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Diagnostic yield of oesophagogastroduodenoscopy in children with abdominal pain

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Abstract

Background: Abdominal pain is the most common indication for oesophagogastroduodenoscopy (OGD) in children. However, existing studies examining the diagnostic outcomes of OGD in children with abdominal pain are limited.

Aim: To examine the diagnostic yield of OGD with biopsy in the evaluation of abdominal pain and to describe the endoscopic and histological findings in patients undergoing OGD for abdominal pain of unclear aetiology.

Methods: We performed a retrospective cross-sectional cohort study in children under 18 years of age who had OGD for the primary indication of abdominal pain, at Texas Children's Hospital and Children's Hospital of The King's Daughters from 1 January 2002 to 30 June 2005.

Results: Overall, OGD was diagnostic in 454 (38.1%) of the 1191 procedures, including reflux oesophagitis (23%, *n* = 271), *Helicobacter pylori* infections (5%, *n* = 55), peptic ulcers (3%, *n* = 32), eosinophilic oesophagitis (2%, *n* = 25), celiac disease (1%, *n* = 9) and Crohn's disease (0.5%, *n* = 7). Male gender, older age, elevated C-reactive protein and vomiting were associated with increased diagnostic yield.

Conclusions: Our findings suggest that OGD is valuable for the evaluation of chronic abdominal pain in children, with a diagnostic yield of 38%. The majority of alarm symptoms and routine laboratory tests are not significantly associated with diagnostic yield.

BACKGROUND

Chronic abdominal pain is common in children and adolescents, affecting 13% of middle school students and 17% of high school students.[1, 2] However, evidence-based guidelines for the evaluation of chronic abdominal pain in this age group are limited.[3–5]

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Oesophagogastroduodenoscopy (OGD) has become a common procedure for the evaluation of chronic abdominal pain in children. Data from Pediatric Endoscopy Database System – Clinical Outcomes Research Initiative (PEDS-CORI) revealed that abdominal pain was the most common indication (38%) in 17,180 OGDs.[6] As OGD is generally not used to evaluate acute abdominal pain and is not a diagnostic test used in the preliminary evaluation of abdominal pain, it can safely be assumed that the majority of these procedures were performed in children with chronic abdominal pain (i.e. conventionally defined as pain for at least 2 months).

Oesophagogastroduodenoscopy is generally not recommended for the evaluation of chronic abdominal pain. A technical report by the American Academy of Pediatrics and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) concluded that in the evaluation of chronic abdominal pain, `there is little evidence to suggest that the use of endoscopy and biopsy in the absence of alarm symptoms has a significant yield of organic disease'.[7] Additionally, the Rome criteria for childhood functional gastrointestinal disorders do not require a negative OGD for diagnosis of abdominal pain-related functional disorders.[8]

In the evaluation of chronic abdominal pain, OGD may be useful if the physician suspects organic pathology [e.g. inflammatory bowel disease (IBD), peptic ulcer disease] and also may provide reassurance to the patient or family.[1] We previously performed a systematic review of the literature to evaluate the yield of OGD in children with abdominal pain by defining the prevalence of endoscopic and histological findings and clinical outcomes (e.g. change in treatment, quality of life, improvement of abdominal pain, cost-effectiveness).[9] We found that the diagnostic yield of OGD in children with abdominal pain was low (4%) in the existing literature; however, available studies were inadequate because of small sample size, variable findings and selection bias. Furthermore, specific histopathological findings such as oesophagitis (reflux or eosinophilic) were not reported as part of the diagnostic yield in most studies.

Therefore, we conducted the current study to examine the diagnostic yield of OGD with biopsy in the evaluation of abdominal pain, and describe the endoscopic and histological findings in patients undergoing OGD for abdominal pain of unclear aetiology in a large cohort of subjects from two centres in the US.

METHODS

Study design

We performed a retrospective cross-sectional cohort study[10] in children under 18 years of age who underwent OGD for the primary indication of abdominal pain at Texas Children's Hospital (TCH) in Houston, TX, and Children's Hospital of The King's Daughters (CHKD) in Norfolk, VA, from 1 January 2002 to 30 June 2005. Both centres are participants in PEDS-CORI, a national paediatruc endoscopy registry. To avoid repeated recording of measurements from patients with multiple examinations during the study period, only the patients' first OGD was included in the study.

We excluded procedures in patients with established IBD, celiac or ulcer disease because the cause of the abdominal pain in these cases is assumed to be known. We also excluded patients with a history of co-morbid medical or psychiatric conditions, such as organ transplant, cystic fibrosis and neurodevelopmental disorders (e.g. cerebral palsy, Down's syndrome, microcephaly), because the aetiology of pain in these patients is likely different from that of the general population.

The PEDS-CORI database was queried to identify procedures in unique patients who met the inclusion criteria in these two centres. Then, a manual chart review was performed on all patients who met the inclusion criteria. The chart review included the procedure note, the pathology report, laboratory reports, and history and physical (H&P) examination carried out within 6 months prior to the procedure.

Patient characteristics

The H&P examination note performed within 6 months prior to OGD was reviewed for underlying disease / diagnosis and the presence of alarm signs or symptoms. For patients without qualifying H&Ps, International Classification of Diseases, 9th Revision (ICD9) codes were reviewed in the electronic medical record to discover any underlying diagnosis prior to the OGD. All clinical information was collected before the procedure information to mask the reviewer of the outcome of the endoscopy. A review of laboratory tests obtained within 1 year prior to the procedure included: haemoglobin level, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and albumin.

We searched the eligible clinical notes for specific alarm symptoms or signs including: involuntary weight loss, deceleration of linear growth, gastrointestinal blood loss, significant vomiting, chronic severe diarrhoea or family history of IBD. Significant vomiting included daily vomiting for >2 weeks or bilious vomiting of any duration.[7] Chronic diarrhoea was defined as the passage of 3 or more watery stools per day for at least 2 weeks.[11] Involuntary weight loss, deceleration of linear growth, gastrointestinal blood loss and family history of IBD were considered present if specifically documented by the physician in the eligible H&P.

Diagnostic yield of OGD

Diagnostic yield was defined in this study based on gross endoscopic findings in procedure notes or histological changes in biopsy reports, and defined as having potential therapeutic or prognostic value.

Procedures that showed none of the abnormalities described above were considered to be without diagnostic yield. These included procedures with nonspecific endoscopic findings (e.g. erythema, increase or loss of vascularity, pallor) and descriptive histological changes (e.g. reactive changes, oedema, mild inflammatory changes).[12, 13]

Review of the final pathology report on biopsies provided the data source for histological diagnosis. Severe histological inflammation of the stomach or duodenum was defined by diffuse inflammatory changes with glandular destruction. Histological evidence of an oesophagitis with more than 20 eosinophils / high-power field (HPF) defined the diagnosis of eosinophilic oesophagitis (EO).[14, 15] We performed a secondary analysis of reports with increased eosinophils in the stomach (i.e. ≥10 eosinophils / HPF) and duodenum (i.e. ≥20 eosinophils / HPF), but did not include these outcomes as part of the diagnostic yield.[16] Original slides were also reviewed for all study subjects, with reported increase in eosinophils counts / HPF.

Medical records were reviewed and abstracted using explicit standardized forms. All collected data were entered into Access 2003 (Microsoft Corp., Redmond, WA, USA). Double entry of a random subset of 20% of the observations was used to identify problematic data entry issues, and discrepancies were solved by consensus.

Statistical analysis

Descriptive statistics were calculated for demographic features (e.g. gender, age) and clinical characteristics (e.g. alarm symptoms, underlying diseases). Chi-squared tests were used to compare patients with and without diagnostic yield for the distribution of categorical variables describing demographics (gender, race), clinical history (alarm symptoms, underlying diseases) and laboratory tests (anaemia, low serum albumin, elevated ESR, elevated CRP).

Logistic regression models were used to investigate the characteristics associated with diagnostic yield while controlling for potential confounding variables. A multivariable logistic regression model was constructed to include variables of interest among patients with available H&P (n = 941). Odds ratio and accompanying 95% C.I. were calculated using the maximum likelihood ratio method. Plots of residuals were reviewed to identify outliers. For all continuous variables in the model (age), linearity was verified by testing the association of the dependant variable with the independent variable. Correlations among independent variables were evaluated to assess for collinearity.

All analyses were performed using NCSS software (NCSS Institute, Inc., Kaysville, UT, USA).

RESULTS

Between 1 January 2002 and 30 June 2005, 1405 OGDs were recorded at the two PEDS-CORI sites, of which 214 (15.2%) were excluded for being repeat endoscopies in the same patient, having exclusion diagnoses or for patient age greater than 18 years. Thus, a total of 1191 OGDs performed in unique patients with a mean age of 11.5 years (s.d. 4.0 years) were included in the analysis. At least 1 biopsy was taken from three anatomic regions (oesophagus, stomach, duodenum) in 1099 (92.3%) of the enrolled patients. Among the included procedures, 661 (55.5%) were from TCH, and 530 (44.5%) from CHKD. The majority of patients were women (n = 714, 60.0%). Race was described as White in 69.5% (n = 828), Black in 16.3% (n = 194), Hispanic in 12.0% (n = 143) and Asian in 2.2% (n = 26). Approximately 22.8% (271) patients had a known condition prior to endoscopy, including gastro-oesophageal reflux (n = 166, 61%), constipation (n = 71, 26%), enteric infection (n = 7, 2.6%), thyroid disease (n = 7, 2.6%), lactose intolerance (n = 2, 0.7%) or pyloric stenosis (n = 2, 0.7%).

Of the 1191 patients, 941 (79.0%) had H&P notes available in the medical record within 6 months of the procedure. In the latter group of patients, 429 (45.6%) had at least one documented alarm symptom, and 133 had ≥2 symptoms reported. A total of 603 alarm symptoms were reported, the most common being weight loss (32.5%, n = 196), followed by RUQ / RLQ pain (22.8%, n = 138), GI bleed (22.6%, n = 136), chronic diarrhoea (7.6%, n = 46), dysphagia (7.0%, n = 42), vomiting (6.0%, n = 36) and growth failure (1.5%, n = 9).

Overall, OGD was diagnostic in 454 (38.1%) of the 1191 procedures, including 388 with histological diagnostic yield and 66 with endoscopic diagnostic yield. Histological diagnoses included reflux oesophagitis (59.7%, n = 271), *Helicobacter pylori* infections (12.1%, n = 55), EO (5.5%, n = 25), severe gastric or duodenal inflammation (3.7%, n = 17), celiac disease (2.0%, n = 9), Crohn's disease (1.5%, n = 7), Barrett's oesophagus (0.4%, n = 2) and *Candida* oesophagitis (0.4%, n = 2). Endoscopic diagnostic yield included peptic ulcers (7.1%, n = 32), hiatal hernias (4.9%, n = 22) and erosive oesophagitis (2.6%, n = 12).

Determinants of diagnostic yield

Procedures with and without diagnostic yield were compared with regard to demographic (e.g. age, gender, ethnicity) and clinical features (e.g. alarm symptoms, underlying disease, laboratory tests) (Table 1). Patients with a diagnostic yield were slightly older than those without (11.8 ± 3.7 vs. 11.3 ± 4.1 years; $P = 0.02$). Male patients had a significantly higher rate of diagnostic OGDs compared to that of female patients (43.4% vs. 34.6%; $P < 0.01$). Patients with one or more alarm symptoms did not have a significantly higher diagnostic yield than those without (38.8% vs. 35.7%; $P = 0.32$). Among specific alarm symptoms, only vomiting was associated with increased diagnostic yield. Vomiting had diagnostic yield in 19 children, including 11 (58%) with reflux oesophagitis, three (16%) with EO, one (5%) with hiatal hernia, one (5%) with peptic ulcer and one (5%) with Crohn's disease. The presence of a pre-existing underlying condition before endoscopy (e.g. gastro-oesophageal reflux, constipation) was not associated with a diagnostic OGD. Among laboratory tests, only elevated CRP was associated with diagnostic yield, whereas anaemia, hypoalbuminaemia and elevated ESR were not significantly associated with diagnostic yield. An elevated CRP was related to diagnostic yield in 26 patients, including 13 (50%) patients with reflux oesophagitis, five (19%) with peptic ulcers, two (8%) with Crohn's disease, two (8%) with *H. pylori* infections and one (4%) with EO.

Multivariable analysis

The multivariable logistic regression model included age, gender, significant vomiting and underlying disease as potential predictors of diagnostic yield (Table 2). After adjusting for all other variables, male gender (+46%), age (+4% per year) and vomiting (+100%) remained independently associated with increased diagnostic yield. There were no significant interaction terms for underlying disease, gender, significant vomiting or age.

Eosinophilic gastroenteritis

In a secondary analysis, we expanded the definition of diagnostic yield to include eosinophilic gastroenteritis, defined by increased eosinophils counts in the stomach (i.e. ≥10 eosinophils / HPF) or duodenum (i.e. ≥20 eosinophils / HPF) (Table 3). The expanded diagnostic yield of OGD increased from 454 to 575 patients (48.3% overall).

DISCUSSION

Our findings suggest that OGD is valuable for the evaluation of chronic abdominal pain in children, with a diagnostic yield of 38%. Reflux oesophagitis (23%) is the most common diagnosis, followed by *H. pylori* (5%), peptic ulcers (3%) and erosive oesophagitis (2%). Male patients with abdominal pain are more likely to have diagnostic findings from OGD procedures. Vomiting and elevated CRP may have predictive value of diagnostic yield; however, the majority of alarm symptoms and routine laboratory tests are not significantly associated with diagnostic yield.

Our data indicate that oesophagitis is the most common abnormal finding (24%) in children with abdominal pain. This was mostly histological oesophagitis consistent with reflux (23%), and rarely gross erosive oesophagitis (1%). This is in agreement with several studies in children that confirm that abdominal pain is a frequent presenting symptom of GERD.[17, 18]

Eosinophilic oesophagitis was present in about 6% of children with abdominal pain. While dysphagia is a common complaint in adults with EO, nonspecific abdominal pain is a more common presentation in children.[19] The normal limits for eosinophilic infiltration in oesophageal biopsies in this study have been employed in most previous EO studies.[14, 20,

[21] Additional features including eosinophil microabscesses, surface layering of eosinophils and degranulating eosinophils are not pathognomonic for EO.[14] OGD with biopsy remains essential to diagnose this condition, which may be increasing in frequency.[19, 20]

The diagnostic yield of OGD considerably increases if eosinophilic gastroenteritis is considered as part of this yield. Histopathology is required for diagnosis of eosinophilic gastroenteritis; however, because the diagnostic criteria remain unclear, eosinophilic gastroenteritis was not included in our primary analysis.[22, 23] One study found 1.9 ± 1.3 eosinophils / HPF in the gastric antrum and 9.6 ± 5.3 eosinophils / HPF in the duodenum in children without apparent pathology.[24] Autopsy studies of children who died unexpectedly revealed eosinophil counts in the stomach that were consistently low (mean 5 / HPF).[25] Abdominal pain is thought to be the most common presentation for eosinophilic gastroenteritis.[26, 27] Evidence in adult patients indicates that duodenal eosinophilia may characterize a subset of patients with dyspepsia.[28] Recent lines of evidence have led to the proposal that the neural-mast cell-eosinophil interaction may cause abdominal pain-related symptoms characteristic of functional disease.[29, 30] Based on our criteria of ≥10 eosinophils / HPF in the stomach and ≥20 eosinophils / HPF in the duodenum, 11.4% of the enrolled patients had significant eosinophilic infiltrates. The diagnostic yield would be approximately 48% with the inclusion of these patients. Further prospective studies are needed to explore the link between eosinophilic gastrointestinal inflammation and chronic abdominal pain.

In this study, only 5% of children enrolled had histological evidence of *H. pylori*. Among 1537 procedures in fourteen previous studies, 461 (30%) were positive for *H. pylori*.[9] This difference is likely reflective of regional as well as cohort differences. A causal relation between *H. pylori* infection and abdominal pain is possible, but has not been confirmed in the absence of ulcer disease.[31–34] Additionally, clinical trials in children have suggested that healing of gastric inflammation and eradication of *H. pylori* may not significantly increase symptomatic relief of abdominal pain.[35] However, there is a trend to offer eradication therapy to *H. pylori*-infected patients with abdominal pain, and OGD with biopsy is the gold standard for detection of *H. pylori*.[31, 36]

In the current study, we found that several alarm symptoms other than vomiting were not significantly predictive of diagnostic yield. Alarm symptoms are traditionally thought to be associated with organic disease. A technical report by the American Academy of Pediatrics and NASPGHAN suggested that alarms symptoms should be used to screen children for endoscopy.[7] However, adult studies suggest that alarm features may not discriminate functional from organic disease.[37] In our study, vomiting was most predictive of oesophageal inflammation, as 11 (58%) patients with vomiting had reflux oesophagitis and three (16%) had EO. The finding of oesophagitis in paediatruc patients with chronic abdominal pain or gastro-oesophageal reflux has been shown to be associated with vomiting.[18, 38] However, the significance of specific alarm symptoms in children with abdominal pain requires further investigation in a prospective manner.

An elevated CRP (i.e. >1 mg / dL) was associated with diagnostic yield in 26 patients, including 13 (50%) patients with reflux oesophagitis, five (19%) with peptic ulcers, two (8%) with Crohn's disease and two (8%) with *H. pylori* infection. Previous data suggest that CRP is a marker of activity in IBD and *H. pylori* infection.[39, 40] Thus, elevated CRP may be a viable marker of inflammation of the gut in children with abdominal pain. Abnormal laboratory tests, including low haemoglobin or albumin, or high ESR, were not associated with diagnostic yield when examined as categorical variables (normal, abnormal). However, it is possible that if examined as continuous variables or categorical with multiple levels

(e.g. very high, or very low), different associations could have emerged. We did not abstract sufficient information to allow these analyses.

There are several limitations to the data collected in PEDS-CORI and our chart review. Generally, paediatruc gastroenterologists do not use standardized systems for reporting endoscopic findings. Therefore, the accuracy of the data depends upon the degree of completion and validity of the physician's documentation. The part of diagnostic yield defined by histological findings in our study may be difficult to interpret, given the relatively weak association with abdominal pain. The current study is not designed to prove causality. However, we attempted to include only findings that may impact medical management, such as oesophagitis and *H. pylori*. Is it also possible that histological findings could have been missed due to sampling error, particularly if only one biopsy was taken from the oesophagus, stomach or duodenum. In addition, secondary analysis of descriptive histological changes (e.g. oedema, reactive changes, mild inflammatory changes) may increase the diagnostic yield further. The study also lacked information regarding medication use (e.g. proton pump inhibitors, antibiotics) prior to OGD. As the laboratory values were collected as categorical variables (i.e. abnormal vs. normal), predictive value based on degree of abnormality could not be assessed. As the study only examined children who underwent endoscopy for abdominal pain, there is a possibility of selection bias towards those with more severe abdominal pain. It is possible that those children examined are actually more likely to have endoscopic pathology than children with abdominal pain in whom physicians choose not to perform invasive testing. Therefore, the study likely overestimates the utility of upper endoscopy in the general population of children referred to paediatruc gastroenterologists for abdominal pain. We also assumed that our children had chronic abdominal pain because, by the time a referral to a paediatruc gastroenterologist is complete and an OGD can be scheduled, our patients will generally have had more than 2 months of abdominal pain.

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Table 1

Comparison of procedures with and without diagnostic yield in 1191 paediatruc patients undergoing oesophagogastroduodenoscopy for abdominal pain between 1 January 2002 and 30 June 2005 in two sites of the Pediatric Endoscopy Database System – Clinical Outcomes Research Initiative Registry

	Diagnostic (%)	Nondiagnostic (%)	*P*-value
Total patients	454 (38.1)	737 (61.9)	
Underlying disease			
Present	90 (19.8)	181 (24.6)	0.06
Absent	364 (80.2)	556 (75.4)	
Gender			
Male	207 (45.6)	270 (36.6)	<0.01
Female	247 (54.4)	467 (63.4)	
Race			
White	311 (68.5)	517 (70.2)	0.13
Black	87 (19.2)	107 (14.5)	
Asian	9 (2.0)	17 (2.3)	
Hispanic	47 (10.3)	96 (13.0)	
Age (years)	11.84 (s.d. 3.7)	11.31 (s.d. 4.1)	0.02
Constipation			
Present	19 (4.2)	51 (6.9)	0.06
Absent	435 (95.8)	686 (93.1)	
Hypoalbuminaemia (<3.5 g/dL)			
Present	15/127 (11.8)	27/251 (10.8)	0.76
Absent	112/127 (88.2)	224/251 (89.2)	
Elevated ESR (>20 mm/h)			
Present	32/143 (22.4)	47/235 (20.0)	0.58
Absent	111/143 (77.6)	188/235 (80.0)	
Elevated CRP (>1 mg/dL)			
Present	26/109 (23.9)	28/205 (13.7)	0.02
Absent	83/109 (76.1)	177/205 (86.3)	
Anaemia (<11.5 g/dL)			
Present	30/195 (15.4)	59/326 (18.1)	0.43
Absent	165/195 (84.6)	267/326 (81.9)	

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 2

Characteristics associated with diagnostic outcome in multivariate analysis among 941 paediatruc patients undergoing oesophagogastroduodenoscopy for abdominal pain between 1 January 2000 and 30 June 2005 in two sites of the Pediatric Endoscopy Database System – Clinical Outcomes Research Initiative Registry

	Adjusted odds ratio	95% Confidence interval
Vomiting		
Absent	Reference	
Present	2.00	1.01–3.90
Gender		
Female	Reference	
Male	1.53	1.17–2.02
Age (per year)	1.04	1.01–1.08
Underlying GI disease		
Absent	Reference	
Present	0.86	0.64–1.16

Table 3

Location of significant gastrointestinal eosinophilia* in 153 paediatruc patients undergoing oesophagogastroduodenoscopy for abdominal pain between 1 January 2002 and 30 June 2005 in two sites of the Pediatric Endoscopy Database System – Clinical Outcomes Research Initiative Registry

Location	*n* (%)
Oesophagus only	17 (11.1)
Stomach only	23 (15.0)
Duodenum only	82 (53.6)
Oesophagus and stomach	3 (2.0)
Oesophagus and duodenum	1 (0.7)
Stomach and duodenum	23 (15.0)
Oesophagus, stomach and duodenum	4 (2.6)

* A total of 20 eosinophils/HPF or greater in oesophagus and duodenum, and 10 eosinophils/HPF or greater in the stomach.