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The concordance of endoscopic and histologic findings of 1000 pediatric EGDs

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Abstract

Background—Pediatric gastroenterologists frequently perform routine endoscopic biopsies despite normal-appearing mucosa during EGD. Older small studies have supported this practice.

Objective—To re-evaluate the concordance between endoscopic appearance and histology in the era of high-definition endoscopy.

Design—Retrospective cohort study.

Setting—Single tertiary care center.

Patients—A total of 1000 pediatric patients undergoing initial EGD.

Main Outcome Measurements—Endoscopic and histologic findings.

Results—The overall rate of an endoscopic finding was 34.7%, which was 40.4% of a histologic finding. Concordance between the presence of any endoscopic finding and any histologic finding in all locations was 69.9% (Cohen's κ coefficient = 0.32). In the esophagus, the concordance between any endoscopic finding and any histologic finding was 82.6% (κ = 0.45). The stomach was 73.2% concordant (κ = 0.18), and the duodenum was 89.3% concordant (κ = 0.42). The κ coefficient decreased when comparing specific findings in each location; it was 0.34 in the esophagus, 0.17 in the stomach, and 0.34 in the duodenum. If biopsy specimens had only been obtained when the endoscopist identified abnormal mucosa, 48.5% of the pathologic findings would have been missed. In patients with histology consistent with eosinophilic esophagitis,

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30.2% had normal-appearing mucosa. For celiac disease, 43% had normal-appearing mucosa. In the stomach, an abnormal endoscopic appearance was more likely to have normal histology.

Limitations—The single-center, retrospective nature and more endoscopists than pathologists.

Conclusions—These data support the routine collection of biopsy specimens in the duodenum, stomach, and esophagus during EGD in pediatric patients.

The concordance between endoscopic findings and histologic findings during EGD is important in the practice of pediatric gastroenterology. Immediately after the endoscopy, the endoscopist reviews the findings of the endoscopy with the family. Being able to give them accurate information is crucial. Families can become confused when they are told that the endoscopic appearance was abnormal, but then the biopsy specimens were normal. An accurate prediction of the likelihood of a histologic finding in the setting of a visually normal endoscopy can help prepare families for unanticipated results. Second, physicians can be tempted to change clinical management based on the endoscopic appearance, such as starting a proton pump inhibitor when the stomach appears to have gastritis. Physicians would be more likely to avoid this behavior if they knew that the endoscopic appearance of gastritis is not predictive of histologic gastritis. Additionally, pathologists usually review the endoscopic findings during the review of the histology. Knowing that there tends to be low concordance would be important for the interpretation of the histology. Finally, depending on the pattern of results, low concordance would also justify routine biopsies in the context of a normal endoscopic appearance despite the increased cost and potentially increased procedural risk.

BACKGROUND

During EGD, adult gastroenterologists tend to perform biopsy only when they notice an endoscopic abnormality, whereas pediatric gastroenterologists frequently perform biopsy, even in the setting of a normal endoscopic appearance. Some adult studies have supported routine biopsies because of low correlation between endoscopic and histologic findings. Carr et al[1] found concordance in endoscopic and histologic diagnoses of gastritis in 66% of 400 cases and argued that accurate diagnosis of gastritis necessitates biopsies. Other adult studies argued for routine duodenal biopsies.[2,3]

Previous studies in children have encouraged routine endoscopic biopsies.[4-6] The few available pediatric studies have found low rates of concordance between endoscopic and histologic findings for EGDs. Dahshan and Rabah[5] reviewed 204 esophageal biopsy specimens and 59 gastric biopsy specimens and found overall agreement with histology to be 63.8% with low specificity and sensitivity of endoscopy. In another study of 94 patients, the endoscopic sensitivity and specificity were 82% and 27%, respectively, in the duodenum and 57% and 47%, respectively, in the gastric body.[7] In an Italian study, endoscopy often underestimated the severity of histologic findings.[8] Oderda et al[9] found a concordance of only 13.8% when comparing 32 biopsies with duodenal damage with their endoscopic findings. Other studies have begun to compare specific endoscopic findings with histologic findings, which also have poor concordance. In a study that evaluated the association

between gastric nodularity and *Helicobacter pylori*, it found that gastric nodularity had a sensitivity of 61% for *H pylori*, arguing for routine biopsies.[10]

Because of the small numbers of patients in these studies and their lack of temporal proximity, a current review of the practice of routine endoscopic biopsies is warranted. The availability of higher-definition endoscopes in the past several years may affect the concordance between endoscopic and histologic findings in children. This study was designed to evaluate the concordance of endoscopic findings with EGD compared with histologic findings among a large cohort of patients in the pediatric setting. We hypothesized that despite advancements in endoscopic technology, concordance between endoscopic and histo-logic findings would remain low.

METHODS

This retrospective cohort study was performed at Children's Hospital Colorado, a large tertiary freestanding hospital, and was approved by the Colorado Multiple Institutional Review Board (protocol number 10-1247, approved November 17, 2010). By reviewing 1642 sequential EGDs between January 2009 and March 2010, we identified 1000 eligible patients undergoing initial diagnostic endoscopy. For the endoscopy to be considered an initial diagnostic endoscopy, patients could not have undergone EGD with biopsy within the previous 5 years. They also had to have had at least 1 biopsy specimen taken from any location in the upper GI tract. Exclusion criteria included patient age of younger than 1 month or older than 18 years and whether or not the EGD was performed to follow a known GI condition. This excluded 9 additional cases with Peutz-Jeghers syndrome, tracheoesophageal fistula, or inflammatory bowel disease.

A single researcher (M.S.) performed all data collection. The cases were initially identified by review of the records of EGDs performed within the time period. The cases were then found in the electronic medical record, and inclusion and exclusion criteria were reviewed for each patient. The electronic medical record was fully implemented in 2004, which allowed us to track previous EGDs. Clinic notes were also reviewed for a history of EGD, and then patient age, sex, physician referring the patient for endoscopy, the top 3 indications for endoscopy, the endoscopist, endoscopic findings, pathologist, and histologic findings were recorded. Three pathologists made the initial histologic determination, and 10 endoscopists had performed the EGDs. The endoscopes that were available during that time period in the endoscopy suite included the Olympus GIF 160, Q180, N180, H180, Q160, XP180N, and XP160 (Olympus America, Center Valley, Pa). The particular endo-scope that was used for each procedure was not recorded in this study. The XP endoscopes were used for patients weighing less than 10 kg. Endoscopies were performed with white light, and narrow-band imaging was used at the discretion of the endoscopist. In our practice, we rarely use narrow-band imaging. We did not use postendoscopy image enhancement technology. Our standard practice was to take 2 biopsy specimens from the duodenum, 2 specimens from the stomach (usually from the antrum and body), 2 specimens from the proximal esophagus, and 2 specimens from the distal esophagus. Endoscopists typically performed additional biopsies at the sites of endoscopic abnormalities. In the case of patients with a high suspicion for celiac disease, additional biopsy specimens are often taken from

the duodenal bulb, although this practice was not standardized. The number of specimens per site was not recorded.

All endoscopic findings were noted, including erythema, white plaques, ridging, and edema, among others. The endoscopic findings were then categorized into general categories such as esophagitis, findings consistent with eosinophilic esophagitis (EoE), and “other” for the esophagus. A pediatric gastroenterologist reviewed all endoscopic findings to ensure correct categorization. All histologic findings were recorded and were similarly categorized as for endoscopic findings. The categories for the esophagus included esophagitis, EoE, other, and none. Histology consistent with EoE was defined as the presence of 15 or more eosinophils per high-power field. The stomach had the categories of gastritis, *H pylori/* nodular gastritis, other, and none. The duodenum had the categories of celiac disease, duodenitis, other, and none. All histologic findings were reviewed by an independent pathologist who had not made the original diagnosis for determination of clinical importance. Mild gastritis was not considered clinically important and was not included.

After data collection, categorization, and determination of clinical importance, concordance was determined. For the first analysis, any positive endoscopic finding in a given location was considered concordant if there were any positive histologic findings. In the second step of the analysis, cases were considered concordant if their endoscopic and histologic findings were of the same category, such as features consistent with esophagitis on endoscopy and histologic esophagitis. To be completely concordant, the esophagus, stomach, and duodenum all had to have concordant positive or negative findings. To be considered partially concordant, 2 of the 3 anatomic locations had to be concordant.

All analyses were conducted using Stata version 13.1 statistical software (StataCorp, College Station Tex). We generated simple counts and proportions to describe the study population, as well as the clinical and histopathologic findings for each site. To assess for concordance between endoscopic findings and histopatholgic findings (overall and by each location), Cohen's κ was used, which is a measure of concordance for nominal categorical variables that adjusts for chance agreements because of base rates and is used to assess interrater reliability. Additionally, we calculated the positive predictive value (PPV) and negative predictive value (NPV) for each location, as well as the false-negative rate, sensitivity, and speci-ficity. The false-negative rate represents cases in which a histologic finding was not seen on endoscopy, and it is calculated as 1 – sensitivity. Finally, we calculated the 95% confidence interval for the κ coefficients for individual endoscopists.

RESULTS

Demographic data and indications are displayed in Table 1. The overall rate of an endoscopic finding was 34.7%, and that of a histologic finding was 40.4%. In the esophagus, 17.4% of patients had endoscopic findings, and 21.9% had histologic findings. Gastric endoscopic findings were found in 15.6% of patients with 24.6% of patients having histologic findings, whereas the duodenum had an endoscopic findings rate of 10.0% with 10.7% of patients having histologic findings. Further discussion of indications and rates of findings were previously published.[11]

When comparing the overall presence of an endoscopic finding with the presence of a histologic finding, 69.9% of endoscopies were completely concordant, and 90.4% were partially concordant. Table 2 displays the PPV, NPV, sensitivity, specificity, and concordance between the presence of any endoscopic and histologic finding by site. Concordance is presented as Cohen's κ coefficient and is the concordance for the endoscopists as a group. In the esophagus, the concordance of the presence of any endoscopic finding and the presence of any histologic finding was 82.3% (Table 3). A total of 171 patients had endoscopic esophageal findings, with 66 of these patients having normal findings on biopsy specimens, whereas 105 patients had histologic findings. A total of 799 patients had normal esophageal mucosa endoscopically, but 106 of these patients had positive histology. The stomach was 73.2% concordant; 153 patients had positive endoscopic findings with only 66 of these patients having positive histology (Table 4). Of the 825 patients with no endoscopic findings in the stomach, 175 had histologic findings. The duodenum was 89.3% concordant (Table 5). Ninety-eight patients had duodenal endoscopic findings, and 49 of these patients had histologic findings. There were 888 patients with no endoscopic findings, but 56 of them had histologic findings.

With regard to the specific categories in each location, 9.8% of patients had endoscopic findings consistent with esophagitis, and 12.4% had histologic esophagitis. EoE was diagnosed in 7.8% of histologic cases, and 5.6% of patients had endoscopy findings consistent with EoE. In 30.2% of the cases with histologic findings consistent with EoE, the endoscopic appearance was normal. Another 30.2% of the histologic cases of EoE had the endoscopic appearance of esophagitis. Gastritis was found in 10.6% of endoscopies and 21.8% of histologic slides. However, endoscopic findings of gastritis predicted histologic gastritis only 31% of the time. Findings consistent with *H pylori* were seen in 3.8% of endoscopies and 2.5% of pathology slides. In 25% of the cases with histologic evidence of *H pylori*, the endoscopic appearance of the stomach was normal. A total of 4.8% of patients had endoscopy consistent with duodenitis and 3.6% had a histologic duodenitis, whereas 3.0% had endoscopic findings of celiac disease and 6.6% had histology consistent with celiac disease. In 43% of cases with histology consistent with celiac disease, the endoscopic appearance of the duodenum was normal.

Comparing specific endoscopic findings with the histo-logic findings yields even lower concordance; Cohen's κ coefficients (all significant at $P < .001$) are presented in Tables 2 through 5 for the esophagus, stomach, and duodenum, respectively. The κ coefficient was 0.45 for concordance between any endoscopic and histologic finding in the esophagus, and it was 0.34 for concordance between specific findings. For the stomach, the κ coefficient was 0.18 for any findings and 0.17 for specific findings. For the duodenum, the coefficient was 0.42 for any findings and 0.34 for specific findings.

The rates of endoscopic findings did vary by endoscopist (Table 6). Table 6 displays the percentage of endoscopic findings by site for each endoscopist along with the percentage of histologic findings. In our endoscopy suite, patients were scheduled according to their preference: the first available physician or their primary gastroenterologist. Therefore, the patients for each endoscopist did vary according to their specialization. This likely explains the difference in the rates of histologic findings for each endoscopist and some of the

variation in their endoscopic finding rates. The κ coefficient, calculated for individual endoscopists, did vary by endoscopist. However, the 95% confidence intervals for the individual κ coefficients overlapped for all but 3 of the endoscopists (who had performed fewer EGDs), indicating that there were not significant differences in the κ values *between* endoscopists. Neither the rate of findings nor the κ coefficient correlated with years of experience. After review by an independent pathologist, there was no difference in the rates of histologic findings for each pathologist.

DISCUSSION

The results of our study illustrate a considerable discrepancy between endoscopic and histologic findings in the pediatric population. There has long been controversy about the role of routine biopsies during endoscopy, with many adult gastroenterologists preferring to avoid biopsies unless there are visible endoscopic findings to suggest pathology. This practice aims to decrease unnecessary costs and adverse events by minimizing the number of biopsy specimens obtained. In this pediatric series, however, such an approach would miss a significant histologic finding in almost half of all patients. EoE represents a prime example of the potential for missed diagnoses, because in more than 30% of EoE patients, the esophagus had a completely normal endoscopic appearance, and only 36% had an endoscopic appearance consistent with EoE. Similar results were found with specific diagnoses such as *H pylori* and celiac disease, in which 25% and 43%, respectively, had normal endoscopic appearances and would presumably have been missed if biopsy specimens had not been taken.

As a diagnostic test overall, endoscopic appearance during EGD in this series performed poorly, with an overall sensitivity of 51%, specificity of 80%, PPV of 69%, and NPV of 65%. In particular, the predictive value of endos-copy in the stomach was poor; patients with positive endoscopic findings in the stomach were more likely to have normal histology. The κ coefficients for the concordance between endoscopic and histologic findings were similar between individual endoscopists, suggesting that the recognition of gross pathology (or the absence thereof) was similar between endoscopists, despite the fact that endoscopic findings correlated poorly with histology. On the whole, these data would support the rationale for routine biopsies in pediatric patients, although our analyses do not address potential incremental adverse event risks that might be associated with the increased number of biopsies or any cost-benefit analysis of biopsy.

In addition to highlighting the benefit of routine biopsies in pediatric patients, regardless of the endoscopic appearance, the poor concordance between endoscopic and histologic appearance illustrates the need for an accepted and validated classification system to define endoscopic lesions in the pediatric population. Previously published data from this same cohort demonstrated the large degree of variability in endoscopic classification among endoscopists as opposed to pathologists.[11] Data from the Peds-CORI database also verified the need for more uniform nomenclature in identifying endoscopic findings and indicated the need for clearer definitions.[12] Developing a clear set of endoscopic criteria for endoscopic diagnoses that were more reliable in predicting pathology would provide several benefits. The first would be a greater degree of confidence in communicating endoscopic

findings to parents immediately after endoscopy, avoiding the need to be purposely vague or noncommittal. The second would be the potential for improvement in the diagnostic detection rate of pediatric pathologists because the greater validity of endoscopic diagnosis could prompt a more targeted and efficient evaluation of the histologic specimens.

This study has limitations to consider that may affect the applicability of the findings. First, this was a single-center, retrospective study with no predetermined definitions for the classification of endoscopic findings. Second, the probability of the specific diagnoses encountered are likely to differ significantly compared with other areas in the United States and abroad, so differences in sensitivity and specificity would be expected at other centers. Finally, there was a small number of interpreting pathologists compared with a large number of endoscopists, which could tend to increase the variability of endoscopic findings while decreasing the variability seen on histology. Our data confirm that there was a large degree of variation across endoscopists, irrespective of their years of experience, potentially biasing these results. As reviewed earlier, this variation in endoscopic interpretation, in contrast to the uniformity of histologic interpretation, highlights the need for a more standardized approach to endoscopic classification and supports the role of routine biopsies in confirming or refuting the endoscopic findings. Although there was no standardized protocol with regard to the number and location of biopsy specimens obtained in the face of normal endoscopic appearance in this retrospective study, practice in this group was fairly uniform, as outlined in the Methods section. Despite the limitation that these factors may pose in the applicability of this study to other groups, we believe that these practices are common across many pediatric centers and therefore remain relevant.

Caution must also be advised in extrapolating these findings to endoscopy in adult patients in whom the type and prevalence of GI pathology would be expected to differ greatly compared with children. Nevertheless, differences in the frequency and number of biopsy specimens routinely collected in adult versus pediatric patients may account for differences in reported adverse event rates.[13,14]

CONCLUSION

This study confirms the findings of previous studies that showed poor concordance between endoscopic and histologic findings of EGD in the pediatric population. Despite the mentioned limitations, our study is the largest current analysis of pediatric endoscopic and histologic concordance, which will allow us to better counsel our patients' parents after endoscopy and support routine biopsies. Even with the recent advances in endoscopy, concordance was moderate to low at all sites and with all types of findings. Concordance was lowest in the stomach, followed by the duodenum and then the esophagus. In this cohort, a normal endoscopic appearance was predictive of normal histology in two-thirds of all patients. If biopsy specimens had only been obtained when the endoscopic appearance was thought to be abnormal, approximately half of the patients with significant pathologic findings would have been missed, supporting the role of routine biopsies at the time of EGD in children.

Abbreviations

EoE	eosinophilic esophagitis
NPV	negative predictive value
PPV	positive predictive value

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TABLE 1

Demographics of the study population[11]

Characteristic	% of total (N = 1000)
Sex	
Male	49.2
Female	50.8
Age, y	
<1	6.6
1-4	23.3
5-12	35.4
13-18	34.7
Primary indication listed on chart	
Abdominal pain	28.7
Reflux	11.7
FTT	9.5
Diarrhea	8.8
Emesis	8.6
Epigastric pain	8.5
Celiac antibodies positive	6.9
Dysphagia	7.3
GI bleeding	6.7
Foreign body	1.6
Feeding issues	0.7
Other	0.6
Stricture	0.4

FTT, Failure to thrive.

TABLE 2

Sensitivity, specificity, false-negative rate, PPV, NPV, and concordance between the presence of any endoscopic and histologic finding by site

	% Any endoscopic finding	% Any histologic finding*	Concordance (Cohen's κ)	PPV (TP/TP+FP)	NPV (TN/TN+FN)	Sens	Spec	False-negative rate (1 – sens)
Esophagus (n = 970)	17.4	21.9	0.45†	62.7	86.8	50.0	91.7	50.0
Stomach (n = 978)	15.6	24.6	0.18†	43.1	78.8	27.4	88.2	72.6
Duodenum (n = 978)	10.0	10.7	0.42†	50.0	93.6	46.7	94.4	53.3
Any site (N = 1000)	34.7	40.4	0.32†	64.8	72.6	55.7	79.5	44.3

PPV, Positive predictive value; *NPV,* negative predictive value; *TP,* true positive; *FP,* false positive; *TN,* true negative; *FN,* false negative; *Sens,* sensitivity; *Spec,* specificity.

*Nonspecific gastritis was not included.

†$P < .001$.

TABLE 3

Concordance between esophageal endoscopic and histopathologic findings *

	Histopathology (frequency)				
Endoscopy (frequency)	**None**	**Esophagitis**	**EoE**	**Other**	**Total**
None	693	82	23	1	799
Esophagitis	43	26	23	3	95
EoE	13	10	27	4	54
Other	10	2	3	7	22
Total	759	120	76	15	970

EoE, Eosinophilic esophagitis.

*$\kappa = 0.34$ ($P < .001$).

TABLE 4

Concordance between gastric endoscopic and histopathologic findings*

	Histopathology (frequency)				
Endoscopy (frequency)	**None**	**Gastritis**	***Helicobacter pylori***	**Other**	**Total**
None	650	168	6	1	825
Gastritis	70	32	0	2	104
Helicobacter pylori	8	11	18	0	37
Other	9	2	0	1	12
Total	737	213	24	4	978

*$\kappa = 0.17$ ($P < .001$).

TABLE 5

Concordance between duodenal endoscopic and histopathologic findings*

	Histopathology (frequency)				
Endoscopy (frequency)	**None**	**Duodenitis**	**Celiac**	**Other**	**Total**
None	824	25	28	3	880
Duodenitis	26	8	12	1	47
Celiac	8	0	21	0	29
Other	15	2	4	1	22
Total	873	35	65	5	978

*$\kappa = 0.34$ ($P < .001$).

TABLE 6

Variability by endoscopist

Endoscopist	No. of EGDs	% Esophageal finding	% Gastric finding	% Duodenal finding	% Any edoscopic finding	% Any histologic finding *	κ coefficient for individual endoscopist	95% CI for κ for individual endoscopist
A	199	25.1	18.6	13.1	45.7	39.7	0.3†	0.31-.043
B	197	12.7	13.7	10.2	33.0	36.0	0.37†	0.31-0.43
C	158	17.7	12.0	8.2	32.3	43.7	0.42†	0.36-0.47
D	108	8.3	10.2	7.4	20.4	41.7	0.45†	0.39-0.50
E	94	17.0	20.2	12.8	35.1	42.6	0.31‡	0.25-0.37
F	93	9.7	11.8	5.4	22.6	36.6	0.37†	0.31-0.43
G	61	21.3	14.8	3.3	34.4	34.4	0.20	0.14-0.26
H	48	29.2	22.9	18.8	54.2	50.0	0.25‡	0.19-0.31
I	35	8.6	22.9	5.7	37.1	42.9	0.17	0.11-0.23
J	7	42.9	28.6	28.6	57.1	85.7	0.36	0.31-0.42

CI, Confidence interval.

*Nonspecific gastritis was not included.

†$P < .000$.

‡$P < .01$.