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Differences in Management of Eosinophilic Esophagitis in Europe: an Assessment of Current Practice.

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Abstract:

Objectives: To assess differences in the diagnosis and management of Eosinophilic Esophagitis (EoE) by European pediatric (PG) and adult gastroenterologists (AG), and their self-reported adherence to guidelines.

Methods: A multiple-choice questionnaire gauged the diagnostic and management strategies of gastroenterologists treating children or adults in 14 European countries and the United Arab Emirates (UAE).

Results: Questionnaires were completed by 465 PG and 743 AG. PG were significantly more likely to take biopsies in patients with symptoms of esophageal dysfunction (86.2% PG vs. 75.4% AG, $p < 0.001$) and to perform endoscopic follow-up (86.3% PG vs. 80.6% AG, $p < 0.001$). After failure of proton-pump inhibitors, topical steroids were the preferred second line therapy, however PG opted more frequently for elimination diets (47.5% PG vs. 13.7% AG, $p < 0.001$). More PG than AG indicated having read recent guidelines (89.4% PG vs. 58.2% AG, $p < 0.001$). Geographic differences in practice were reported, with respondents from the United Kingdom, Portugal and Spain more often adhering to recommended biopsy protocols. Physicians in the UAE, France, Lithuania and Poland tended to opt for steroid therapy or elimination diets as first line therapy, in contrast to most other countries.

Conclusions: Significant differences in general practice between PG and AG were demonstrated with notable divergence from consensus guidelines. International practice variations are also apparent. Among other strategies, educational activities to highlight current recommendations may help harmonize and optimize clinical practice.

Keywords – pediatric, adult, esophagitis, diagnosis, treatment

What is known:

- Eosinophilic esophagitis (EoE) is a chronic inflammatory disease affecting both adults and children.
- Guidelines for management of EoE have changed markedly over the last decade and include few differences for diagnosis and management in children versus adults.

What is new:

- Significant practice differences exist regarding diagnosis and management of EoE, both between pediatric and adult gastroenterologists, as well as between European countries, often diverging from consensus guidelines.
- These inter-colleague and international disparities indicate the need for intensified education and national guidelines based on international consensus in order to optimize and harmonize clinical management.

Introduction

Eosinophilic esophagitis (EoE) is a chronic immune mediated esophageal disease resulting from eosinophil-predominated inflammation, triggered by ongoing exposure to dietary or, rarely, environmental stimuli [1]. Studies have described a steady rise in the prevalence of this disease [2-4]. This is explained both by an increased awareness by physicians as well as a true rise of incidence.

The most recent European guidelines on EoE, published in 2017 by Lucendo *et al.* [1], call for a similar approach in children and adults. They emphasize the need for esophageal endoscopy with tissue sampling, including at least 6 biopsies from multiple esophageal levels, as the primary tool for the diagnosis and follow up of EoE, even in the presence of an endoscopically normal esophagus. In the presence of compatible symptoms, a minimum of 15 eosinophils per high power field (HPF) on esophageal biopsy is considered diagnostic for EoE in the absence of an alternative cause for esophageal eosinophilia. Because symptoms do not correlate accurately with histologic disease activity, and currently no accurate biomarker for disease activity has been found, endoscopic evaluation with multiple biopsies is necessary for disease follow-up and evaluation of response to treatment. Guidelines now negate the need for non-response to proton-pump inhibitor (PPI) therapy to confirm EoE diagnosis [1, 6]. Rather, PPI therapy is considered to be one of the possible treatment options.

Despite similar recommendations for adult and pediatric patients, practice differences may have implications as to the rate of diagnosis, adequate treatment and continuity of care which could potentially be detrimental to patient care, especially in the context of patient transition from pediatric to adult practice [7, 8].

The aim of this study, performed by the ESPGHAN EGID Working Group, was to assess differences in current diagnostic, therapeutic and follow-up practices for patients with suspicion of, or diagnosed with EoE among gastroenterologists treating pediatric and adult patients across a broad range of European countries. Furthermore, differences in national management practices between gastroenterologists practicing in the participating countries were investigated.

Methods

Data collection was performed using a structured multiple-choice questionnaire consisting of 23 questions gauging physician demographics, self-reported diagnostic and endoscopic practice, therapeutic preferences, awareness of current guidelines and need for further national publications on EoE.

Questionnaires were distributed among gastroenterologists in 14 European countries (*Table 1*) both digitally (utilizing the web-based survey platform SurveyMonkey®) as well as in paper-based questionnaires, both answered anonymously. Among different countries, multilingual questionnaires were used following local language validation of the translations. Participation was requested by addressing the respective gastroenterological societies on a national level, as well as personal distribution of paper copy questionnaires at national gastroenterology society meetings. Questionnaires were solicited between October 2017 and October 2018. A distinction was made between gastroenterologists treating a primarily pediatric (PG) or adult (AG) patient population. Gastroenterologists treating both pediatric and adult patients were excluded from comparative statements, because they could not be assigned to either group. The number of active gastroenterologists in the participating countries was estimated using the 2014 Eurostat registry [9] and society reported numbers. As the most recent guidelines [1, 6] had not been

published for the entire period of data collection, proton-pump inhibitor trials were still included in the survey.

Data processing and statistical analyses were performed using SPSS Version 25 (IBM, Chicago, IL, USA). Population characteristics are summarized as frequencies and percentages for categorical variables. Chi-square or Fisher's exact tests were used to assess statistical differences between PG and AG for qualitative variables and to assess geographic differences. A two-tailed p-value of less than 0.05 was considered statistically significant.

Consent of respondents was inferred by their submission of the completed survey.

Results

Both PG and AG from 14 European countries and the United Arab Emirates participated in the international EoE survey, however German AG chose not to engage. A total of 1208 gastroenterologists (465 PG and 743 AG) completed the survey, representing respectively 23.1% and 4.2% of all active PG and AG in the participating regions. Seventy-eight participants were excluded because they indicated to still be in training and senior physician opinion was preferred. Significant differences between PG and AG, concerning practice setting, self-reported interest in EoE and number of EoE patients under their direct care, as well as country specific response rates and demographic characteristics are portrayed in *Table 1*.

Practice differences between Pediatric and Adult Gastroenterologists:

Diagnostic strategies differed significantly between the studied groups. In terms of biopsy practice, PG reported practices that were concordant with published guidelines more often than did AG, on almost all examined topics. They take esophageal biopsies more frequently in cases of dysphagia – even when the esophagus appears normal endoscopically (86.2% PG vs. 75.4%

AG, $p < 0.001$), in cases with gastro-esophageal reflux disease (GERD) -like symptoms in the presence of distal erythema or inflammation (60.1% PG vs. 15% AG, $p < 0.001$) and when performing endoscopy for reasons other than esophageal dysfunction (32.7% PG vs. 17.0% AG, $p < 0.001$). However, biopsy practices were similarly low after removal of esophageal foreign bodies/food boluses with normal macroscopic esophageal findings (61.6% PG vs. 66.3% AG, $p = 0.101$). The intent to collect the recommended ≥ 6 biopsies from a minimum of 2 different esophageal locations when suspecting EoE, is markedly low, at 9.3% of gastroenterologists, with comparable results between the two groups. Endoscopic follow up, rather than symptom based follow up, is performed significantly more frequently by PG (86.3% PG vs. 80.6% AG, $p < 0.001$). PG are also more likely to take gastric as well as duodenal biopsies when performing the first endoscopic assessment in suspicion of EoE (84.3% PG vs. 41.3% AG, $p < 0.001$).

Therapeutic management strategies are depicted in *Figure 1*. PPIs are the preferred first line treatment for both PG and AG ($p=0.21$), however significant differences between the two groups exist following PPI failure, with PG being more inclined to use elimination diets. For patients presenting with significant stenosis, endoscopic dilation is the most frequently implemented first line treatment strategy (44.4% PG and 46.2% AG), followed by topical steroid therapy (22.8% PG and 24.6% AG) and PPI treatment (16.2% PG and 25.5% AG), again without significant differences between PG and AG. However, 16.7% of PG reported recommending systemic steroids when significant strictures are present compared to only 3.7% of AG ($p < 0.001$). Despite the fact that esophageal dilation does not treat the underlying inflammatory process, a small minority of both PG and AG respondents reported recommending dilation without any other EoE directed treatment for their patients with strictures (3,0% PG and 5,0% AG). AG were more

likely to refer all their diagnosed patients for allergic counselling (48.1% PG vs. 54.5% AG, $p < 0.001$). 24.2% of PG and 24.6% of AG ($p = 0.466$) only did so for atopic patients.

Of physicians implementing elimination diets for treatment of EoE, the most common recommendations by PG as well as AG are the six-food elimination diet (37.2% PG vs. 30.6% AG, $p = 0.27$), elimination diets based on allergy testing (33.5% PG vs. 19.1%, $p < 0.001$) or a combination of the latter with additional empiric elimination (32.6% PG vs. 16.7% AG, $p < 0.001$). However, in general, AG used these elimination diets significantly less frequently. PG were more likely to utilize elemental formula diets as options for nutritional treatment in EoE (15.1% PG vs. 2.2% AG, $p < 0.001$), however such use remained relatively uncommon. PPI-treatment (57.8% PG vs. 60.6% AG, $p = 0.428$) and topical steroids (61.2% PG vs. 60.1% AG, $p = 0.662$) were indicated as equal options for maintenance therapy, with only a minority (3.0% PG vs. 5.0% AG, $p = 0.173$) not using any type of maintenance therapy at all for EoE.

When gauging awareness of the most recent guidelines, 70.3% of respondents indicated they had read at least one of the most recent guidelines [1, 5, 10, 11] with a significant majority being PG (89.4% PG vs. 58.2% AG, $p < 0.001$). 116 respondents (9.6%) admitted to having no knowledge of the existence of these publications. Both PG and AG alike (86.3% PG vs. 85.5% AG, $p = 0.733$) support the publication and promotion of guidelines on a national level. The majority of AG (62.5%) reported that they would be comfortable taking over care of adolescent patients transitioning from pediatric care, with this percentage rising to 86.6% for patients who had completed their diagnostic work up before transition.

Geographic variance in EoE patient care:

Certain trends were identified when assessing international differences in EoE-practice. Respondents from Poland, Spain and Germany were following markedly more EoE patients each and more often reported a special interest in EoE than physicians from other countries.

Notable differences in endoscopy and biopsy sampling strategies between countries are depicted in *Figures 2 and 3*. The percentage of GIs reporting that they take esophageal biopsies in patients with dysphagia even with normal macroscopy was highest in Switzerland, Spain and Germany, although adherence to the recommendations on the number of biopsies was maximal in the United Kingdom, Portugal and Spain. Endoscopic follow up was reported most persistently in Germany (100%), Slovenia (91.9%) and Poland (91.3%).

In the majority of countries PPI-treatment remained the first treatment option after endoscopic diagnosis of EoE. In the UAE, France, Lithuania and Poland however topical steroid therapy or elimination diets were more common first line choices. Gastroenterologists in Spain (29.7%), France (46.3%) and Italy (46.3%) were least likely to refer their patient to a dietician. Although uncommon in general, elemental formula-based diets were most often recommended in Germany (38.5%) and Macedonia (16.2%) as options for treatment, while none of the Italian respondents indicated using elemental formula diets. Referral for allergy counselling was common in Lithuania (65.8%) and Italy (61.2%). The use of elimination diets based on allergy testing, despite being dissuaded in the most recent guidelines, was most prevalent in the UAE (56%) and Italy (51.2%).

Awareness of current guidelines was maximal in Spain (98.2%) and Germany (97.4%) with the lowest percentages being reported in The Netherlands (50.7%) and France (45.7%). (Detailed data on international differences presented as Supplemental Table 1-3, Supplemental Digital Content, <http://links.lww.com/MPG/B792>).

Discussion:

Our results demonstrate the existence of considerable differences between AG and PG in diagnostic and endoscopic practice concerning the management of suspected or substantiated EoE. However, the clinical relevance of these differences remain of course to be assessed individually. Our findings confirm the results of a recent study of Israeli gastroenterologists [7]. A large survey of AG in Germany (N=1393) corroborate the substantial variation in the adherence to published EoE guidelines even between AG in Germany [12]. With its broad, international setting, our research further expands the scope of this diversity onto an international level.

We found that despite the higher prevalence of EoE in an adult population [2-4], PG more often reported having special interest in EoE. Participant PG were more likely to be active within academic settings and had a greater number of EoE patients under their direct care. This academic orientation may be a consequence of the structure of health care systems in most European countries where pediatric gastroenterology, in contrast to adult gastroenterology, is almost solely practiced in academic clinics. This special interest in EoE and the academic setting of practice likely influenced PG's adherence to consensus guidelines - the vast majority of PG (89,4%) indicated that they were aware of and had read recent guidelines, compared to only 58.2% of AG - and therefore their opinion on EoE management. In light of the fact that a greater proportion of AG reported caring for very few EoE patients compared to PG, we re-analyzed the data including only GIs treating more than four EoE patients. In this analysis, results did not generally differ significantly (data not shown) from those previously reported, except for less referral to allergologists, less use of PPIs as first line treatment, more maintenance treatment and

more knowledge of guidelines. This would indicate that the differences identified are inherent to the adult vs. pediatric GI practice, rather than the number of patients being treated.

Esophageal sampling practice during endoscopy (in diverse clinical scenarios) is far from uniform, in contrast to evidence based recommendations [1, 5, 10, 11]. Surprisingly, even in the presence of dysphagia - the most common symptom leading to evaluation of EoE in adolescents and adults - we found that only 75% of AG (and 86% of PG) reported taking biopsies when the esophagus appeared normal endoscopically. This is despite substantiated data demonstrating that endoscopy may be normal in about 10-32% of cases [13, 14]. This may be partially explained by AG's tendency to have a lower index of suspicion for EoE because of the very high prevalence of GERD as a cause of esophageal dysfunction in the population for which they care. Furthermore, current guidelines on management of GERD in adults do not strictly recommend taking biopsies in the absence of esophageal abnormalities [15, 16]. Similarly, pediatric guidelines on GERD state there is insufficient evidence to support the use of endoscopy with/without biopsy for the diagnosis of GERD [17, 18], possibly discouraging physicians from performing endoscopy and taking biopsies in patients presenting with esophageal symptoms. These issues raise the importance of the need for harmonization between guidelines concerning different but overlapping fields.

While guidelines recommend at least 6 multi-level biopsies to diagnose EoE, the actual proportion of physicians reporting compliance with these recommendations was surprisingly low (9.3%). Research by Gonsalves et al., showing that a single biopsy only had a sensitivity of 55% and that at least 5 multilevel biopsies are needed to reach maximal diagnostic sensitivity [19], highlights that current practices reported by gastroenterologists pose important risks for an under- or even misdiagnosis of EoE. The reason for this discrepancy is unclear, but economic

factors (cost of pathological assessments), length of procedures and demands for high patient turnover in endoscopy units, decreased suspicion of EoE and lack of acquaintance with diagnostic guidelines, may all contribute.

Our finding that PG more often performed endoscopic follow up than those treating adults was corroborated by others [20]. However, whether the detection of persistent residual esophageal eosinophilia in asymptomatic patients warrants more aggressive therapy and whether surveillance improves outcomes remains unclear. Current data, however, does not support the use of symptom scores in lieu of endoscopy with histology [21-23].

While first line PPI-treatment did not differ between groups, as second line treatment PG prescribed elimination diets significantly more often. Elimination diets are efficacious at achieving symptom resolution and histologic remission [24], although recent guidelines do not recommend diets based on skin prick or IgE testing. Higher rates of dietary elimination in children may stem from stricter cooperation with such diets by children and parents, the desire of parents not to give chronic medication to children because of potential side effects, the lack of dietician support and knowledge about dietary management by AG, or the poorer QoL reported by patients on elimination diets [25].

Huang et al. demonstrated heterogeneity in EoE-related practice preferences between institutions within the United States [26]. However, our research represents the first study confirming and further exploring these differences on an international level. Economic factors such as public versus private health insurance coverage for visits, endoscopies, biopsies and medication are likely to influence international differences in follow-up and treatment choices by physicians. Patient access to facilities, resources available to physicians and the level of experience in caring for EoE patients may also be contributing factors. Although Lucendo and colleagues determined

that academic settings and the clinical experience of the reporting physician were unrelated when analyzing differences in EoE patient management in Spain [27], we found that in general, countries in which a significant proportion of responding physicians work in academic settings reported a higher interest in EoE and were likely to follow guidelines more thoroughly (*Supplemental table 2*, Supplemental Digital Content, <http://links.lww.com/MPG/B792>). Alternatively, international variation may once again be based on gastroenterologists not agreeing or not being acquainted with recent evidence-based guidelines [28]. This hypothesis is supported by our observation that countries with the highest proportion of GI indicating to have read recent guidelines (i.e. Spain, Portugal, Germany and the UK) demonstrating a higher tendency to concur with evidence-based practice. Furthermore, local presence of international expertise may raise awareness because of EoE and its recommended treatments being highlighted within those countries. Increased practice consistency has been observed for EoE following the publication of the first EoE guidelines over a decade ago [29], thus, further education and dissemination of practice guidelines nationally may increase adherence to newer iterations and changes in the recommendations.

This study's strengths include its significant number of responses, its focus on academic as well as non-academic settings and its broad geographic scope, making this research the first of its kind within EoE practice-based literature. However, it also has limitations which should be acknowledged. Despite gathering more than 1200 responses, given the international setting, response rates were low especially within the AG community. This led to certain national cohorts being relatively small and therefore possibly not representative of the respective country as a whole. Additionally, since survey candidates were also approached at societal meetings, some selection bias may have been introduced, excluding physicians less prone to attend

gatherings. Nevertheless, they might still be included, as the respective representatives of individual national societies were addressed digitally. We collected physician's information both from before and after the release of the most recent consensus guidelines that introduced PPI-responsive eosinophilic esophagitis (PPI-REE) as part of the EoE-spectrum, possibly affecting our data on PPI-trials. As this study focused on primary and secondary therapeutic strategies, advanced therapeutic options such immunomodulatory drugs, leukotriene receptor antagonists and biologicals were not included.

In conclusion, this is the first study demonstrating significant differences in diagnostic, endoscopic and therapeutic practice concerning EoE between PG and AG across Europe. Differences were especially apparent when focusing on endoscopic practice and adherence to guidelines appeared to be critically low regarding biopsy protocol, potentially leading to under-diagnosis and affecting long-term health outcomes. Geographic variance in practice was also found. These inter-colleague and international disparities indicate a need for intensified education and clear national guidelines based on international consensus in order to optimize and harmonize the clinical management of EoE patients on a broader platform.

Disclaimer:

Although this paper is produced by the ESPGHAN EGID Working Group, it does not necessarily represent ESPGHAN policy and is not endorsed by ESPGHAN.

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Legends

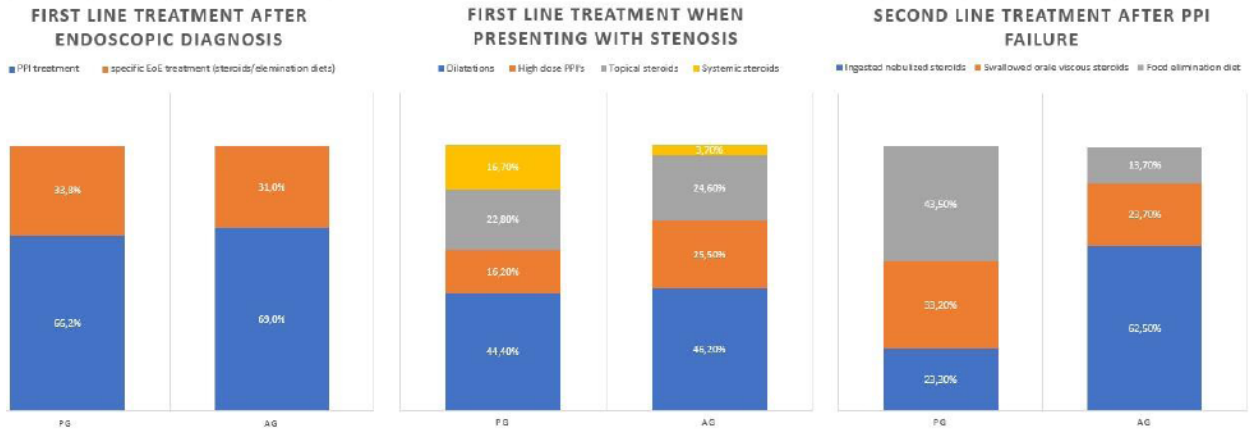


FIGURE 1 - First and second line treatment preferences among Pediatric (N= 465) and Adult gastroenterologists (N=743).

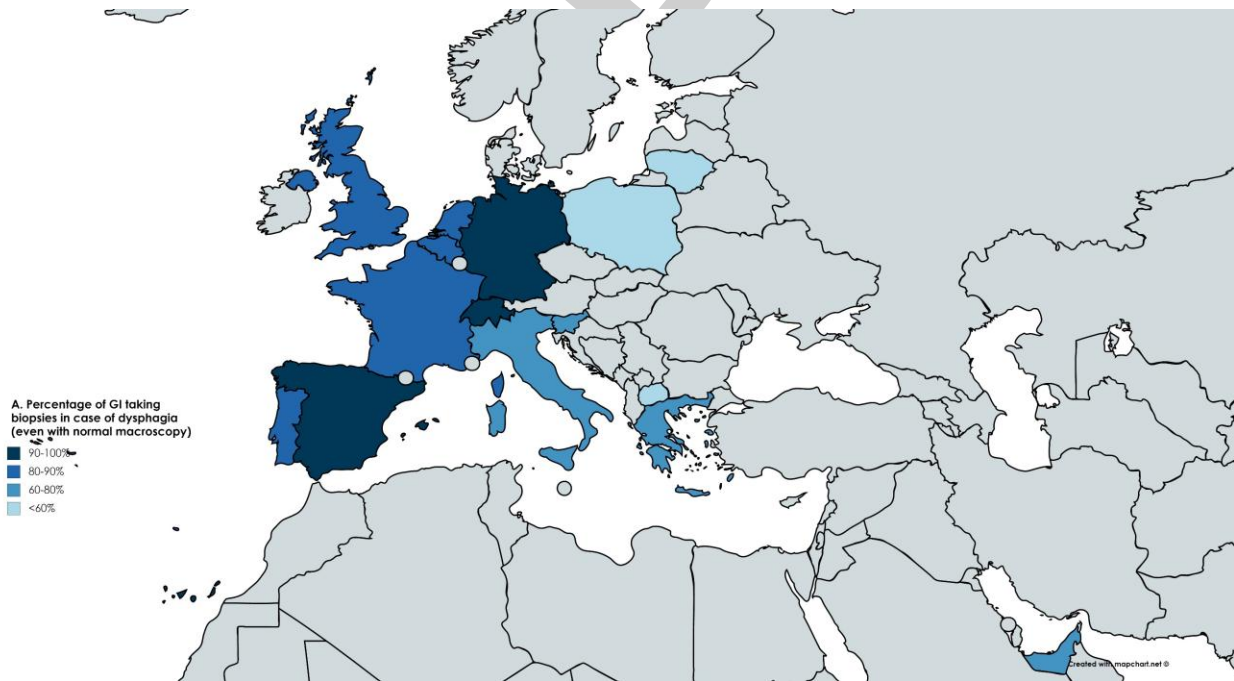


FIGURE 2 – Country specific percentages of gastroenterologists taking esophageal biopsies in case of dysphagia (even without macroscopic abnormalities).

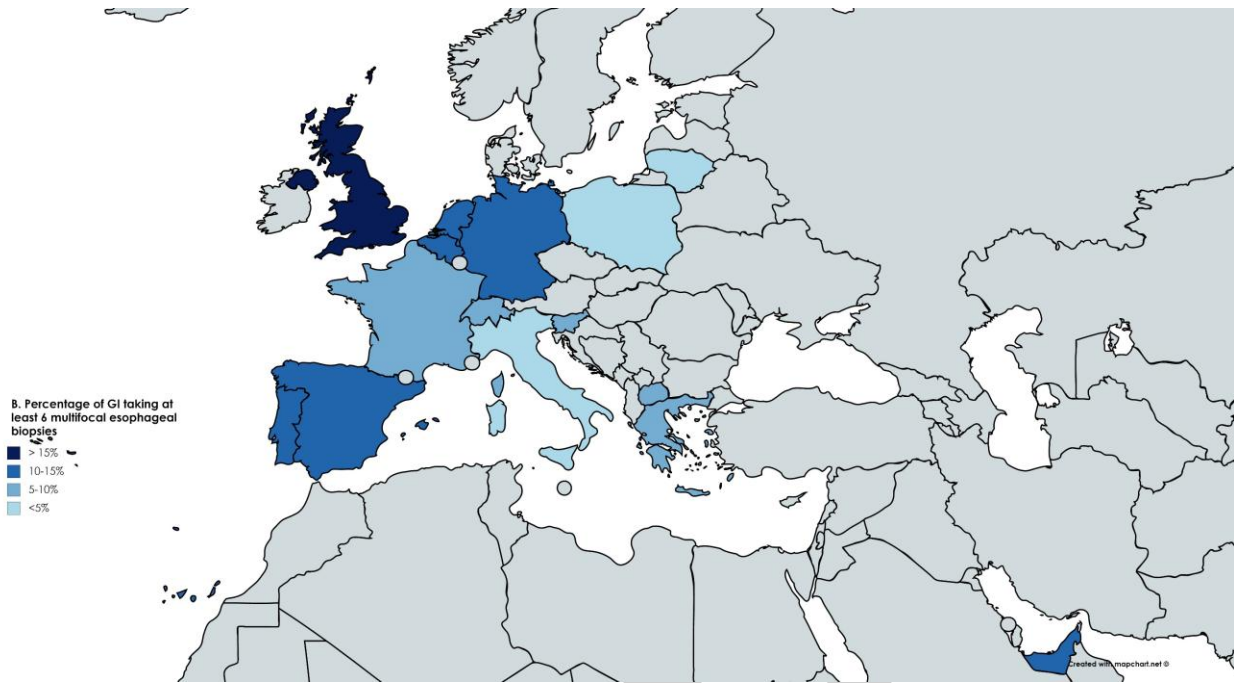


FIGURE 3 - Country specific percentages of gastroenterologists taking at least 6 multi-level esophageal biopsies when suspecting eosinophilic esophagitis.

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TABLE 1 – Country specific response rates and physician demographics.

PG = Pediatric Gastroenterologists, AG = Adult Gastroenterologists, EoE = Eosinophilic Esophagitis.

	PG (n=465)	AG (n=743)	
	N, (% of all PG)	N, (% of all AG)	p-value
Country			<0,05*
Belgium	33 (66%)	31 (4.1%)	
France	52 (16.3%)	110 (3.0%)	
Germany	39 (19.9%)	/	
Greece	20 (66.7%)	148 (24.7%)	
Italy	27 (13.5%)	40 (1.3%)	
Lithuania	15 (39.5%)	23 (20.2%)	
Macedonia	2 (50%)	10 (41.7%)	
Poland	35 (38.9%)	34 (4.2%)	
Portugal	9 (36%)	24 (4.1%)	
Slovenia	8 (47.1%)	29 (32.2%)	
Spain	98 (47.1%)	87 (3.1%)	
Switzerland	23 (76.7%)	90 (36%)	
The Netherlands	22 (51.2%)	112 (21.6%)	
United Arab Emirates	22 (84.6%)	3 (1,7%)	
United Kingdom	60 (33.5%)	2 (0.1%)	

Active in academic setting	337 (72.5%)	224 (30.1%)	<0.001*
Over 7 years of clinical experience	299 (64.3%)	509 (68.5%)	0.149
Special interest in EoE	339 (72.9%)	334 (45.0%)	<0.001*
Number of EoE patients under your care			
3 or less	116 (24.9%)	391 (52.6%)	<0.001*
4 or more	349 (75.1%)	352(47.4%)	<0.001*

* Significant differences were found between the response rates by PG and AG for each country individually.