CME

Adherence to Celiac Disease and Eosinophilic Esophagitis Biopsy Guidelines Is Poor in Children

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ABSTRACT

Objectives: Celiac disease (CD) and eosinophilic esophagitis (EoE) are underdiagnosed gastrointestinal conditions, which adversely affect children's health. Previous studies have shown that diagnostic guidelines for CD are not consistently followed in adults. The aims of the present study are to assess the frequency with which endoscopists comply with diagnostic guidelines for CD and EoE in children, and to determine whether an association exists between adherence to biopsy guidelines and disease detection in pediatric patients.

Methods: We reviewed pathology reports from 9171 children (ages 0–18) with at least 1 duodenal biopsy, and 8280 children with at least 1 esophageal biopsy, with specimens submitted to a national pathology laboratory. Frequency of adherence to diagnostic guidelines and recommendations for CD and EoE were determined, and the effect of this upon detection of CD and EoE.

Results: Overall, 35% of cases were biopsied according to the 2006 American Gastroenterological Association guidelines for CD diagnosis; 8% were biopsied according to the 2007 American Gastroenterological Association EoE consensus recommendations. Detection of CD and EoE increased with the number of biopsies collected (P for trend in each <0.001). Adherence to diagnostic guidelines was particularly poor among those found to have histologically normal mucosa in both cohorts. The likelihood of CD and EoE diagnosis was significantly associated with adherence to diagnostic guidelines (odds ratio for CD 6.3, 95% confidence interval 4.4–8.9; odds ratio for EoE 2.4, 95% confidence interval 1.9–2.9).

Conclusion: Adherence to established guidelines is poor, and improved guideline adherence is associated with greater disease detection rates for CD and EoE.

Key Words: celiac disease, children, endoscopy, eosinophilic esophagitis, guidelines, pediatric

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What Is Known

- Both celiac disease and eosinophilic esophagitis require biopsy for diagnosis, and each condition may be present despite grossly normal mucosal appearance.
- In adult patients, compliance with 2006 American Gastroenterological Association guidelines has shown increased diagnostic yield of celiac disease, whereas no such data exist in pediatric groups for celiac disease or for eosinophilic esophagitis in any age group.

What Is New

- Compliance with AGA celiac disease guidelines and eosinophilic esophagitis consensus statements for children undergoing upper endoscopy is poor.
- Greater adherence to biopsy guidelines is observed in cases in which celiac disease and eosinophilic esophagitis are ultimately diagnosed, and is poorer when disease is not suspected during the procedure.
- Greater disease detection for both celiac disease and eosinophilic esophagitis is associated with appropriate guideline adherence, and disease detection rates increase with increased mucosal sampling.

Both celiac disease (CD) and eosinophilic esophagitis (EoE) are conditions that may impair growth in children and require a heightened index of suspicion and appropriate endoscopic biopsy practices for optimal detection (1–3).

CD is an autoimmune condition in which gluten induces an inflammatory response in individuals with specific genetic haplotypes (HLA DQ2 and/or DQ8) (4). At this time, the prevalence of CD worldwide is approximately 1%, although in most populations only a fraction of these patients are diagnosed (1,5). Sequelae of undetected CD can be significant, including growth failure, anemia, diarrhea, abdominal pain, and malabsorption. More severe consequences such as neurologic disorders and increased risks of malignancy may occur (1,2,6).

EoE, an eosinophil mediated inflammatory condition, may cause symptoms of reflux, abdominal pain, or food impactions. The precise pathophysiology of EoE is not currently known. Studies suggest that EoE does not occur solely as an IgE-mediated response, but may be related to other immune processes (7). Esophageal biopsy is required to diagnose EoE and a suspected diagnosis can be confirmed for patients with esophageal eosinophil infiltration in the context of clinical symptoms (8). Morbidity can be significant, given that nutritional deficits, feeding difficulties, and esophageal stricture can occur with untreated disease (3).

The 2006 American Gastroenterological Association (AGA) guidelines for CD diagnosis recommend 4 to 6 duodenal biopsy specimens for optimal detection of CD (9). For the diagnosis of EoE, the 2007 AGA consensus recommendations suggest that esophageal specimens be collected from different esophageal locations (10). There is evidence of poor adherence to these guidelines with regard to small bowel biopsy for CD in adult patients (11,12), and among adults, adherence to CD diagnostic guidelines has been shown to increase detection of CD (11). Adherence to biopsy guidelines for CD has not been assessed in children, nor have adherence practices to EoE biopsy guidelines or related outcomes been evaluated for children.

The aims of the present study were to assess adherence to established biopsy guidelines for CD and EoE in children, and secondarily to examine the association between adherence to biopsy recommendations and diagnosis rates of CD and EoE in children.

METHODS

The present study examined deidentified biopsy data from consecutive, unique children ages 0 to 18 years who had at least 1 duodenal biopsy (n = 9171) or at least 1 esophageal biopsy (n = 8280) collected during an approximately 5-year period from 2008 through early 2013 by a national outpatient pathology laboratory in the United States (Miraca Life Sciences, Irving, TX). Data were organized into duodenal and esophageal biopsy cohorts, respectively. The laboratory receives biopsy specimens collected by gastroenterologists from 43 states, the District of Columbia, and Puerto Rico. Specimens were interpreted by approximately 40 gastrointestinal pathologists who use a standardized approach to specimen handling, diagnostic criteria, and terminology (see Supplemental Digital Content, Appendix, http://links.lww.com/MPG/A949). Wherever a patient had >1 upper gastrointestinal endoscopy, specimens collected during the first procedure were considered. For all patients, data regarding the number and site of biopsies received by the laboratory (bulb vs distal duodenum; distal, mid, proximal, unspecified esophagus) were analyzed.

Duodenal Biopsy Cohort and Celiac Disease Definition

Initially, 9171 patients among the duodenal biopsy cohort fulfilled our inclusion criteria. A histopathologic diagnosis of CD was rendered when duodenal biopsy specimens showed blunting or flattening of the villi accompanied by intraepithelial lymphocytosis (see Supplemental Digital Content, Appendix, http://links.lww.com/MPG/A949, for diagnostic criteria). Descriptive statistics were performed based on grouping this cohort into 3 categories: patients with a new diagnosis of CD based on the current biopsy (new CD); patients with a history of CD who were undergoing repeat endoscopy (known CD); and patients without evidence of CD (non-CD).

Determination of Guideline Adherence

Our primary outcome measure for the duodenal biopsy cohort was the frequency of adherence to the 2006 AGA biopsy guidelines for CD diagnosis, current at the time during which patients in the cohort were biopsied (9). Guideline adherence was defined as cases in which at least 4 duodenal biopsy specimens were submitted, and was determined among all 9171 cases in this cohort.

Determination of Celiac Disease Detection Rates According to Guideline Adherence

To address our secondary aim, we determined and compared CD detection rates between those biopsied according to and apart from AGA diagnostic guidelines.

Esophageal Biopsy Cohort and Eosinophilic Esophagitis Definition

Initially, 8280 patients in the esophageal biopsy cohort fulfilled our inclusion criteria. A diagnosis of EoE was rendered based upon the following criteria: ≥15 eosinophils per high-power field (HPF); sampling from >1 esophageal site and/or compatible endoscopic or clinical information (Supplemental Digital Content, Appendix, http://links.lww.com/MPG/A949, for diagnostic criteria). As in the CD cohort, descriptive statistics were performed based on grouping cases into the following categories: patients with a new diagnosis of EoE based on the current biopsies (new EoE); those with a known history of EoE (known EoE); and those with neither current evidence nor history of EoE (non-EoE).

Determination of Guideline Adherence

Our primary outcome measure for the esophageal biopsy cohort was the frequency of physician adherence to the 2007 AGA consensus recommendations for diagnosis of EoE, current at the time of the start of the study period (10). As these guidelines called for histologic inspection of distal and proximal esophageal mucosa and of any specific areas that appeared grossly abnormal, we defined minimal adherence to these recommendations as collection of at least 1 esophageal biopsy specified to be from each of at least 2 separate locations. Cases in which multiple biopsies were submitted from a single unspecified location were classified as ''nonadherent'' given that the precise locations of biopsy could not be confirmed.

Determination of Eosinophilic Esophagitis Detection According to Guideline Adherence

To address our secondary aim for this cohort, we compared EoE detection rates between those biopsied according to and apart from the 2007 AGA diagnostic recommendations.

Sensitivity Analyses

We additionally conducted analyses to determine how endoscopist suspicion for a CD or EoE diagnosis before endoscopy may have influenced adherence rates. In one analysis, we separately examined adherence to guidelines among patients determined to have histologically normal duodenal and esophageal mucosa (as a surrogate for grossly normal mucosa), which may have driven down adherence rates, and compared this with cases in which there were some duodenal or esophageal histologic abnormalities (though not necessarily CD or EoE) noted. In a second analysis, we compared respective guideline adherence rates for those with suspected or known history of CD or EoE with the remainder of each cohort to determine to what extent index of suspicion influenced guideline adherence rates.

Statistical Analyses

For normally distributed continuous variables, relationships were tested using a *t* test. Certain variables, such as patient age and number of biopsies collected were not normally distributed, however. As a result, a 2-sample Wilcoxon rank sum (Mann-Whitney) test was used for nonparametric variables. A nonparametric test of trend (extension of Wilcoxon rank sum test) was used to analyze the relationship between the number of biopsies collected and the proportion of those diagnosed with CD or EoE. A 2-sample test

TABLE 1. Duodenal biopsy practices and patient characteristics

	All Patients (N = 9171)	New CD (N = 190)	Known CD (N = 92)	Non-CD (N = 8906)	*P* (new vs non-CD)
Median age (IQR), y	14 (8–17)	13 (7–17)	16 (11–17)	14 (8–17)	0.1
Sex (%F)	56.8	67.4	61	56.6	0.005
Median No. duodenal biopsy specimens (IQR)	3 (2–4)	5 (4–6)	5 (4–7)	3 (2–4)	<0.001
Adherence to AGA guidelines	3250 (35.4%)	149 (78.4%)	70 (76%)	3048 (34.2%)	<0.001

AGA = American Gastroenterological Association; CD = celiac disease; IQR = interquartile range.

of proportions was used to compare proportions in certain cases, whereas logistic regression was used for this purpose wherein multivariate analyses were indicated. The probability of a diagnosis of CD and EoE in the setting of guideline adherence was determined in a multivariate regression model, controlling for a history of and suspected disease. Data analyses were performed using Stata/IC 13.0 for Windows (College Station, TX). The present study was determined to be exempt from review by the Institutional Review Board of Columbia University Medical Center.

RESULTS

Duodenal Biopsy Cohort

General Patient and Biopsy Details

The median age of the 9171 patients in the duodenal biopsy cohort was 14 years (Table 1). Females were predominant in the duodenal biopsy cohort (56.8%). A median of 3 duodenal biopsies were submitted for each patient. Significantly more fragments were submitted for those cases found to have CD.

Adherence to Guidelines for Celiac Disease Diagnosis

Of the 9171 patients in the entire cohort, 3250 (35.4%) were biopsied according to the 2006 AGA guidelines for CD diagnosis. Patients newly diagnosed with CD were more frequently biopsied according to these guidelines than patients without evidence of CD on biopsy (Table 1). There was no significant difference in guideline adherence according to sex (odds ratio [OR] 0.9, 95% confidence interval [CI] 0.9–1.1). Older patient age predicted a greater likelihood of biopsy according to CD guidelines (OR 1.03, 95% CI 1.03–1.04).

Celiac Disease Detection With Adherence to Diagnostic Guidelines

CD was detected with significantly greater frequency for patients who were biopsied in accordance with diagnostic guidelines when compared with those biopsied apart from these guidelines (5% detection vs 0.7%, $P < 0.001$). When controlling for those with a history of CD or suspected CD in a multivariate model, the OR of detecting CD while adherent to biopsy guidelines was 6.3 (95% CI 4.4–8.9). Overall, the likelihood of diagnosing CD escalated in relation to the number of duodenal biopsies collected (Fig. 1) (P for trend < 0.001). In a separate analysis excluding those with a history of CD or suspected CD (based on mention of CD serologies in the pathology report), this trend was unchanged ($P < 0.001$).

Sensitivity Analyses

Of the 7594 patients in this cohort noted to have a histologically normal duodenum, wherein the gross mucosal appearance was presumed to be normal as well, adherence to CD biopsy guidelines was 33.1% (n = 2516). In contrast, significantly greater adherence to CD biopsy guidelines was found among the 1577 cases in which the mucosa was not histologically normal (46.5%, $P < 0.001$). Of the 92 patients with either a history of CD or suspected CD, 76% were biopsied according to the 2006 AGA guidelines, significantly greater than the remainder of the cohort (35%, $P < 0.001$).

Esophageal Biopsy Cohort

General Patient and Biopsy Details

Among 8280 children who had at least 1 esophageal biopsy, the median age was 13 years (Table 2). There was a slight female predominance (53.4%). The most common number of esophageal biopsies collected was 2, inclusive of all locations biopsied.

Adherence to Consensus Recommendations for Eosinophilic Esophagitis Diagnosis

Of the 8280 children in the cohort, 8.2% had at least 2 biopsies collected from separate locations in the esophagus, as recommended by the 2007 AGA consensus recommendations. Biopsies from unspecified locations were collected for 68% of patients. Those whose biopsies indicated new EoE diagnoses were more frequently biopsied according to the AGA recommendations than those without EoE (Table 2). Males were significantly more likely to undergo biopsy according to these guidelines (OR 1.6, 95% CI 1.4–1.9), as were older patients (OR 1.03, 95% CI 1.02–1.05).

Eosinophilic Esophagitis Detection With Adherence to Diagnostic Recommendations

EoE detection overall was 9.3%. Patients with known or newly diagnosed EoE had significantly more esophageal biopsies

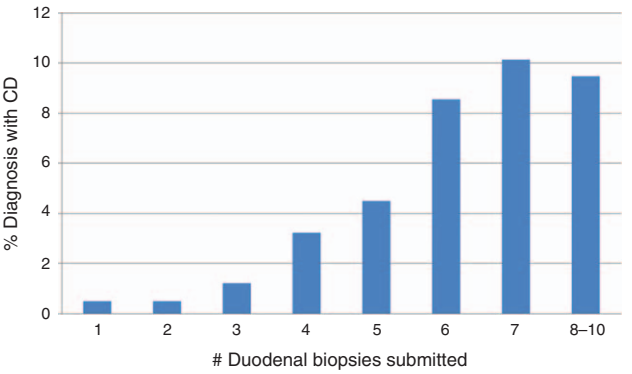

FIGURE 1. Proportion of celiac disease diagnosis according to the number of biopsies collected, entire cohort. CD = celiac disease.

TABLE 2. Esophageal biopsy practices and patient characteristics

	All Patients (N = 8280)	New EoE (N = 747)	Known EoE (N = 22)	Non EoE (N = 7511)	*P* (new vs non-EoE)
Age, y	13 (8–17)	12 (7–17)	10 (7–17)	13 (8–17)	0.01
Sex (%F)	53.4%	26.2%	36%	56.1%	<0.001
Median No. esophageal biopsy specimens (IQR)	2 (2–4)	4 (3–6)	4 (3–5)	2 (2–4)	<0.001
Adherence to AGA consensus recommendations	680 (8.2%)	160 (22.1%)	11 (50%)	473 (6.7%)	<0.001

AGA = American Gastroenterological Association; EoE = eosinophilic esophagitis; IQR = interquartile range.

collected than those without EoE history or EoE on biopsy (Table 2). EoE was detected with significantly greater frequency for patients who were biopsied in accordance with diagnostic guidelines when compared with those biopsied apart from these recommendations (25.5% vs 7.9, $P < 0.001$).

When controlling for those with a history of EoE or suspected EoE, the OR of detecting EoE while adherent to biopsy guidelines was 2.4 (95% CI 1.9–2.9). A direct relationship was noted between the number of esophageal biopsies collected and a diagnosis of EoE (Fig. 2) (P for trend < 0.001). This relationship persisted in a separate analysis excluding patients with a history of EoE or suspected EoE.

Sensitivity Analyses

Among the 4642 cases in which histologically normal esophageal mucosa was found, adherence was noted in 6.6% of cases, significantly fewer than when compared with adherence in 3638 cases in which esophageal histologic abnormalities were noted (10.2%, $P < 0.001$). When cases of known or suspected EoE were considered separately (n = 862), adherence to biopsy guidelines was still only 27.9%, although this remained significantly greater than for the remaining 7418 patients in this cohort (5.9%, $P < 0.001$).

DISCUSSION

These data demonstrate that adherence to biopsy guidelines for CD and EoE is poor among pediatric endoscopists, and that an important advantage of such guideline adherence in children is a greater probability of detection of CD and EoE. For children undergoing endoscopic biopsy, this is the first description of guideline adherence rates for CD and EoE and of the potential to improve diagnosis of these disorders with adherence to biopsy guidelines. The analysis of histopathologic data collected, processed, and diagnosed in a standardized manner and originating from a wide variety of patients and endoscopy practices provides valuable insight into biopsy practices utilized across the United States.

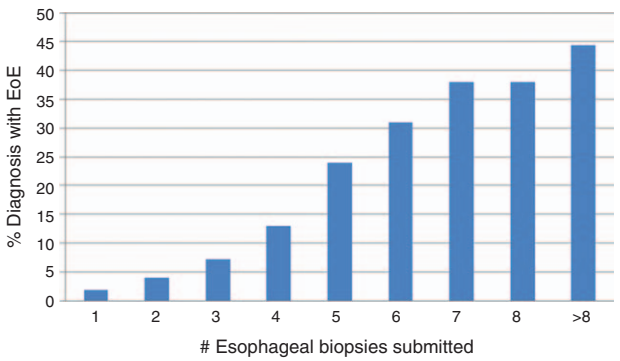

FIGURE 2. Proportion of eosinophilic esophagitis diagnosis according to the number of biopsies collected, entire cohort. EoE = eosinophilic esophagitis.

The outcomes of our sensitivity analyses highlight potential flaws in current endoscopic practice. First, grossly normal mucosa is biopsied far less frequently than when there is mucosal inflammation. Second, guideline adherence is frequently reserved for those with known or suspected disease, and even among these high-risk cases, guideline observance is suboptimal. Because of this clear link, highly suspected disease likely triggered greater adherence in many instances, although this is not likely to explain the entirety of the association between adherence and disease detection—in separate analyses, trends in biopsy rates persisted even after exclusion of known or suspected cases for both disorders, with rates of detection of both conditions escalated in relation to the number of biopsy fragments submitted. This is evidence for better disease detection attributable in part to sufficient collection of mucosal biopsies.

CD detection in the United States is low. Although approximately 0.7% of participants in the United States National Health and Nutrition Examination Survey had CD, 83% of these individuals were previously undiagnosed (5). Lack of awareness of the clinical manifestations of CD likely contributes to this gap (13) and failure to biopsy adequately when these manifestations arise is common (12). Collection of at least 4 duodenal biopsies has been shown to increase CD detection among adults (14). Lebwohl et al (11) demonstrated that detection of CD among adults biopsied according to the 2006 AGA CD guidelines surpassed that of patients for whom fewer biopsies were collected. Endoscopic appearance does not always point to the presence of CD (15); 43% of children with histologic evidence of CD in 1 study had no gross clues during endoscopy (16). Missed CD diagnoses resulting in diagnostic delay may result in need for future endoscopy, and diagnostic delays have been linked to poorer health-related quality of life outcomes (17). The most recent CD diagnostic guidelines published by the American College of Gastroenterology in 2013 recommend even more stringent biopsy practices than those studied in this cohort, calling for sampling of the duodenal bulb in addition to the distal duodenum for optimal diagnosis (18). These updated guidelines are likely to further improve CD detection, although our data suggest that the gap between current practice and these American College of Gastroenterology guidelines may be even wider than what we observed in the present study.

Likewise, examination of sufficient esophageal biopsies is critical to establishing an EoE diagnosis (19). Accordingly, more recent guidelines for EoE diagnosis now recommend collection of a minimum of 2 biopsy fragments from *each* of 2 locations (20–22). Only half of patients with known EoE and 27% of those whose biopsy reports indicated suspected EoE were biopsied according to the earlier consensus recommendations, however. As in CD, visual inspection is not a reliable method of EoE detection (23) and in

many cases of EoE, the esophagus may be grossly normal (24,25). Approximately half of patients with histologically normal mucosa studied in this cohort were biopsied according to practices recommended for EoE assessment. Despite current biopsy recommendations, the benefits of adherence for diagnosis of EoE have not been well described to date. Additionally, our data demonstrate that the likelihood of a diagnosis of EoE is directly proportional to the number of biopsies submitted, and that there may be benefit to collecting more than 2 to 4 biopsies, as we observed an ongoing rise in EoE diagnoses with 6 to 8 submitted biopsy fragments and in cases wherein >8 biospy fragments were submitted.

Our study has several limitations, mainly related to its retrospective design. We analyzed data exclusively from an independent pathology laboratory, with the majority of cases considered from outpatient centers. No data from hospital-based or academic practices with their own pathology services were included. This likely explains the skewed age distribution toward older children, as younger children would likely require general anesthesia and thus a hospital setting for endoscopic procedures, and may have limited our data regarding biopsy practices for very young children. Additionally, lack of inclusion of more varied practice settings may also have influenced biopsy trends we observed. Lastly, we did not have access to family history or other patient history that might have influenced endoscopy practices, and clinical information and the endoscopist's gross impressions in this dataset were limited. Although our sensitivity analyses were conducted to control for endoscopist visual impressions, data may not have been adequately recorded by the gastroenterologist in all cases. Thus in cases in which guideline adherence predicted disease diagnosis, we do not know how gross abnormalities influenced the extent of mucosal biopsy, particularly concerning instances wherein a particularly high quantity of esophageal or duodenal biopsies was submitted.

Despite these limitations, this population-based study of several thousands of children undergoing upper endoscopy demonstrates that adherence to biopsy guidelines for these 2 conditions is insufficient, and suggests that improved adherence to biopsy guidelines increases detection of both CD and EoE.

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