution and presence of fibrosis or strictures.**

Keywords: Esophagus; Inflammation; Trends; Omeprazole; Fluticasone.

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory disease typically presenting with symptoms of esophageal dysfunction.[1] Left untreated, symptoms and inflammation tend to persist, leading to esophageal fibrous remodeling, stricture formation, and functional damage.[2,3] The chronic and progressive nature of EoE and its recurrent symptoms impact on health-related quality of life[4] and clearly indicates a need to treat symptomatic patients.

After almost 3 decades since first being characterized as a distinctive disorder,[5] the ideal regimen to treat EoE remains undefined.[6] As a particular food allergy triggered predominantly by food antigens, several modalities of dietary therapy have demonstrated effectiveness in inducing and maintaining disease remission.[7] Multiple trials and meta-analyses have shown swallowed topical steroids as being effective in inducing EoE histologic remission[8,9]; novel esophagus-targeted formulations also have induced symptom improvement.[10,11] Proton pump inhibitors (PPIs) are an anti-inflammatory therapy[12] able to achieve histologic and symptomatic remission[13–15] in half of patients. Finally, esophageal dilation provides symptom relief in up to 95% of patients[16] and should be considered in cases of esophageal strictures or narrow caliber esophagi with persistent symptoms despite being under an efficient anti-inflammatory therapy.[17]

Over the last decade, consensus documents and clinical practice guidelines have provided a structured, evidence-based framework to manage patients with EoE.[1,6,18] However, substantial variations in adherence to guidelines regarding identification of the disease,[19,20] treatment choice, and assessment of response are documented.[21–23] These limit the evaluation of the actual effectiveness of therapies for EoE and prevent the optimization and harmonization of its clinical management.

The aims of the present study were to evaluate the effectiveness of the different options as first-line therapies for EoE in real-world practice, and subsequent second therapies, generally introduced after previous diet or drug-based intervention failure. To identify the factors associated with the choice of therapy was also pursued.

Patients and Methods

Study Protocol

Patients of all ages of the EoE CONNECT database who received at least 1 therapeutic intervention were included. EoE CONNECT is a large, prospectively maintained European database promoted by United European Gastroenterology, as a part of the Link Award program "Harmonizing diagnosis and therapy of Eosinophilic Oesophagitis across Europe (HaEoE-EU)" and managed by EUREOS, the European Society of Eosinophilic Oesophagitis. EoE CONNECT was initiated in 2016.

To be included on the registry patients are required to have a confirmed diagnosis of EoE and to have provided informed consent. Information registered includes patients' demography, treatment details, visits to clinics, and allergologic issues. As treatment options, EoE CONNECT collect information on the use and effectiveness of PPIs and topical and systemic steroids; dietary interventions (including exclusive feeding with elemental diets, empiric food elimination diets, allergy testing-directed food elimination, and other options) and endoscopic dilation; and other therapies. Prospective treatment data are registered sequentially, and new sequences are created each time a different treatment (active principle, formulation, or dose) is administered to a patient. Clinical and histologic response to therapies are also registered.

The EoE CONNECT registry was approved by research ethics committees in all participating centers. All coauthors had access to the study data and reviewed and approved the final manuscript.

Data Collection

Information was imputed onto EoE CONNECT by practitioners during face-to-face clinical appointments. Variables collected for this study were sex, age, time of diagnosis, starting date of any therapy used for EoE, response to therapy, end date in case of no response, and

alternative treatment. Endoscopic finding in the baseline endoscopy were assessed by the EREFS scoring system[24]; rings and strictures were classified as fibrotic findings, whereas edema, furrows, and exudates were defined as inflammatory features.[17] The database was monitored and individual treatment data manually revised to ensure the correct date order of therapies; duplicates were removed, and queries were resolved by contacting centers to ensure data quality.

Definitions

Active disease. Active disease was defined as a peak eosinophilic infiltrate by ≥15 cells per high power field (hpf) at any esophageal level together with ≥5 points in the Dysphagia Symptoms Score (DSS), a nonvalidated measure instrument previously used in trials assessing drugs[25,26] and diets[27,28] involving adult and adolescent EoE patients. Briefly, the score assessed frequency of dysphagia, ranging from none (0) to several times per day (5); the intensity of dysphagia, ranging from unhindered swallowing (0) to long-lasting complete obstruction requiring endoscopic intervention (5); and the duration of dysphagia, ranging from no attacks (0) to lasting up to endoscopic removal of the impacted food (5). Total scores ranged from 0 to 15. A DSS ≥8 was considered as severe dysphagia. Subjective symptom intensity reported by either children or parents was considered for younger children.

Evaluation of response. Histologic remission was defined as an eosinophil peak count of <5 eos/hpf at all esophageal levels after therapy; histologic response was considered as a peak count between 5 and 14 eos/hpf.

Symptomatic improvement was independently assessed by changes in DSS reported by patients and by clinicians' perception. A decrease of more than 50% in baseline DSS after therapy was considered clinical remission in older children and adults, as previously defined[27,28]; a symptomatic improvement ≤50% from baseline was considered as clinical response (Supplementary Methods). For younger children, any subjective improvement in symptoms reported by either children or parents was considered as clinical remission. In addition, clinicians semiquantitatively scored changes in symptoms since the initiation of therapy in complete clinical remission, partial remission, or no response.

Clinical and histologic response was defined as the simultaneous combination of symptomatic remission or improvement and all degrees of histologic remission (peak eosinophil count <15 eos/hpf) in the same patient after therapy.

Lack of efficacy was defined either as maintenance or worsening of patient's symptoms combined with histologic persistence of histologic activity of the disease at the end of at least 6–12 weeks of therapy, or a situation that led the physician to escalate the dose of treatment or change to another alternative drug or diet.

What You Need to Know

Background

Topical steroids, proton pump inhibitors (PPIs), and dietary interventions are recommended first- and second-line therapies for eosinophilic esophagitis (EoE), yet little is known about their effectiveness in real-world clinical practice.

Findings

In an analysis of data from a large cohort of patients with EoE in Europe, topical steroids were the most effective at inducing clinical and histologic remission, but PPIs were the most frequently prescribed. Treatment approaches varied among institutions and based on the presence of fibrosis or strictures.

Implications for patient care

Future studies on the effectiveness of the different treatment options for EoE in other populations will help to standardize clinical practice.

Statistical Analysis

Means and standard deviations were reported for continuous variables and proportions for categorical data. Frequency tables were generated for treatment use and effectiveness according to each treatment line. Contingency tables to assess demographic and clinical factors influencing treatment choice were produced and analyzed by chi-square (univariate) test. A multinomial logistic regression was performed to assess the overall effect of treatment over variables identified in univariate analyses. All analyses were carried out using PASW version 18.0 statistical analysis software (SPSS Inc, Chicago, IL). Statistical significance was considered when $P < .05$.

Results

Study Population

On the search date, July 2, 2019, 665 patients were registered on EoE CONNECT as having demographic data completed. First-line and second-line treatment data were available for 589 and 344 patients, respectively, recruited at 10 hospitals in Spain and 1 in Italy. The main demographic and clinical characteristics of EoE patients included are summarized in Table 1.

Choice of First-Line Therapies for Eosinophilic Esophagitis

The frequencies of choice for first-line treatment options are described in Table 2. PPIs as the preferred option were used in 450 patients (76.4%), with topical

Table 1. Demographic and Clinical Characteristics of the Patients for Each Line of Treatment

	First-line	Second-line
Number of patients	589	344
Male, n (%)	458 (77.8)	270 (78.5)
Mean age (SD), *y*	33.7 (14.4)	33.3 (13.6)
Children, n (%)	88 (14.9)	47 (13.8)
Country of origin, n (%)		
Spain	528 (89.6)	322 (93.6)
Italy	61 (10.4)	22 (6.4)
Phenotype at diagnosis, n (%)		
Inflammatory[a]	375 (71.0)	230 (70.3)
Mixed[a]	95 (18.0)	53 (16.2)
Stricturing[a]	58 (11.0)	44 (13.5)
No data[b]	61 (10.4)	17 (4.9)
Dysphagia symptoms score, n (%)		
0–4 points[a]	51 (14.0)	27 (14.2)
0–7 points[a]	124 (34.0)	65 (34.2)
5–15 points[a]	314 (86.0)	163 (85.8)
8–15 points[a]	241 (66.0)	125 (65.8)
No data[b]	224 (38.0)	154 (44.8)
Endoscopic signs of fibrosis, n (%)		
Yes[a]	310 (67.8)	193 (72.3)
No[a]	147 (32.2)	74 (27.7)
No data[b]	132 (22.4)	77 (22.4)

NOTE. Patients younger than 18 years old were considered children.
SD, standard deviation.
[a]Percentages are calculated over the total number of patients with information available.
[b]Percentages calculated over the full series of patients.

steroids as the second most common choice (62 patients; 10.5%). Dietary therapies were initially used only in 46 patients (7.8%). Endoscopic dilation and combinations of 2 different treatments (both options introduced on the same day) were rarely chosen as first-line treatments.

Among PPIs, omeprazole was the most commonly prescribed drug, representing 53.2% of PPI prescriptions (Supplementary Table 1). As for topical steroids, fluticasone propionate was used in almost all patients (97.3%) (Supplementary Table 2). In 30 out of 73 patients it was administered as nasal drops ampoules (400 μg per dose), swallowed instead of inhaled; the remaining patients were treated with aerosolized fluticasone propionate applied over the tongue and then swallowed.

Regarding dietary therapy, an empirical elimination diet (EED) was selected in 70% of patients, with a 6-food elimination diet (SFED) being the most commonly used variant (Supplementary Table 3). The length of each treatment option used in first or second lines before assessing its effectiveness is shown in Supplementary Table 4.

Table 2. Frequency of Choice of Each Treatment as First and Second Lines for Patients With EoE

	First-line		Second-line	
Type of treatment	patients, n	%	patients, n	%
Proton pump inhibitors	450	76.4	100	29.1
Swallowed topical steroids	62	10.5	64	18.6
Dietary interventions	46	7.8	162	47.1
Proton pump inhibitors + swallowed topic steroids	13	2.2	1	0.3
Endoscopic dilation	10	1.7	16	4.6
Proton pump inhibitors + endoscopic dilation	4	0.7	—	—
Proton pump inhibitors + dietary interventions	3	0.5	1	0.3
Dietary interventions + endoscopic dilation	1	0.2	—	—
Total	589	100	344	100

EoE, eosinophilic esophagitis.

Effectiveness of First-Line Therapies for Eosinophilic Esophagitis in Real-World Practice

Table 3 provides details on the effect of main first-line therapies on histology and symptoms. Swallowed topical steroids were the most effective option to induce histologic response or remission in patients with EoE by reducing peak eosinophil counts below the threshold of 15 eos/hpf in 67.7% of patients overall. PPIs used as initial therapy achieved histologic response or remission in 49.7% of patients, as did EED in 48.1% of patients. Because most patients received PPIs, results for topical steroids and EED should be interpreted cautiously, due to the low number of patients in both groups.

Regarding clinical improvement, topical steroids displayed the highest ability to improve EoE symptoms; 55.8% of patients had complete clinical remission, and additionally 27.9% had symptomatic response. The overall efficacy of EED to induce remission of symptoms was 52.0% and a further response was achieved by 28.0% of patients. PPIs induced clinical remission and response in 47.8% and 24.0% of patients, respectively. Because of the low number of cases with a measured clinical response in the topical steroids and EED groups (43 and 25 patients, respectively) results needed to be viewed with caution. Furthermore, all but 1 patient among the 14 who underwent endoscopic dilation (alone or combined with anti-inflammatory therapies) and had symptoms assessed, had a response.

Considering histologic and clinical responses together, topical steroids were the most effective treatment, after induced clinical and histologic response or remission in 67.7% of EoE patients (n = 31). PPI and EED were equally effective in achieving clinical and histologic response or remission in 50.2% (n = 337) and 52.0% (n = 25) of patients, respectively.

The effectiveness of therapies to achieve clinical and histologic response did not improve when their duration increased beyond 10 weeks for diets, 12 weeks for PPI, or 16 weeks for topical steroids. Nor were differences in

Table 3. Histologic and Symptomatic Response Rates for First- and Second-Line Therapies for EoE

	First-line therapy						Second-line therapy					
	PPI		Topical steroids		EED		PPI		Topical steroids		EED	
	Patients, n	%	Patients, n	%	Patients, n	%	Patients, n	%	Patients, n	%	Patients, n	%
Histologic response												
Remission (<5 eos/hpf)	122	36.1	17	54.8	5	18.5	37	52.1	20	60.6	40	31.5
Response (5–14 eos/hpf)	46	13.6	4	12.9	8	29.6	9	12.7	6	18.2	10	7.9
Eosinophil reduction	17	5.0	2	6.5	1	3.8	2	2.8	2	6.0	10	7.9
No response	153	45.3	8	25.8	13	48.1	23	32.4	5	15.2	67	52.7
Not assessed	112	—	31	—	6	—	29	—	31	—	21	—
Total	450	100	62	100	33	100	100	100	64	100	148	100
Symptomatic response												
Complete response (>50% decrease in DSS)	161	47.8	24	55.8	13	52.0	45	62.5	24	60.0	61	50.8
Partial response (≤50% decrease in DSS)	81	24.0	12	27.9	7	28.0	15	20.8	14	35.0	21	17.5
No response	95	28.2	7	16.3	5	20.0	12	16.7	2	5.0	38	31.7
Not measured	113	—	19	—	8	—	28	—	24	—	28	—
Total	450	100	62	100	33	100	100	100	64	100	148	100

NOTE. Number of patients and percentage for each category of response according to type of treatment option and line of therapy are shown. Patients with endoscopic dilation or combined treatments were not included.
DSS, Dysphagia Symptoms Score; EED, empiric elimination diets; eos/hpf, eosinophils per high power field; EoE, eosinophilic esophagitis; PPI, proton pump inhibitor.

effectiveness observed between PPIs used at single or double doses.

Second-Line Therapies for Eosinophilic Esophagitis

Among the 344 patients with EoE who switched to a second-line therapy, dietary interventions were the most common choice (162 patients; 47.1%), followed by PPIs (100 patients; 29.1%) and swallowed topical steroids (64 patients; 18.6%), whereas endoscopic dilation was scarcely used (Table 2).

Among dietary therapies, EED were the preferred option for 91.4% of patients (Supplementary Table 3), chosen by 50.6% and 42.9% of patients who failed with PPIs and topical steroids, respectively. A subsequent new diet was also used by 32.3% of patients who failed with the first one. An analysis of sequences for first- and second-line therapy for EoE is shown in Supplementary Table 5. PPIs were the most common rescue therapy in the subgroups of patients who failed endoscopic dilation and dietary therapies. Among them, omeprazole remained the most (55.9%) prescribed drug (Supplementary Table 1). Fluticasone propionate was the most common topical steroid prescribed in second-line therapy (73.8%) followed by budesonide (26.2%) (Supplementary Table 2). Overall 23 patients out of 48 received swallowed fluticasone in nasal drops; the remaining patients were treated by swallowed aerosolized fluticasone. Budesonide was administered from viscous formulations in all cases.

Effectiveness of Second-Line Therapies for Eosinophilic Esophagitis in Real-Life Practice

As shown in Table 3, topical steroids induced histologic response or remission (defined as peak eosinophil counts <15 eos/hpf) in 78.8% of patients treated with this drug as second-line choice, although only 33 patients were fully assessed. PPIs also induced response or remission in 64.8% of patients. Both drugs worked better here than when used as first-line options, contrary to EED, which had a slightly higher efficacy when used as a first-line option (48.1% vs 39.4%).

PPIs and topical steroids induced complete clinical remission in around 60% of EoE patients who received them as second-line therapies, acting better also than when used as initial therapies. Both drugs were also relevant for inducing partial clinical response (20.8% and 35.0%, respectively). The lowest response rate in second-line therapy was found to be EED, which achieved a 50.8% complete response rate and 17.5% partial response. Nine of the 16 patients who underwent endoscopic dilation were evaluated for clinical response, with all of them reporting complete or partial symptomatic improvement.

When clinical and histologic remission or response rates were assessed together, the highest effectiveness was found among patients who received swallowed topical steroids (80.7%; 25/31), followed by PPIs (69.2%; 45/65), with EED being the least effective choice (41.7%; 48/115).

As it happened for first-line treatment, effectiveness was not affected by treatment duration. However, we

Table 4. Multinomial Logistic Regression for the Variables Identified in the Univariate Analysis as Associated With First- or Second-Line Treatment Choice (Except for Country of Origin)

Variable	Comparison	Proton pump inhibitors	Topical steroids		Dietary interventions	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
First-line therapies						
Age	Children vs adults	ref	1.7 (0.8–3.9)	.183	2.2 (1.0–3.9)	.055
Recruiting hospital	Tomelloso vs other	ref	3.1 (1.6–6.1)	.001	3.3 (1.6–6.7)	.001
EoE phenotype	Stricturing vs inflammatory	ref	4.6 (2.0–10.5)	< .001	2.6 (1.0–7.1)	.059
Second-line therapies						
Recruiting hospital	Tomelloso vs other	ref	0.5 (0.2–1.2)	.121	2.3 (1.2–4.3)	.008
	Tomelloso vs other	—	ref	—	4.8 (2.0–11.5)	< .001
Endoscopic fibrotic features	Absence vs presence	—	ref	—	3.6 (1.1–11.6)	.030

CI, confidence interval; EoE, eosinophilic esophagitis; OR, odds ratio; ref, reference treatment.

detected a significant change in clinical and histologic remission or response for PPIs as second-line treatment depending on if patients were previous PPI-responders or whether they received another treatment as first-line therapy (88.9% vs 25.0%).

Associations and Determinants for Therapy Choice in Eosinophilic Esophagitis

We searched for statistical differences in the choice of EoE therapy according to patients' age and sex, country and referral hospital, EoE phenotype, features of fibrosis in baseline endoscopy (rings and strictures), and severity of dysphagia. Because of the limited number of cases, patients undergoing endoscopic dilation and combined therapies were excluded.

For first-line therapies, significant differences were found for the following variables according to univariate analysis: age ($P < .001$), referral hospital in Spain ($P < .001$), EoE phenotype ($P = .026$), and country of origin ($P = .041$). Dietary interventions and topical steroids were more commonly chosen for children, whereas PPIs were preferred for adults (Supplementary Table 6). Topical steroids and dietary interventions were selected as first-line treatment options in Tomelloso General Hospital 2–3 times more frequently than in other centers. Patients with a stricturing phenotype were, more commonly, initially treated with swallowed topical steroids. Finally, Italian patients used swallowed steroids the most and dietary therapies the least. When these variables were analyzed in a multinomial logistic regression model, only referral center and the presence of endoscopic features of fibrosis remained as independently associated with the choice of a first-line therapy (Table 4).

Regarding second-line therapies for EoE, univariate analysis identified referral hospital ($P < .001$), country of recruitment ($P < .001$), stricturing EoE phenotype ($P = .031$), and endoscopic features of fibrosis ($P = .048$) as associated with therapy choice (Supplementary Table 6). A multinomial logistic regression model found having been recruited at the Tomelloso General Hospital as independently and significantly associated with using dietary interventions over drugs (PPIs or topical steroids) as the second-line treatment option, whereas lack of fibrosis favored dietary interventions over topical steroids (Table 4).

Determinants for Therapy Effectiveness in Eosinophilic Esophagitis

Finally, we seek whether clinical and demographic characteristics of patients could determine response to therapy. Neither patients' age nor sex, referral hospital in Spain, EoE phenotype, features of fibrosis in baseline endoscopy (rings and strictures), severity of dysphagia at baseline, or type of therapy used were significantly associated to effectiveness of first-line therapy to induce clinical and histologic remission of EoE. Milder symptoms and treatment option were revealed as significantly associated with effectiveness of second-line therapy for EoE in univariate analysis. However, only therapy choice remained as significantly associated with clinical and histologic remission or response of EoE after multivariate analysis (Supplementary Table 7).

Discussion

Current recommendations for treating patients with EoE consist of drugs and diets with anti-inflammatory efficacy, which might be combined with esophageal dilation in cases of strictures.[1] No direct comparative data have been provided to support one pharmacologic or dietary approach over the other, therefore registries of clinical practice are essential in understanding the potential of each therapy when used in real-world practice, and in documenting variations among centers. This study provides the first analysis of EoE CONNECT, a multicenter database designed to produce high-quality information on the management of EoE in Europe.

PPIs were the most prescribed first-line option overall in three-quarters of patients, followed by topical

steroids and dietary therapies. Endoscopic dilation and combinations of 2 options from the above were very uncommon. When the effectiveness in inducing clinical and histologic disease remission or response was assessed together, topical steroids were the most effective first-line therapy, inducing remission or response in two-thirds of patients treated. Notably, off-label swallowed fluticasone was given to almost all patients. However, these results should be viewed cautiously because they were obtained from 31 patients only. For PPIs, our results reproduced the overall effectiveness of ~50% rate of histologic remission and ~65% of symptomatic improvement provided by a meta-analysis.[13] As for EED, 52% of patients achieved clinical and histologic disease remission or response when used as first-line therapy. Almost 40% of patients with EED went to a SFED (with an expected potential effectiveness of 70%), and the remaining followed less restrictive 4-food or 2-food elimination diets, with reported effectiveness ranging between 45% and 60%.[7] The choice of a first-line therapy was independently associated with stricturing phenotype in endoscopy and recruiting center in Spain. Several previous studies that tried to define the factors that determine the choice of a therapeutic option for EoE[23,29,22] documented a wide variability in clinical practice, with institutional or provider preferences largely driving initial treatment approaches. Survey-based assessments of clinical practice also documented topical steroids as the preferred first-line therapy for EoE in the United States,[23,29,30] which contrasts with the choice of PPIs as the preferred option to induce EoE remission found in this study. A recent survey carried out in Germany also showed that PPI and topical steroids (or combination of both) to be equally preferred approaches as initial therapies for EoE,[21] thus revealing differential continental trends that might be related to the European initiative identifying PPIs first as an anti-inflammatory therapy for EoE instead of as a diagnostic tool for PPI-responsive esophageal eosinophilia.[1,12,31]

After switching to a first-line anti-inflammatory treatment, dietary therapy was the most common rescue option in almost half of patients, in agreement with previous studies.[21,29,30] Contrary to other reports, a 2-food elimination diet instead of a SFED was the most common choice in this study. The involvement in EoE CONNECT of centers that contributed to developing the sequential 2-4-6 diet for EoE represents a certain selection bias, which is in contrast to the expansive preference for SFED by German gastroenterologists.[21] The potential advantages in identifying and excluding food triggers from patients' diets as the only therapy that targets the cause of the EoE, however, is in conflict with its limited effectiveness in inducing clinical and histologic remission or response. This was achieved in only 41.7% of patients treated with diets, but in 80.7% of those who received swallowed topical steroids and in 69.2% of those treated with PPIs after an initial therapy.

We found a trend toward the use of highly effective steroid-based options in patients with esophageal strictures and endoscopic finding of fibrous remodeling. Marked differences were still identified depending on the site at which a patient was treated, with a significantly greater trend to prefer dietary therapies among Spanish patients compared with Italians overall, and even greater among those treated in Tomelloso General Hospital. Provider-based differences previously identified[21–23,29,30] were also found in our study, according to which EoE therapy is strongly influenced by local experience and resources available. The participation of expert centers in the registry provided greater adherence to current guidelines than to that found in previous assessments of practice patterns in general gastroenterologists.[21] Regarding the potential determinants of effectiveness, our study could not identify clinical or demographic aspects of patients that determined a response to the different treatment options, beyond the treatment itself for second-line therapy. The identification of predictive factors that allow selecting the most effective alternatives to treat each patient remains one of the practical aspects that need to be clarified in EoE.

Our study has several strengths, 1 of which is the use of a large, multicenter series of patients with EoE. Patients were recruited by physicians engaged with EoE. The prospective nature of the registry and the active monitoring of data ensured reliability.

Some important limitations should be also acknowledged. To begin with, symptoms were assessed with the nonvalidated DSS that is of limited utility to document changes in symptoms of EoE in the short term. In addition, only a minority of patients (~15%) were younger than 18 years old, thus limiting the external validity of our results for pediatric populations. Most recruiters were gastroenterologists attending adult patients and therefore potential differences in patient management compared with allergists and pediatricians were not explored. Most patients were recruited at Spanish sites, so their management could not be representative for management in other countries. The effectiveness of different doses of PPIs or steroids was not assessed, to avoid very small comparison groups with reduced statistical power. The small number of patients treated with some first- and second-line options could make some results due to chance. Finally, our study focused exclusively on the ability of the different therapies to induce histologic remission or response and/or clinical improvement in EoE and did not evaluate their long-term effectiveness.

In conclusion, this research provides evidence on the effectiveness of drug and diet-based anti-inflammatory therapies for EoE in real-world practice and confirms their role as first- and second-line therapies. Site-related preferences, stricturing phenotype, and features of fibrous remodeling in baseline endoscopy explained variations in clinical practice.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2012.11.00.

References

1. Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United Eur Gastroenterol J 2017;5:335–358.
2. Dellon ES, Kim HP, Sperry SLW, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014;79:577–585.
3. Lipka S, Kumar A, Richter JE. Impact of diagnostic delay and other risk factors on eosinophilic esophagitis phenotype and esophageal diameter. J Clin Gastroenterol 2016; 50:134–140.
4. Lucendo AJ, Arias-González L, Molina-Infante J, et al. Systematic review: health-related quality of life in children and adults with eosinophilic oesophagitis—measure instruments and determinant factors. Aliment Pharmacol Ther 2017; 46:401–409.
5. Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993;38:109–116.
6. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: proceedings of the AGREE Conference. Gastroenterology 2018;155:1022–1033.
7. Molina-Infante J, Lucendo AJ. Dietary therapy for eosinophilic esophagitis. J Allergy Clin Immunol 2018;142:41–47.
8. Murali AR, Gupta A, Attar BM, et al. Topical steroids in eosinophilic esophagitis: systematic review and meta-analysis of placebo-controlled randomized clinical trials. J Gastroenterol Hepatol 2016;31:1111–1119.
9. Chuang M-YA, Chinnaratha MA, Hancock DG, et al. Topical steroid therapy for the treatment of eosinophilic esophagitis (EoE): a systematic review and meta-analysis. Clin Transl Gastroenterol 2015;6:e82.
10. Lucendo AJ, Miehlke S, Schlag C, et al. Efficacy of budesonide orodispersible tablets as induction therapy for eosinophilic esophagitis in a randomized placebo-controlled trial. Gastroenterology 2019;157:74–86.
11. Dellon ES, Katzka DA, Collins MH, et al. Budesonide oral suspension improves symptomatic, endoscopic, and histologic parameters compared with placebo in patients with eosinophilic esophagitis. Gastroenterology 2017;152:776–786.
12. Molina-Infante J, Lucendo AJ. Proton pump inhibitor therapy for eosinophilic esophagitis: a paradigm shift. Am J Gastroenterol 2017;112:1770–1773.
13. Lucendo AJ, Arias A, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016; 14:13–22.
14. Molina-Infante J, Rodriguez-Sanchez J, Martinek J, et al. Long-term loss of response in proton pump inhibitor-responsive esophageal eosinophilia is uncommon and influenced by CYP2C19 genotype and rhinoconjunctivitis. Am J Gastroenterol 2015;110:1567–1575.
15. Gutiérrez-Junquera C, Fernández-Fernández S, Cilleruelo ML, et al. High prevalence of response to proton-pump inhibitor treatment in children with esophageal eosinophilia. J Pediatr Gastroenterol Nutr 2016;62:704–710.
16. Moawad FJ, Molina-Infante J, Lucendo AJ, et al. Systematic review with meta-analysis: endoscopic dilation is highly effective and safe in children and adults with eosinophilic oesophagitis. Aliment Pharmacol Ther 2017;46:96–105.
17. Lucendo AJ, Arias A, Molina-Infante J, et al. The role of endoscopy in eosinophilic esophagitis: from diagnosis to therapy. Expert Rev Gastroenterol Hepatol 2017;11:1135–1149.
18. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3–20.
19. Hiremath G, Vaezi MF, Gupta SK, et al. Management of esophageal food impaction varies among gastroenterologists and affects identification of eosinophilic esophagitis. Dig Dis Sci 2018;63:1428–1437.
20. Wallach T, Genta RM, Lebwohl B, et al. Adherence to celiac disease and eosinophilic esophagitis biopsy guidelines is poor in children. J Pediatr Gastroenterol Nutr 2017;65:64–68.
21. Miehlke S, von Arnim U, Schlag C, et al. Clinical management of eosinophilic esophagitis: a nationwide survey among gastroenterologists in Germany. Z Gastroenterol 2019;57:745–752.
22. Lucendo AJ, Arias A, Molina-Infante J, et al. Diagnostic and therapeutic management of eosinophilic oesophagitis in children and adults: results from a Spanish registry of clinical practice. Dig Liver Dis 2013;45:562–568.
23. Huang KZ, Jensen ET, Chen HX, et al. Practice pattern variation in pediatric eosinophilic esophagitis in the Carolinas EoE Collaborative: a research model in community and academic practices. South Med J 2018;111:328–332.
24. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013; 62:489–495.
25. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010;139:1526–1537.
26. Miehlke S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut 2016; 65:390–399.
27. Gonsalves N, Yang G-Y, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012; 142:1451–1459.
28. Molina-Infante J, Arias Á, Alcedo J, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2-4-6 Study. J Allergy Clin Immunol 2017;141:1365–1372.
29. Peery AF, Shaheen NJ, Dellon ES. Practice patterns for the evaluation and treatment of eosinophilic oesophagitis. Aliment Pharmacol Ther 2010;32:1373–1382.
30. Spergel JM, Book WM, Mays E, et al. Variation in prevalence, diagnostic criteria, and initial management options for eosinophilic gastrointestinal diseases in the United States. J Pediatr Gastroenterol Nutr 2011;52:300–306.

31. Molina-Infante J, Bredenoord AJ, Cheng E, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. Gut 2016;65:521–531.

Reprint requests
Address requests for reprints to: Emilio J. Laserna-Mendieta, EuSpLM, PhD, Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos, s/n, 13700 Tomelloso, Ciudad Real, Spain. e-mail: ejlaserna@sescam.jccm.es; fax: + 34 926 525 870; or Alfredo J. Lucendo, MD, PhD, FEBGH, Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos, s/n, 13700 Tomelloso, Ciudad Real, Spain. e-mail: ajlucendo@hotmail.com; fax: + 34 926 525 870.

Conflicts of interest
The authors disclose no conflicts.

Funding
Emilio J. Laserna-Mendieta is a recipient of a Rio Hortega grant (CM17/00003) from Instituto de Salud Carlos III, Spanish Ministry of Health, Social Services and Equality, which is partly funded by the European Social Fund (period 2014-2020). EoE CONNECT was established with funds from the United European Gastroenterology, and is supported by the European Society of Eosinophilic Esophagitis. No financial assistance was needed to carry out this study.

Supplementary Methods

Symptoms reported by patients at baseline and changes induced by treatment were assessed with the DSS, a nonvalidated measure instrument previously used in adults and adolescents with EoE. At present, no validated instrument to assess symptoms in EoE patients is available in most European languages, including Spanish and Italian; therefore, we were not able to use the EEsAI symptoms score[1] or the DSQ[2] for this research, but rather the nonvalidated DSS. In addition, both validated questionnaires are protected by copyright and its use is not for free.

The DSS has been repeatedly used in previous papers to document changes in dysphagia in patients with EoE in research performed in the United States and Europe. A reduction of 50% or more regarding the baseline DSS score was defined in previous research as the criterion for clinical remission of EoE.[3–5] In previous studies, a complete remission (as no or minimal point in the score) was not achieved by patients, despite significantly reducing the score regarding the baseline. The intrinsic characteristics of the DSS makes it difficult to achieve the minimum score after a short-term treatment, because the recall period of this score is as long as 1 year. The first component of the score (dysphagia frequency) can only be scored 0 after 1 year of treatment (0 = no attacks during the last year, 1 = 1 or 2 attacks/year, 2 = 1 attack/3 months, 3 = 1 attack/month, 4 = 1 attack/week, and 5 = at least 1 attack/day). Because the effectiveness of each of the therapies used for EoE was assessed after 6–12 weeks, the overall score provided by a patient after a short course of treatment is highly influenced by the baseline DSS before therapy. A complete remission involving "0 dysphagia episodes during the last year" could potentially be achieved after 1 year of effective therapy, which is not meaningful in the practical management of EoE patients in the clinic, because the recall period of the DSS could be as long as 1 complete year.

As a result, the DSS is of limited utility to document changes in symptoms of EoE in the short term, even if a patient is completely asymptomatic at the moment of assessment. Because of this limitation, the EoE CONNECT registry includes a second point of evaluation that is provided by the clinician after the assessment of symptoms from the institution of a therapy for EoE, to capture the short-term effectiveness of an intervention.

References

1. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology 2014;147:1255–1266.
2. Dellon ES, Irani A-M, Hill MR, et al. Development and field testing of a novel patient-reported outcome measure of dysphagia in patients with eosinophilic esophagitis. Aliment Pharmacol Ther 2013;38:634–642.
3. Gonsalves N, Yang G-Y, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012;142:1451–1459.
4. Molina-Infante J, Arias A, Barrio J, et al. Four-food group elimination diet for adult eosinophilic esophagitis: a prospective multicenter study. J Allergy Clin Immunol 2014;134:1093–1099.
5. Molina-Infante J, Arias Á, Alcedo J, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2-4-6 Study. J Allergy Clin Immunol 2018;141:1365–1372.

Supplementary Table 1. PPIs Used as First- and Second-Line Therapies for Patients With EoE

Drug, dose and frequency	First-line therapy		Second-line therapy	
	Patients, n	%	Patients, n	%
Omeprazole	250	53.2	57	55.9
40 mg twice daily	30	12.0	3	5.3
20 mg 3 times daily	3	1.2	0	0.0
40 mg once daily	184	72.8	14	24.6
20 mg once daily	31	13.2	35	61.4
Unknown	2	0.8	5	8.7
Pantoprazole	85	18.1	18	17.6
40 mg twice daily	51	60.0	1	5.6
40 mg once daily	28	32.9	13	72.2
20 mg once daily	6	7.1	4	22.2
Esomeprazole	62	13.2	11	10.9
40 mg twice daily	45	72.6	6	54.5
40 mg once daily	15	24.2	4	36.4
20 mg once daily	2	3.2	1	9.1
Lansoprazole	56	11.9	13	12.7
30 mg twice daily	35	62.5	5	38.5
30 mg once daily	21	37.5	8	61.5
Rabeprazole	17	3.6	3	2.9
20 mg twice daily	15	88.2	2	66.7
20 mg once daily	2	11.8	1	33.3
Total	470	100	102	100

NOTE. Treatments are ordered by their frequency of use as first-line therapy. Both patients exclusively treated with PPIs or in combination with other options are included. Four hundred and six (86.4%) received double PPI doses as first-line therapy (consisting in omeprazole at 40, 60, or 80 mg/day; pantoprazole and esomeprazole at 40 or 80 mg/day; lansoprazole at 60 mg/day; and rabeprazole at 40 mg/day). Only 48 patients (47.1%) received double doses of PPI as second-line therapy.
EoE, eosinophilic esophagitis; PPI, proton pump inhibitor.

Supplementary Table 2. Topical Steroids and the Doses Used as First- and Second-Line Therapy for Patients With EoE, Regardless of Whether They Were Used as a Single Therapy Combined With PPI

Drug	First-line		Second-line	
	Patients, n	%	Patients, n	%
Fluticasone	73	97.3	48	73.8
1 mg/day or higher	16	21.9	14	29.2
750–800 μg/day	14	19.2	13	27.1
100–500 μg/day	35	47.9	15	31.2
Unknown	8	11.0	6	12.5
Budesonide	2	2.7	17	26.2
4 mg/day	0	0.0	1	5.9
2 mg/day	2	100.0	13	76.5
1 mg/day or lower	0	0.0	2	11.7
Unknown	0	0.0	1	5.9
Total	75	100	65	100

EoE, eosinophilic esophagitis; PPI, proton pump inhibitor.

Supplementary Table 3. Frequency of Choice of Dietary Interventions as First- and Second-Line Therapies for Patients With EoE

Type of dietary intervention	First-line		Second-line	
	Patients, n	%	Patients, n	%
Empiric food elimination diets	35	70.0	149	91.4
6-food	13	37.1	42	28.2
2-food	11	31.4	62	41.6
4-food	7	20.1	38	25.5
Single food	4	11.4	7	4.7
Allergy testing–driven food elimination	6	12.0	7	4.3
Elemental diets	4	8.0	3	1.8
Other types of diets	5	10.0	4	2.5
Total	50	100	163	100

EoE, eosinophilic esophagitis.

Supplementary Table 4. Treatment Length for Each of the Main Treatment Options for EoE, From its Establishment to the Endoscopic Assessment of Response

Type of therapy	First-line	Second-line
Proton pump inhibitors, *d* (median), IQR	73 (60–107)	120 (66–271)
Swallowed topical steroids, *d* (median), IQR	129 (92–532)	87 (55–151)
Food elimination diet, *d* (median), IQR	64 (44–116)	57 (43–97)

NOTE. Data for the combined treatments were not included because of the low number of patients in those groups.
EoE, eosinophilic esophagitis; IQR, interquartile range.

Supplementary Table 5. Second-Line Treatment Choice Based on First-Line Options

		Second-line therapies								
		Proton pump inhibitors		Swallowed topical steroids		Dietary interventions		Endoscopic dilation		No data
		Patients, n	%	Patients, n	%	Patients, n	%	Patients, n	%	Patients, n
First-line therapies	Proton pump inhibitors	64	26.3	50	20.6	123	50.6	6	2.5	207
	Swallowed topical steroids	20	40.8	5	10.2	21	42.9	3	6.1	13
	Dietary interventions	10	32.3	5	16.0	10	32.3	6	19.4	15
	Endoscopic dilation	4	44.4	1	11.1	3	33.4	1	11.1	1

NOTE. Number and percentage of patients classified according to their first-line treatment for each type of second-line choice.

Supplementary Table 6. First- and Second-Line Therapies Used for EoE According to Patients' Age, Referral Center, EoE Phenotype, Country of Origin, and Endoscopic Findings of Fibrosis

	First-line therapies						Second-line therapies					
	Proton pump inhibitors		Topical steroids		Dietary interventions		Proton pump inhibitors		Topical steroids		Dietary interventions	
	Patients, n	%	Patients, n	%	Patients, n	%	Patients, n	%	Patients, n	%	Patients	%
Patients age												
Children	50	62.5	16	20.0	14	17.5	14	29.8	8	17.0	25	53.2
Adults	386	84.3	40	8.7	32	7.0	85	30.9	55	20.0	135	49.1
P value			< .001						.846			
Recruiting center												
Tomelloso Hospital	117	67.6	32	18.5	24	13.9	30	21.7	12	8.7	96	69.6
Other centers	293	87.7	20	6.0	21	6.3	61	36.3	42	25.0	65	38.7
P value			< .001						< .001			
EoE phenotype												
Inflammatory	301	82.0	36	9.8	30	8.2	71	31.8	33	14.8	119	53.4
Mixed	65	79.2	13	15.9	4	4.9	11	21.6	17	33.3	23	45.2
Stricturing	31	64.6	11	22.9	6	12.5	11	30.6	9	25.0	16	44.4
P value			.026						.031			
Country of recruitment												
Spain	410	80.8	52	10.3	45	8.9	91	29.8	54	17.6	161	52.6
Italy	40	78.4	10	19.6	1	2.0	9	45.0	10	50.0	1	5.0
P value			.041						< .001			
Endoscopic features of fibrosis												
Absence	127	87.6	9	6.2	9	6.2	24	33.8	7	9.9	40	56.3
Presence	234	81.9	27	9.4	25	8.7	55	30.1	43	23.5	85	46.4
P value			.306						.048			

NOTE. Patients younger than 18 years of age were considered as children.
EoE, eosinophilic esophagitis.

Supplementary Table 7. Univariate and Multivariate Statistical Analyses of Those Variables That Could Affect Treatment Outcome Measured as Number of Patients With Clinicohistologic Response or Remission

		First-line treatment			Second-line treatment		
Variable		% response	*P* value (univariate)	*P* value (multivariate)	% response	*P* value (univariate)	*P* value (multivariate)
Sex	Male	51.9	.905	n.d.	57.9	.318	n.d.
	Female	51.1			48.9		
Age	Children	48.2	.562	n.d.	57.7	1.000	n.d.
	Adults	53.3			56.3		
Recruiting center (Spain)	Tomelloso	49.2	1.000	n.d.	46.9	.114	n.d.
	Other	49.8			58.7		
Phenotype	Inflammatory	51.1	.307	n.d.	55.3	.946	n.d.
	Mixed	54.7			57.1		
	Stricturing	38.9			52.4		
Dysphagia score at baseline	0–7 points	58.6	.108	n.d.	76.9	.029	.131
	8–15 points	47.1			56.1		
Presence of fibrosis at baseline endoscopy	No	58.9	.083	n.d.	54.5	.594	n.d.
	Yes	48.0			59.5		
Treatment option	PPI	50.2	.173	n.d.	69.2	< .001	< .001
	TS	67.7			80.6		< .001
	EED	52.0			41.7		ref

NOTE. Multivariate analysis was only performed for variables showing significant association in the univariate analysis. *P* values for type of treatment in the multivariate analysis for second-line therapy are expressed using EED as the reference category.
EED, empiric elimination diets; n.d., not done; PPI, proton pump inhibitors; TS, topical steroids.