The Yield of Upper Gastrointestinal Endoscopy at a Pediatric Tertiary Care Center

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ABSTRACT: **Background:** The number of investigative esophagogastroduodenoscopies (EGD) in children has increased over several decades, despite their unclear diagnostic yields.

Objectives: To evaluate the indications for performing EGD, their diagnostic yields, and consequences on pediatric patient management.

Methods: A retrospective chart review was performed of consecutive pediatric patients aged 0–18 years, who underwent EGD between January and August 2014.

Results: During the study period, 547 EGD were performed on 478 children. The most frequent indications were suspected celiac disease, chronic non-specific abdominal pain, persistent *Helicobacter pylori* infection, and gastrointestinal hemorrhage. The yield of the diagnostic EGD was 59.2%, and the most common new diagnoses were celiac disease (28%), *Helicobacter pylori*-positive gastritis (16.5%), and Crohn's disease (5.4%). Of the patients with documented follow-up, 74.1% reported improved symptoms. Procedures performed for chronic unexplained abdominal pain had significantly lower yields (26.2%) and only 39.3% improved at follow-up.

Conclusions: Our findings suggest a general high diagnostic yield for EGD in pediatric patients, stemming mainly from patients in whom a specific condition was suspected a priori. However, the role of the procedure in the diagnosis and management of non-specific gastrointestinal complaints was minor suggesting that EGD may be superfluous for some of these patients.

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During the past two decades there has been a dramatic increase in the number of esophagogastroduodenoscopies (EGD) performed as part of the evaluation of children with gastrointestinal symptoms [1]. This increase may be explained in part by the increased availability of endoscopic equipment, technological advancements, a rise in the number of pediatric endoscopists, more accessible anesthesia, changes in incidence rates of gastrointestinal diseases, and an increase in our understanding of the pathophysiological mechanisms of the diseases leading to changes in the indications for endoscopy [2].

However, while the number of procedures has increased, it is not clear whether there has been a corresponding increase in the diagnostic yield of EGD in the pediatric population, nor is it clear how the procedures affect patient management and health. Few studies have assessed the yield of EGD in children and explored which patient characteristics or indications favor higher diagnostic yields [2-11]. Chronic abdominal pain or recurrent abdominal pain of childhood is often investigated with endoscopy despite international guidelines recommending that invasive investigations are not necessary in such instances [12,13]. The presence of warning signs, such as dysphagia, weight loss, failure to thrive (FTT), chronic diarrhea, vomiting, significant anemia, nocturnal pain or a substantial loss of function, may be associated with an increased yield of objective findings on EGD. However, procedures are often performed even in the absence of such symptoms.

This study aimed to review a large cohort of patients who underwent EGD at a tertiary pediatric gastroenterology center in order to assess the yield of the procedures and their role in the diagnosis and management of children.

PATIENTS AND METHODS

This was a retrospective cohort study of consecutive pediatric patients aged 0–18 years, who underwent a diagnostic, follow-up, or interventional EGD between January and August 2014 at the Institute of Gastroenterology, Nutrition and Liver Diseases, Schneider Children's Medical Center of Israel, a tertiary healthcare facility. Patients' electronic medical records were reviewed and relevant data were extracted. Patient files were followed through the date of data extraction, and not less than one year after the index endoscopy. Data collected included demographics, age at procedure, presenting symptoms, patient and family history, laboratory findings, indications for procedure, endoscopic and pathologic findings, new diagnosis and treatment, date of last follow-up and the patient's condition. A positive diagnostic yield was defined as an endoscopic or histological finding leading to a new diagnosis or change in treatment.

STATISTICAL EVALUATION

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA), as well as R version 3.4.1 (Single Candle, Copyright 2017, The R Foundation for Statistical Computing). Univariate analysis of binary or categorical variables was performed using the Chi-square test for independence, while the examination and statistical analysis of continuous variables were conducted using descriptive statistics methods.

When comparing the distribution of various indications between the age groups, the Chi-square test for uniform distribution was conducted, and in cases where the expected values of the examined groups were too small, permutation tests with 10,000 repetitions were executed to simulate the *P* value. A *P* value of ≤ 0.05 was considered significant.

The study was approved by the institutional review board. Formal consent was waived by the ethics board.

RESULTS

During the study period, 547 EGD were performed on 478 children; 74% of which were diagnostic EGD. The mean age was 9.1 years (range 0.1–18.2) and 51.7% were females. The index procedure was the patient's first upper endoscopy in 82.2% (393/478) of children, and 43.9% (210/478) had no known specific gastrointestinal (GI) or non-GI diagnoses documented prior to the procedure. Of those who did have known GI diagnoses prior to the procedure (n=190), the most common was eosinophilic esophagitis (EoE) [Table 1].

Mucosal biopsies were taken during 86.4% of diagnostic procedure. Ileocolonoscopy was performed at the time of 52 of the EGD. Endoscopic interventions were performed in 14.8% of the total procedures, mainly esophageal balloon dilation (n=40) and percutaneous endoscopic gastrostomy (PEG) insertion (n=13). Procedures were performed emergently or semi-emergently in 15.3% (n=84) of the total cases.

The most common clinical symptom which led to the referral of the patient to diagnostic endoscopy was abdominal pain (59.4%, n= 242). These children could be subdivided into four groups based on ancillary test results: suspected celiac disease (positive anti tissue transglutaminase IgA (TTG) or anti-endomesial (EMA) IgA (n=115), chronic unexplained abdominal pain (n=61), positive non-invasive *Helicobacter pylori* (*H.pylori*) tests (n=42), and clinical symptoms or laboratory results suggestive of inflammatory bowel disease (IBD) (n=24). Other common indications for referral for diagnostic EGD were FTT (4.9%, n=20) and GI hemorrhage (6.8%, n=28) [Table 2].

A new diagnosis was registered following 59.2% (241/407) of the diagnostic procedures. The most common were celiac disease (n=114; 28%), *H. pylori* positive gastritis (n=67; 16.5%), and Crohn's disease (n=22; 5.4%). Females and children between the ages 5 and 12 years had the highest yields of diagnosis (64.4%, *P* = 0.019, and 72.8%, *P* < 0.0001, respectively). [Table 3].

A change in patient management was initiated following 211/407 (51.8%) diagnostic procedures based on the EGD findings. The most common treatments initiated were gluten free diets (25.3%), gastric acid suppression (10.1%), and triple therapy for *H. pylori* infection (8.1%) [Supplemental Table A, available on the online version].

Informative follow-up data were available for 279/407 (68.5%) of children undergoing diagnostic procedures who were later followed in the hospital outpatient clinics. The

Table 1. Patient characteristics

Characteristics		Age group, years					
		Total (n=478)	< 1 (n=25)	1–4 (n=115)	5–12 n=176)	13–18 (n=162)	*P* value
Gender	Male	231 (48.3%)	14	58	85	74	0.741
	Female	247 (51.7%)	11	57	91	88	
Previously diagnosed gastrointestinal conditions	EoE	19 (4%)	0	4	6	9	0.704
	Celiac disease	16 (3.3%)	0	4	7	5	
	GERD	13 (2.7%)	2	2	6	3	
	Crohn's disease	5 (1%)	0	0	2	3	
	Ulcerative colitis	1 (0.2%)	0	0	1	0	
	other	136 (28.5%)	10	31	45	50	
	No disease	288 (60.3%)	13	74	109	92	
Ethnicity (origin)	Israeli Jewish	150 (10.5%)	12	35	50	53	0.004
	Israeli Arab	81 (17%)	5	17	33	26	
	unknown	247 (51.6%)	8	63	93	83	

P values denote differences across age groups

EoE = eosinophilic esophagitis; GERD = gastroesophageal reflux disease

Table 2. Primary indications for performing diagnostic esophagogastroduodenoscopy

Indications	Age group, years					
	Total (n=407)	< 1 (n=19)	1–4 (n=89)	5–12 (n=153)	13–18 (n=146)	*P* value
Suspected celiac disease	115	0	40	64	11	< 0.001
Unexplained abdominal pain	61	0	5	21	35	< 0.001
Persistent *H.pylori* infection	42	0	1	16	25	< 0.001
Gastrointestinal bleeding	28	5	4	6	13	0.763
Vomiting/gastroesophageal reflux	23	6	5	6	6	0.998
Failure to thrive	20	2	9	4	5	0.1577
Suspected IBD	24	0	0	10	14	< 0.001
Dysphagia	13	0	0	4	9	< 0.001
Suspected EoE	11	1	5	2	3	0.447
Other	70	5	20	20	25	0.005

P values concern differences across age groups

EoE = eosinophilic esophagitis, *H. Pylori* = *Helicobacter pylori*, IBD = inflammatory bowel disease

Table 3. New diagnoses following pediatric esophagogastroduodenoscopy*

	Total	Male, years					Female, years				
New diagnosis/ Age		Total	< 1	1–4	5–12	13–18	Total	< 1	1–4	5–12	13–18
Celiac	114	38		8	25	5	76		32	38	6
H.pylori gastritis	67	21		2	11	8	46	2	2	20	22
Crohn's disease	22	12			4	8	10			3	7
Esophagitis/GERD	12	10	1	3	4	2	2				2
EOE	10	5		1	3	1	5	2	3		
Non-*H.pylori* gastritis	9	5	1	2	1	1	4	1		1	2
Ulcer/erosion	5	3				3	2			1	1
Ulcerative colitis	4	2			2		2		1		1
EGID (non EoE)	3	2		1		1	1			1	
Other	14	9	1	1	7		5		1	3	1
Total new diagnoses**	260	107	3	18	57	29	153	5	39	67	42
Total procedures	407	185	12	42	70	61	222	8	50	81	83
% New diagnosis***	63.8%	57.8%	25%	42.8%	81.4%	47.5%	68.9%	62.5%	78%	82.7%	50.6%

*Diagnoses were made by the treating physician based on findings during pediatric upper gastrointestinal endoscopies

**19 patients received two new diagnoses during the procedure

****P* value for new diagnosis = 0.019 between genders and < 0.0001 between age groups

H. Pylori = Helicobacter pylori , GERD = gastroesophageal reflux disease, EGID = eosinophilic gastrointestinal diseases, EoE = eosinophilic esophagitis

median follow-up was 1 year (IQR 0.4–2.0 years). Symptom improvement was reported by 207 (74.1%) children. Improvement was more frequent in children age 1–13 years old than infants or children older than 13 years (infants: 63.6%, 1–4 years old: 81%, 5–12 years old: 82.7%, 13–18 years old: 62.4%, $P = 0.004$). No significant differences were found between males and females.

The highest diagnostic yields were found in children with suspected celiac disease (97.3%, 112/115), persistent *H. pylori* (85.7%, 36/42), and suspected IBD (75%, 18/24). In contrast, when the indication for endoscopy was chronic unexplained abdominal pain, the diagnostic yield was lower (26.2%, 16/61). In these patients the most frequent diagnoses were non-specific gastritis or esophagitis [Supplemental Table B, available on the online version]. A diagnosis of EoE was made in 6/11 (54.5%) in whom the condition had been suspected. A source of blood loss could be found in 46.4% of patients undergoing a procedure for upper GI bleeding [Supplemental Table B, available on the online version].

Complications after EGD were defined as early complications if identified during the procedure or in the recovery area, and late complications as those identified following discharge from the endoscopy suite through several days. No early complications were documented during the study period; however, five late complications were reported, including one esophageal perforation following an esophageal dilation, two febrile episodes (one of which was associated with hematochezia and abdominal pain), and two cases of pneumonia treated with intravenous antibiotics.

DISCUSSION

In our cohort of patients at a tertiary children's hospital, the general diagnostic yield of EGD was 59.2%, with the highest yield seen in children aged 5–12 years (72.8%) and in females (64.4% vs. 53% in males). These diagnostic yields are similar to the outcomes described by Nobel et al. [14] in 2008 who identified abnormal findings during EGD in 55% of the cases. However, in contrast to our study, Nobel's group reported that older age (> 13 years) was a significant predictor of having findings during endoscopies. However, Sheiko et al. [2] reported significantly lower diagnostic yields in 1000 children undergoing diagnostic endoscopy (macroscopic abnormalities in 34.7%, and histological abnormalities of 40.4%). In their study, patients aged 13 to 18 years were most likely to have an endoscopic abnormality, but those aged 5 to 12 years were most likely to have histological abnormality. Recent studies have demonstrated a similar low diagnostic yield of EGD. Aydin and colleagues [15] reported pathological findings in 45% of pediatric patients undergoing upper endoscopy. This finding was in contrast to Thomson and co-authors [16] who found an even lower combined diagnostic yield of EGD and ileocolonoscopy in a tertiary gastroenterology center of 39.2%, and of EGD alone as only 18.9%. The differences in the general frequency of findings and the breakdown in age groups may be attributed to differing study methodologies, definitions of positive findings, differing characteristics of the patient cohorts or referral practices.

In our study, unexplained generalized abdominal pain (which was characterized as abdominal pain without any addi-

tional symptoms and signs and without laboratory abnormalities suggesting a specific diagnosis such as celiac disease, *H. pylori* gastritis, or IBD) was the indication for the procedure in 15% of the cases, significantly lower than in the study by Sheiko et al. [2] (28.7%) but similar to Thakkar et al. [17] (15.3%). However, while in our study the primary indication (28.2%) was suspected celiac disease, the cohort reported by Sheiko et al. included only 6.9% with this indication. Because in patients with suspected celiac disease there is a very high pretest probability for positive findings, these differences between the cohorts would alter the total diagnostic yields found. Thomson and colleagues [16] did not report the indications for the endoscopies. Clearly, referrals with higher pretest probability increase the diagnostic yield of the procedures.

While we evaluated the rates of positive findings, negative results also have value for patient care. Thomson's group [16] reported that 45% of the patient's management was actively changed due to EGD findings (endoscopically and histopathological), but further expanded that negative test results equally contributed to patient care. The impact of normal tests on patient management is more difficult to quantify than those of positive findings.

The role of EGD as part of the investigation of unexplained chronic abdominal pain has also been debated especially because it remains one of the most frequent indications for EGD in children. Although consensus recommendations conclude that in the majority of cases these patients have functional disorders [18], and even though in 2016 the ROME IV criteria defined functional pain as a primary diagnosis making the need to exclude other diseases unnecessary, both Thakkar et al. [3] and Akbulut et al. [19] recently argued that the procedure is valuable for the diagnosis of children with such an indication. Our data indicate that the diagnostic yield of EGD in patients with chronic unexplained abdominal pain was 26.2%, with the main findings being non-specific gastritis and esophagitis. Only 21.3% (13/61) of those children were given a new treatment following the procedure, but 39.3% (24/61) reported symptom improvement at their last visit [compared to 74.1% (207/279) of the general cohort], emphasizing the vague contribution of EGD in these children.

LIMITATIONS

This study has several limitations which must be acknowledged. The retrospective nature of the study did not enable collection of complete data sets for all patients. In order to limit the possibility of a selection bias of patients, we included sequential patients who underwent endoscopy during the study period. Because multiple physicians reported either clinical, endoscopic, or pathological findings (or lack thereof), there was not a single, systematic method of reporting which could easily allow comparison between across cases. Follow-up of cases was not universal because some patients belonged to health organizations, and we did not have access to medical records beyond the referral, endoscopy reports, pathology results, and laboratory test results for which we did have access. Furthermore, some patients were lost to follow-up. Our study included procedures performed over an 8-month period. This timing may have introduced a bias in terms of seasonality of complaints or findings. We feel that this would be minimal at best because the vast majority of signs and symptoms leading to procedures were chronic in nature, and the reported follow-up extended across seasons. Nevertheless, we believe that the large size of our cohort, the fact that a single researcher physician reviewed all patient files and consulted when possible with the treating physicians when questions arose minimized the influence of these factors.

CONCLUSIONS

We report the indications and yields of upper endoscopy in clinical practice in pediatrics, the minor role of the procedure in unexplained GI complaints, and its role in changing management. While EGD is an extremely safe procedure, it carries risks, as well as significant healthcare costs; therefore, pretest probability of having findings should be a part of the decision-making process when referring patients for procedures. Future studies to assess whether better utilization of endoscopy has been made are needed.

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Capsule

Lipid restriction enhances suppression

Regulatory T cells (T_{regs}) suppress immune responses to maintain tolerance and limit autoimmunity. Lipid metabolism is crucial for the activity of T_{regs}. **Field** and colleagues explored the role of the lipid chaperone fatty-acid binding protein 5 (FABP5) in mouse and human T_{reg} function. Targeting FABP5 through either genetic or pharmacological means caused mitochondrial dysfunction, which depressed oxidative phosphorylation and promoted a switch to glycolysis. FABP5 inhibition enhanced the suppressive activity of T_{regs} through a mechanism involving mitochondrial DNA release and subsequent cGAS-STING-dependent type I interferon signaling. The researchers found that the lipid-restrictive nature of the tumor microenvironment influenced *Fabp*5 gene expression and facilitated T_{reg} suppressor function.

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Eitan Israeli

Capsule

Targeting the core of atherosclerosis

A major villain in heart attacks and stroke is the inflamed necrotic core of atherosclerotic plaque. When the plaque ruptures, debris from this necrotic core, which largely consists of dead and dying cells, is released into the bloodstream, where it can cause blood clots and arterial blockage. **Flores** and co-authors designed and tested a nanoparticle-based therapy aimed at inducing certain immune cells to clear away the dead cells. They loaded single-walled carbon nanotubes with a drug that stimulated macrophages localized within atherosclerotic plaque to engulf and destroy dead and dying cells by a process called efferocytosis. Administration of the nanoparticles to mice predisposed to develop atherosclerosis reduced plaque burden without detectable damage to healthy tissue.

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Eitan Israeli

Capsule

Targeting acidity in jaundice

Neonatal hyperbilirubinemia, also called jaundice, is a pediatric condition caused by high bilirubin levels. When associated with acidosis, jaundice can trigger neurotoxicity and lead to neurological impairments. **Lai** et al. investigated the link between acidosis and jaundice in human samples and animal models. In samples from children with concomitant acidosis and jaundice, neuronal injury was increased compared to children with jaundice and no acidosis. In mice, bilirubin potentiated the activity of acid-sensing ion channels (ASICs) in neurons, increased firing, and caused cell death. Hyperbilirubinemia and acidosis also promoted cognitive impairments in mice, but these were prevented by ASIC deletion. Targeting ASICs could be a promising way to prevent neurological impairments associated with jaundice.

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