Practice Differences in the Diagnosis and Management of Eosinophilic Esophagitis Among Adult and Pediatric Gastroenterologists in Israel

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ABSTRACT

Objectives: Eosinophilic esophagitis (EoE) guidelines call for similar practices in adults and children with EoE. We compared the diagnostic and management practices of gastroenterologists treating adult and pediatric patients suspected of having, or diagnosed with, EoE.

Methods: A 19-question multiple-choice questionnaire was given to gastroenterologists treating either adults or children. Questions explored 4 areas of interest: physician demographics, diagnosis and tissue sampling practices, management, and the need for societal publications on EoE.

Results: Completed questionnaires were returned by 85/180 adult and 30/40 pediatric gastroenterologists (PGs). Compared to PGs, adult gastroenterologists (AGs) took esophageal biopsies significantly less frequently in the following scenarios: endoscopy without esophageal symptoms or macroscopic endoscopic findings (10% vs 57%; $P < 0.001$), dysphagia without macroscopic findings (83% vs 100%; $P = 0.019$), and gastroesophageal reflux symptoms with distal esophageal erythema (44% vs 100%; $P < 0.001$). Significantly fewer AGs reported taking gastric and duodenal biopsies when EoE was suspected (29% vs 90%; $P < 0.001$). AGs more often followed patients clinically (30% vs 0%; $P < 0.001$) rather than endoscopically, and were far less inclined to implement elimination diets compared to PGs (23% vs 68%; $P < 0.001$).

Conclusions: Significant disparities exist between gastroenterologists treating adult and pediatric patients with EoE. These findings may impact rates of diagnosis, appropriate treatment, monitoring, long-term outcomes, and may affect negatively transition from pediatric to adult care.

Key Words: children, oesophagitis, transition

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What Is Known

- Esophageal biopsies serve as the main tool to both diagnose and follow patients with eosinophilic esophagitis.
- International practice guidelines call for similar practices in both adult and pediatric patients.

What Is New

- Significant disparities exist in the management practices of gastroenterologists caring for adult or pediatric patients suspected of, or diagnosed with eosinophilic esophagitis.
- Gastroenterologists treating adult patients with eosinophilic esophagitis take fewer esophageal biopsies compared to those treating pediatric patients in clinically relevant scenarios.
- There are significant differences in treatment regiments recommended by gastroenterologists treating adult and pediatric patients.

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory condition affecting the esophagus (1), triggered by ongoing exposure to dietary and/or environmental antigens (2–4).

The incidence of EoE has been rising during the past 2 decades, owing both to increased awareness and a true rise in incidence (5–7). The clinical manifestations range from very mild food avoidance or gastroesophageal reflux, to severe dysphagia, food impaction, and vomiting associated with esophageal strictures. Because no pathognomonic symptoms or signs exist for EoE, and the clinical presentation broadly overlaps with other disorders, endoscopy with esophageal biopsies serves as the main tool for both diagnosis and follow-up. Adequately sensitive and specific noninvasive biomarkers of the presence or activity of EoE have yet to be described. Consensus guidelines state that an esophageal biopsy with $\geq$15 eosinophils per high-power field (HPF) is required for diagnosis of EoE. Until the most recent European guidelines (1), the lack of a full response to high-dose proton pump inhibitors (PPIs) was also required for diagnosis of EoE. The 2017 guidelines include PPI use as a treatment option for EoE rather than a diagnostic exclusionary procedure. Although macroscopic esophageal findings such as furrowing, white exudates and esophageal rings are suggestive of EoE, they are neither sensitive nor specific enough to obviate the need for biopsies. Thus, when EoE is in the differential diagnosis of a patient, esophageal biopsies are recommended even in the presence of a normal appearing esophagus (2–4,8,9).

Recommendations for the diagnosis and treatment of EoE in children and adults are almost identical (4). The clinical practices of

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gastroenterologists treating adults, however, often differ from their colleagues treating children. This may relate to differences in the frequencies of the pathologies seen by pediatric gastroenterologists (PGs) and adult gastroenterologists (AGs), variance in underlying pathophysiological mechanisms, dissimilar clinical presentations at different ages, and differences in response to treatment. Patient acceptance of therapeutic regimens may also differ between children and adults. Practice differences between AGs and PGs may influence not only the frequency of EoE diagnosis but also affect the management, adherence to treatment, prognosis, and patients' satisfaction. This may be of particular importance when patients diagnosed before adulthood are transitioned from pediatric to adult care.

In this pilot study we aimed to characterize the diagnostic and management practices of AG and PG in Israel treating patients who may have EoE and to describe differences between these 2 gastroenterologist cohorts.

METHODS

A structured multiple-choice questionnaire, consisting of 19 questions, was given to both AGs and PGs to be answered anonymously. The questions explored 4 areas: physician demographics, diagnosis and tissue sampling practices, management, and need for societal publications on EoE. In this study PPI trials were addressed, as the guidelines by Lucendo et al (1) had not yet been published when the physicians answered the questions, and the answers address adherence to available recommendations.

Differences between AGs and PGs were analyzed using χ^2 test. When one of the groups contained 5 or less cases a Fisher exact test was used instead. P value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS-23 software (SPSS, Armonk, NY). As this study did not involve any patient information, and filling of the questionnaire indicated consent to do so, formal ethical clearance was waived by the local (Rabin Medical Center) ethics committee.

RESULTS

The study questionnaire was handed out to AGs and PGs at the yearly joint conference of the Israeli Gastroenterology Society and the Israeli Society for Pediatric Gastroenterology, Hepatology and Nutrition, in February 2016. A total of 220 gastroenterologists received questionnaires (180 AGs and 40 PGs). Completed questionnaires were returned by 85 (47.2%) AGs and 30 (75%) PGs. Two physicians were removed from analysis, as they responded that they treat both adults and children and thus could not be assigned exclusively to either study group.

The demographic characteristics of responders are presented in Table 1. Although both the practice setting and years in practice were similar, only few AG reported an interest in EoE, whereas half of the PG reported having such an interest ($P = 0.007$). On average, PGs have more EoE patients under their care than their adult counterparts ($P < 0.001$).

Biopsy practices during esophago-gastro-duodenoscopy (EGD) in several clinical scenarios were explored (Table 2). Compared to AGs, PGs were significantly more inclined to take esophageal biopsies during EGD performed in the absence of symptoms of esophageal dysfunction and without macroscopic findings on endoscopy in the presence of dysphagia but with no macroscopic abnormalities, in the presence of symptoms of gastroesophageal reflux disease (GERD) with erythema in distal esophagus on endoscopy. PGs reported taking both gastric and duodenal biopsies when suspecting EoE more often than AGs. Moreover, of those taking esophageal biopsies in EGD performed for GERD, PGs reported sampling more esophageal levels than their adult counterparts.

TABLE 1. Demographic and general characteristics of responders

Question	AG N, (%)	PG N, (%)	P
Responders	85	30	
Academic hospital practice	75/85 (88.2)	29/30 (96.6)	0.28
Duration of practice			
Still in fellowship	20/84 (23.5)	9/30 (30)	0.48
Over 7 years of experience	41/84 (48.8)	11/30 (36.7)	0.27
Special interest in EoE	22/84 (26.2)	16/30 (53.3)	0.007
Number of EoE pt. under your care			
3 or less	72/84 (85.7)	11/30 (36.7)	
4 or more	12/84 (14.3)	19/30 (63.3)	<0.001

AG = adult gastroenterologists; EoE = eosinophilic esophagitis; PG = pediatric gastroenterologists.

No significant differences were found between groups in biopsy practices following foreign body or food bolus impactions (FBIs) ($P = 0.11$).

Both physician groups reported similar high rates of high-dose PPI treatment in patients with esophageal eosinophilia, as recommended, rather than skipping directly to an EoE-specific treatment (diet or medication) (2–4) (Fig. 1A). AGs more often assessed response to medical or dietary interventions according to changes in clinical symptoms compared to PGs who universally reported endoscopic re-evaluation (Fig. 1B).

There were significant preference differences between the 2 physician groups regarding initial EoE-specific treatments when most PGs prefer elimination diets (any form of dietary elimination) whereas most AGs prefer topical corticosteroids as their first-line treatment. Moreover, although all PGs used some form of elimination diet in the management of EoE, about one-quarter of AGs responders never utilized this treatment (Fig. 1C).

TABLE 2. Biopsy practices in different clinical scenarios

Question	AG N, (%)	PG N, (%)	P
Takes esophageal biopsies Neither symptoms of esophageal dysfunction nor macroscopic findings	8/84 (9.5)	17/30 (56.7)	<0.001
Dysphagia with no macroscopic findings	69/84 (82.1)	30/30 (100)	0.019
GERD with erythema in distal esophagus—any biopsies	36/81 (44.4)	30/30 (100)	<0.001
Biopsies from different levels (of those taking any biopsies)	8/81 (9.9)	14/30 (46.7)	0.036
After removal of foreign body or food bolus impaction	62/81 (76.5)	27/30 (90)	0.11
Biopsies taken from multiple levels when suspecting EoE			
2 different levels	39/57 (68.4)	15/27 (55.6)	
3 different levels	18/57 (31.6)	12/27 (44.4)	0.25
Takes both gastric and duodenal biopsies when suspecting EoE	23/80 (28.8)	27/30 (90)	<0.001

AG = adult gastroenterologists; EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease; PG = pediatric gastroenterologists.

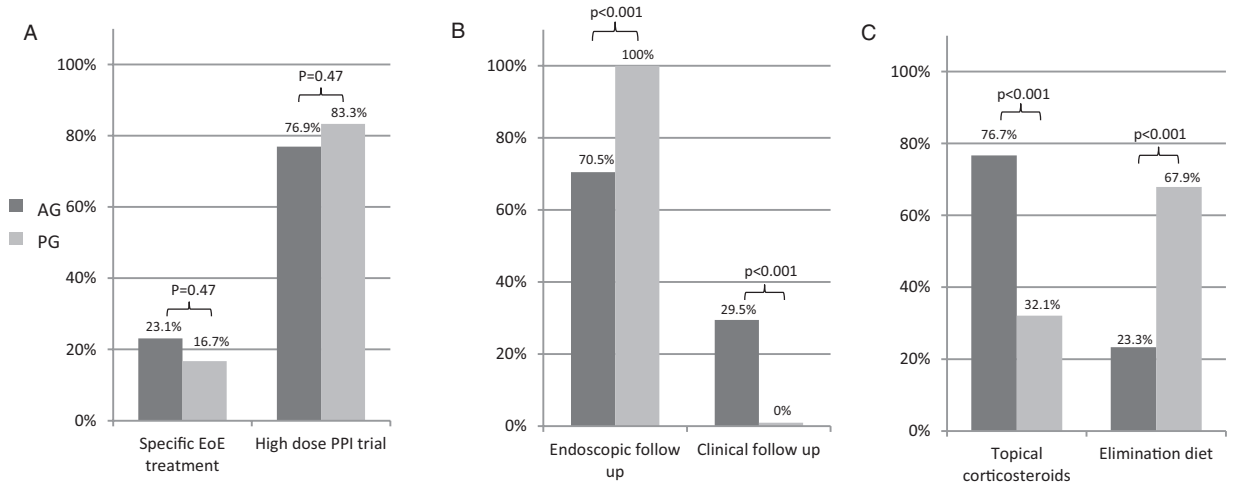

FIGURE 1. Treatment and follow-up preferences among adult gastroenterologists (AGs, dark grey) and pediatric gastroenterologists (PGs, light grey). A, Initial treatment after esophageal eosinophilia is found (AGs—78, PGs—30). B, Type of follow-up to assess response to treatment for a patient with dysphagia and esophageal eosinophilia (AGs—78, PGs—30). C, Initial treatment choice for a patient diagnosed with eosinophilic esophagitis with dysphagia (AGs—73, PGs—28).

Referral of EoE patients for allergic assessment was high in both groups, whereas PG more often reported working with a nutritionist experienced in EoE dietary counseling (Fig. 2).

Slightly more than half (54.4%) of the AGs felt comfortable transferring an 18-year-old patient with EoE from a PG practice to their care while still in the process of dietary reintroduction following a 6-food elimination diet. Nevertheless, 35.4% said they would only allow transfer of care after the whole process of food reintroduction had been completed, and 10.1% said they would not transfer the patient into their care even after a completed evaluation.

The vast majority of PG (93.3%) reported that they had read at least 1 of 3 available position papers compared to only 43.8% of AG ($P < 0.001$). Conversely, 91.1% of AGs responded that publication of a position paper authored by national societies would help them care for their EoE patients compared to only 73.3% of PG ($P = 0.016$).

DISCUSSION

This study found significant differences in EoE diagnostic and management practices between a cohort of AG and PG in Israel, including endoscopic tissue sampling practices and treatment choices. Past publications assessing these issues are scarce. A retrospective study by Rassbach et al (10), reviewing patients with esophageal eosinophilia, found that pediatric patients were more likely to have received a diagnosis of EoE, to be referred for allergy testing and to receive EoE-specific therapy (either topical steroid or dietary modification) compared to adult patients. In addition, pediatric patients underwent a second endoscopy with esophageal biopsies more often than adult patients. However, as the study by Rassbach was retrospective and only examined patients already found to have esophageal eosinophilia, the physician characteristics (eg, PGs vs AGs) and attitudes toward diagnosis and management were not assessed. A small survey by Dellon et al (11) of 18 eosinophilic gastrointestinal (GI) disease researchers concentrated on tissue sampling practices for eosinophilic disorders. They reported that of these 18 physicians, PGs more often sampled the stomach and duodenum when EoE was suspected than did AG. Their results, indicative of highly focused researchers, however, may not be representative of the broader physician population who treat EoE.

In our study, interest in EoE was noted more frequently by PGs compared to AGs. PGs tended to be more aggressive in assessing for EoE and to abide by diagnostic consensus guidelines. PGs were much more inclined to obtain esophageal biopsies than

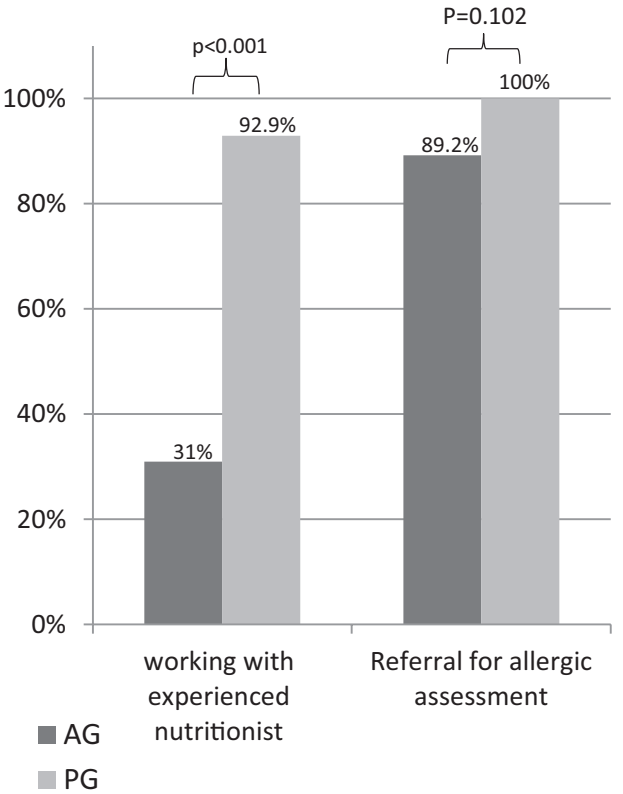

FIGURE 2. Referral of eosinophilic esophagitis patients for allergic assessment and access to an experienced nutritionist among adult gastroenterologists (AGs, dark grey) and pediatric gastroenterologists (PGs, light grey). Allergic assessment (AGs—74, PGs—29); experienced nutritionist (AGs—71, PGs—28).

AGs, in certain clinical scenarios. Regarding the practice of performing esophageal biopsies in a normal appearing esophagus during EGD, it is imperative to recognize that EoE may be found histologically even in a macroscopically normal esophagus (2–4,9,12,13). A recent study by Teriaky et al (14) found that among 1297 patients with macroscopically normal EGD, 20% had abnormal histological findings. Among the 502 patients with abnormal histology there were 13 (3%) who were diagnosed with EoE. Another retrospective study reviewing 1000 EGDs performed in pediatric patients, Sheiko et al (15) found that 23/76 (30.2%) of patients with esophageal eosinophilia had no macroscopic findings. Teriaky et al (14) have noted that the additional cost of obtaining biopsies from normal appearing mucosa should be weighed when sampling is considered. Thus the clinical scenario under which endoscopy is performed should be taken into consideration when deciding to biopsy the esophagus.

As dysphagia is one of the leading presenting symptoms of EoE (especially in adolescents and adults) (3,9,16) it is not entirely clear why only 83.1% of AG obtain esophageal biopsies rather than universally as reported by the PGs in cases of dysphagia. Suggested explanations may be decreased suspicion of EoE, perceived higher rates of alternative causes of dysphagia in a normal appearing esophagus such as dysmotility (diagnosed by alternative modalities), or higher rates of patient turnover in the adult endoscopy units.

In contrast to dysphagia, GERD is very common, especially in adults. Furthermore, adult guidelines state that in cases of suspected GERD without macroscopic findings, taking esophageal biopsies cannot be recommended (17). In the pediatric age group however, societal guidelines for GERD do recommend esophageal biopsies to rule out other diseases (18). Thus, our finding that all PG take esophageal biopsies in case of suspected GERD but with no esophageal mucosal breaks on endoscopy, while 36/81 (44.4%) of AG do the same, is not surprising. Although erosive esophagitis is, however, not typical of EoE, erythema of the distal esophagus in the absence of mucosal breaks may be found in some patients with EoE, and thus biopsies should none the less be considered.

Regarding FBI, EoE was diagnosed in 18% to 62% of patients presenting with FBI (19,19–23). Reflecting the common practice, Philpott et al (24) reviewed a 10-year period of experience with FBI. Among 1132 patients treated endoscopically for FBI, esophageal biopsies were obtained in only 278 (24.6%). Of note, 85 (30.6%) of these were diagnosed with EoE. In our study most physicians, both AGs and PGs, reported taking esophageal biopsies at either the time of disimpaction or at another endoscopy dedicated to re-assessment and tissue sampling.

The American College of Gastroenterology clinical guidelines for EoE recommended that gastric and duodenal biopsies be obtained in all children and in adults with intestinal symptoms or endoscopic abnormalities (3). We found that when EoE was suspected, 27/30 (90%) of PG reported complying with the recommendation compared to 23/80 (28.8%) of AG ($P < 0.001$). These findings are corroborated by those of Dellon et al (11) who surveyed a consortium of eosinophilic GI disease researchers and found that while all 11 PGs took gastric and duodenal biopsies for patients suspected of having EoE, only 4/7 (57%) AGs with special research interest in eosinophilic GI diseases did so. Lucendo et al (13) reported that gastric and duodenal biopsies were obtained in 47.8% and 40.8% (respectively) of endoscopies in 705 EoE patients, with no difference between pediatric and adult patients. The above study reported eosinophilic infiltration in only 1% and 2.1% of gastric and duodenal biopsies, respectively.

Overall, in this study, AGs were far less inclined to obtain biopsies in clinical scenarios that may raise suspicion of EoE. Thus, they may be more prone to miss or delay the diagnosis. This may be due to decreased interest in EoE, a lower index of suspicion, or lack of knowledge of clinical guidelines.

While all PG reported following recommendations to perform endoscopic follow-up after PPI treatment or treatment changes, only 70.5% of AG did so ($P < 0.001$), a finding similar to what was reported by Rassbach et al (10). Several studies have found that symptom assessment does not adequately correspond to histological response in EoE as it may in other esophageal conditions (25,26), and therefore should not be used in place of endoscopy.

Treatment preferences also differed significantly between the physicians groups. We found that the majority (68%) of PG prefer elimination diets as initial therapy for EoE for a theoretical patient with symptoms of dysphagia, while 77% of AG favored topical steroids ($P < 0.001$). Similarly, while all PG use some form of elimination diet in their EoE patients, only 76% of AG do so ($P = 0.003$). In the study by Rassbach et al (10) pediatric patients with EoE were much more likely to have received dietary intervention compared to adult patients. These significant practice differences may be due to several reasons. PG may prefer elimination diets over steroid treatment because of the perception that topical treatment may be associated with growth impairment as has been demonstrated for inhaled steroids in asthma (27) in conjunction with adrenal suppression in pediatric EoE treated with topical steroids (28–30). On the other hand, AGs may be under the impression that adult EoE is less responsive to allergen removal. In addition, access and referral of patients to dieticians with experience in guidance for balanced elimination diets may be limited in AGs practice. Another explanation may be that adult patients may be less inclined to attempt dietary interventions, though this study assessed physician treatment preferences and not patient preferences. Alternatively, lack of familiarity with protocols for elimination and food reintroduction may also play a role. Finally, guidance for dietary interventions are much more time consuming for the treating physician and lack of reimbursement may be additional factors affecting management practices.

Sperry et al (31) have shown that the uniformity of diagnostic criteria for EoE increased following the publication of consensus guidelines. While 93% of PGs, however, had read 1 of the main EoE guidelines (2–4), only 44% of AGs had done so ($P < 0.001$). This, again, is likely secondary to the decreased interest of AG in EoE. Despite this, 91% of AGs said that publication of position papers by the local professional organizations would help them care for their EoE patients.

As all pediatric EoE patients eventually reach adulthood and require transition to AG care, it is imperative this subject be addressed. Eluri et al (32) recently reported, using a questionnaire filled by EoE patients aged 16 to 25 years and their parents, a low level of transition knowledge and readiness of transition, especially when compared with other chronic conditions. Dellon et al (33) elucidated a constellation of obstacles for such a transition and suggested a framework for a transition program. In our study only 54.4% of AG felt comfortable with the transition of 18-year-old EoE patients still in the process of food re-introduction to their care. Moreover, 10.1% of the responders stated they would not transfer such a patient even after completing the food re-introduction phase. These findings may be in part due to decreased interest in EoE, not being familiar with gastroenterology societal position papers and low experience with dietary treatment for EoE or time allocation or reimbursement issues. It seems that increased awareness and interest in EoE as well as publication of gastroenterology societal position papers may increase the willingness of AG to transfer of such patients into their care. In addition, the differing first-line treatments preferred by PG and AG may cause confusion and

patient dis-satisfaction in adolescents transferred to adult practice after a recent diagnosis of EoE.

Our study has some inherent limitations. First, the cohort of physicians responding to the questionnaire was not large, which may have introduced some selection bias. It was limited to those practicing in Israel, which may not be representative of the international community of gastroenterologists treating EoE. This study is, however, the first to address these issues, and thus may act as a pilot study, which will trigger a broader, international study to address these findings. Although response rates were suboptimal, these rates were consistent with physicians' response rates in reviews of physician surveys (34,35) and are higher than electronic questionnaire surveys reported for EoE (36). Nevertheless, we were able to identify significant and clinically meaningful differences in the surveyed areas of practice, which we feel have clinical, in addition to statistical significance. Second, the study involved self-reported practice patterns, and did not examine actual practice. As such there may be differences between the reports and real life practice. There is, however, no reason to believe that this would skew the results differently between the 2 physician groups. The majority of responding physicians in both groups practice in an academic hospital setting, which reflects the national situation. In Israel, most gastroenterologists practice at least part time in academic hospitals. Thus, those practicing solely in community clinics may be underrepresented in our study. Furthermore, this study is representative of a national cohort and as such may not represent gastroenterologist practices in other countries.

In summary, this study suggests significant disparity in the management practices of gastroenterologists caring for adult or pediatric patient suspected of, or diagnosed with EoE. Lower biopsy rates may lead to underdiagnosis of EoE or eosinophilic gastroenteritis in adult patients. Substantial differences exist in treatment regiments used. These findings may impact rates of diagnosis, plasticity of patients' response to treatment and long-term health outcomes. They may also have significant impact on the success of transition of EoE patients from pediatric to adult care. It will be necessary to assess if the differences found in this study are generalizable in different practice settings and geographic regions. Future studies may also elucidate the reasons for the reported differences outside of specialized EoE care centers, in order to optimize patient care.

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