PEDIATRIC ENDOSCOPY AND SEDATION

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PEDIATRIC ENDOSCOPY AND SEDATION

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EDITORIAL
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Editorial: Pediatric Endoscopy and Sedation

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Keywords: endoscopy, children, pediatrics, sedation, gastrointestinal

Editorial on the Research Topic

Pediatric Endoscopy and Sedation

Gastrointestinal (GI) endoscopic procedures are central and critical components in diagnosing, managing and monitoring numerous pediatric conditions affecting the GI tract (1). Undergoing GI endoscopy can be uncomfortable for young patients, and typically requires sedation. Consequently, ensuring the safe and effective undertaking of procedures in children of all ages is important. In recent years, there have been numerous advances in methods and in technology that are now regular features of pediatric GI endoscopy. This Research Topic aimed to draw together a series of reports focusing on various relevant and topical aspects of endoscopy and sedation in children and adolescents.

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GENERAL ASPECTS OF ENDOSCOPY IN CHILDREN

Cox et al. provide an excellent overview of endoscopy in children and adolescents. This review describes the history of pediatric endoscopy, as well as hints of its future advances and challenges. Within their report, the authors review aspects of sedation, common and advanced procedures, as well as complications that may occur. Practical aspects for the future of endoscopy mentioned include artificial intelligence, robot assistance, and disposable endoscopes.

Fachler et al. reviewed the yield and appropriateness of 329 endoscopic procedures in children at an Israeli children's hospital. Overall, there were no significant complications arising in this cohort. The primary indication in 88 (26%) of the children was pain: 36% of this subgroup had significant diagnostic findings. Diagnostic findings were seen in 43% of the children with other indications.

Optimal bowel preparation is critical to the performance of ileo-colonoscopy (2). While it may be the least pleasant aspect of this procedure from the patient's perspective, it is also the most important. Mamula and Nema review aspects of bowel preparation for ileo-colonoscopy in children: these include the type and method of preparation, safety, and outcomes.

The world has been rocked by the coronavirus pandemic from early 2020 to now. The ramifications of this include disruptions to regular healthcare activities, including endoscopy. Shaoul and Day provide an overview of the impacts of the pandemic upon endoscopy services. One key aspect has been the variations and constantly changing landscape over the duration of the pandemic. A number of national and international guidelines have arisen during this time. In addition, a number of novel approaches and initiatives have been developed.

SEDATION FOR ENDOSCOPY IN CHILDREN

Lee et al. evaluated the use of non-anesthetist administered propofol (NAAP) in 496 children undergoing endoscopic procedures at one North American hospital and compared outcomes to 433 children having their procedure under general anesthetic (GA). The adverse event rate was lower in the NAAP group, with respiratory events being particularly prominent in the GA group. The authors concluded that NAAP had an acceptable safety profile, that was similar to that seen in adults undergoing NAAP procedures (3).

A similar adverse event rate (3.8%) was observed in a second report focusing on anesthesiologist sedation regimens for endoscopy in children (Hartjes et al.). This study retrospectively evaluated outcomes in 258 children who underwent upper and/or lower endoscopy procedures. The authors highlighted wide unwarranted variations in endoscopic sedation as administered by anesthesiologists (with 29 different regimens noted), as a factor for future improvement initiatives.

Another approach to sedation for endoscopy may be hypnosis. Tran et al. reported their prospective evaluation of hypnosis in 140 children. Most (82.9%) successfully underwent endoscopy under hypnosis in combination with sedation (midazolam and/or nitrous oxide, with only 11 requiring rescheduling for GA. These results provide a promising novel approach to sedation for endoscopy in children and need to be evaluated further.

ENDOSCOPY IN SPECIFIC ESOPHAGEAL CONDITIONS IN CHILDREN

The diagnosis of eosinophilic esophagitis (EE) relies on assessment of the endoscopic appearance and evaluation of mucosal biopsies (4). Nguyen et al. review the role of endoscopy in this increasingly prevalent condition and highlight new and upcoming developments.

Esophageal atresia (EA) is a significant condition presenting at birth, requiring surgical intervention early and with life-time consequences (5). One risk is the development of anastomotic stricture, which then requires dilatation or resection. Baghdadi et al. report their experience with an early endoscopic assessment of esophageal diameter in the prediction of future need for management of stricture. One hundred and twenty-one children with EA underwent endoscopy at a median of 22 days post-operatively. Smaller anastomotic diameter was strongly associated with risk of subsequent resection (Odds Ratio of 12.9) and need for dilatations. Whilst these data need further evaluation and validation, they do provide strong support for early endoscopic evaluation as part of the routine care of these children.

RECENT ADVANCES IN ENDOSCOPY AND THERAPEUTIC ENDOSCOPY IN CHILDREN

Since it's development and uptake, endoscopic ultrasound (EUS) has now become accepted in adult gastroenterology, but been adopted more slowly in children. Piester and Liu reviewed their collective experience over approximately two and half years. The indications and outcomes of 98 EUS procedures conducted in 72 children were reviewed. Overall, EUS was performed safely for a variety of indications. The authors also provided their perspectives of the future application of EUS in children, with mention for further exciting applications and evolutions of this methodology.

Cohen and Oliva reviewed the field of capsule endoscopy (CE) in children. Aspects covered included indications of CE and issues relating to performance in children (such as capsule placement). This review provides an excellent overview of the role of CE and pan-enteric CE in children.

Endoscopy also increasingly enables a range of therapeutic applications. Schluckebier et al. provide a comprehensive review of various therapeutic endoscopic procedures. Various future advances will continue to expand this area.

CONCLUSIONS

Together the articles in this special issue provide important and timely updates about the current status of GI endoscopy and sedation in children and adolescents. Endoscopy has come a long way in the last decades.

The included articles also highlight many aspects of the future of endoscopy in children: these topics include machine learning/AI in endoscopy, remote control endoscopy and ultrathin endoscopy, as well as advances in therapeutic endoscopy. Other aspects of endoscopy such as green endoscopy are also very relevant to pediatric endoscopists. Endoscopy remains a key component of the pediatric gastroenterology practice now and in the coming times.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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BRIEF RESEARCH REPORT
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Outcomes of Non-anesthesiologist-Administered Propofol in Pediatric Gastroenterology Procedures

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Background and Aims: Non-anesthesiologist-administered propofol (NAAP) has been found to have an acceptable safety profile in adult endoscopy, but its use remains controversial and pediatric data is limited. Our aim was to examine the safety and efficacy of NAAP provided by pediatric hospitalists in pediatric endoscopy.

Methods: We retrospectively reviewed 929 esophagogastroduodenoscopy (EGD), colonoscopy, and combined EGD/colonoscopy cases in children aged 5–20 years between April 2015 and December 2016 at a large children's hospital. We analyzed the data for adverse events in relation to demographics and anthropometrics, American Society of Anesthesiologists physical classification score, presence of a trainee, comorbid conditions, and procedure time.

Results: A total of 929 cases were included of which 496 (53%) were completed with NAAP. Seventeen (3.4%) of NAAP cases had an adverse event including the following: 12 cases of hypoxia, 2 cardiac, and 3 gastrointestinal adverse events. General anesthesia cases had 62 (14.3%) adverse events including the following: 54 cases of hypoxia, 1 cardiac, 7 gastrointestinal, and 1 urologic adverse event. No adverse events in either group required major resuscitation. NAAP vs. general anesthesia had a lower overall adverse event rate (3.4 vs. 14.3%, $p < 0.0004$) and respiratory adverse event rate (2.4% vs. 12.5%, $p < 0.0004$). Overall, cardiac and gastrointestinal adverse event rates between the two groups were comparable. When accounting for all captured factors via logistic regression, both younger age ($P < 0.001$) and general anesthesia ($P < 0.0001$) remained risk factors for an adverse event.

Conclusion: The overall adverse event rate of NAAP was low (3.4%) with none requiring major resuscitation or hospitalization. This is comparable to studies of NAAP in adult endoscopy and suggests that NAAP provided by pediatric hospitalists has an acceptable safety profile.

Keywords: endoscopy, sedation, pediatric endoscopy, pediatric sedation, propofol

INTRODUCTION

Sedation is important in pediatric endoscopy, as it is necessary for young children to tolerate procedures. Pediatric patients typically require a deeper level of sedation than adult patients in order to avoid discomfort and promote patient cooperation (1). A deeper level of sedation increases the risk of cardiovascular instability (2), and children tend to be at greater risk for airway obstruction given their larger epiglottis and smaller upper airway (1). Outcomes of sedation in pediatric endoscopy are becoming more widely studied. While the methods of sedation vary widely between providers and institutions, recent studies have shown a trend in propofol use in pediatric gastroenterology (3). Propofol is becoming favored as it has limited effect on the gastrointestinal tract, does not increase secretions, and has a rapid onset with a short duration (4, 5). However, propofol has a narrow therapeutic index and can cause respiratory depression and hypotension (4, 5). Due to these effects, propofol use may be restricted to anesthesiologists at some centers.

Recently, there has been a trend toward non-anesthesiologist-administered propofol (NAAP). NAAP has been well-studied and found to be safe in adult endoscopy (6, 7), but studies in children are limited (1, 8–10). In this study, we aim to characterize pediatric patients who underwent non-anesthesiologist administered propofol (NAAP) administered by trained pediatric hospitalists and determine its safety and efficacy. To our knowledge, this is the first study that seeks to examine the outcomes of non-intubated deep sedation administered by a pediatric hospitalist-run sedation program.

METHODS

A retrospective chart review was conducted of all consecutive esophagogastroduodenoscopy (EGD), colonoscopy, or combined EGD/colonoscopy cases between April 2015 and December 2016 at the main campus of Texas Children's Hospital. All procedures included in the study were performed in a GI procedure suite. Complex procedures such as foreign body removals, stricture dilations, motility catheter placements, esophageal variceal surveillance, and banding were excluded, as these procedures are typically ineligible for hospitalist sedation due to a need for deeper anesthesia or airway protection in these cases. Two cases of foreign body removal scheduled non-emergently were included as there was no foreign body visualized or removed. Colonoscopies that led to polypectomies were included in both groups. Data was collected for adverse events related to sedation or anesthesia, including respiratory adverse events such as hypoxia (defined as $SpO_2 < 90\%$ by pulse oximetry for longer than 1 min) or need for positive pressure ventilation or intubation, cardiovascular adverse events such as arrhythmias (defined as sustained non-sinus cardiac rhythm seen on cardiac monitors) or symptomatic hypotension (defined as sustained blood pressure <5th percentile for age or <90/50 mmHg for children >10 years), gastrointestinal adverse events such as nausea or vomiting requiring antiemetics, and need for evaluation in the emergency room after the procedure. Events up to 24 h post-procedure that could be attributed to anesthesia-related adverse events were included in the study. Data for adverse events was obtained from vital signs recorded routinely by the anesthesiologist/sedationist during the procedure per a standardized hospital protocol, nursing notes from post-anesthesia care unit (PACU) or telephone calls post-procedure, and documented emergency room (ER) visits. The occurrence of adverse events was analyzed in relation to age, gender, body mass index (BMI), weight, American Society of Anesthesiologists (ASA) physical classification score, presence of a trainee, comorbid condition, and procedure time. IRB approval was obtained for this study.

Statistical Analyses

Data was analyzed using Fisher exact chi square, Student's t-test, Mann–Whitney U-test, and logistic regression on IBM SPSS v25. Logistic regression was conducted using the Enter method in SPSS with dependent variable being the presence of an adverse event and independent variables including sedation method, age at time of scope, patient weight percentile, BMI percentile, presence of comorbid condition, presence of a trainee, ASA score, total procedure time, and whether patient was inpatient at time of procedure.

Hospitalist Sedation and General Anesthesia

All deep sedation cases included in this study were performed by two pediatric hospitalists specializing in sedation. All general anesthesia cases had anesthesia performed and managed by a pediatric anesthesiologist. Patients are referred for deep sedation or general anesthesia by the gastroenterologist performing the procedure. Procedural monitoring in all cases includes the use of pulse oximetry, capnography, blood pressure, and cardiac rhythm monitoring. All deep sedation cases included the use of supplemental oxygen with 2 L nasal cannula (due to end-tidal CO_2 monitoring affixed to a nasal cannula). For hospitalist sedation, propofol infusion rates are typically 150 mcg/kg/min and decreased as the case progresses. Induction doses average about 2 mg/kg but with titration to effect. Boluses of propofol during the case are on an as-needed basis. Procedural details including supplemental oxygen use and modality, prophylactic medications, and anesthetics are detailed in **Supplementary Table 1**.

The Hospitalist Sedation Team

The hospitalist sedation team at Texas Children's Hospital comprises physicians who are board eligible or board certified in critical care medicine, emergency medicine, cardiology with advanced subspecialty training in cardiac intensive care, or pediatrics. Initial training involves working directly with a pediatric anesthesiologist for 5 days in a high-volume, rapid turnover operating room with high risk for airway events, 5 days in the diagnostic imaging suite, at least 20 cases working with a more experienced sedationist or anesthesiologist while leading the sedation, as well as sedation simulation training in emergency resuscitation scenarios. For credentialing, sedationists must score >90% on a deep sedation credentialing exam and must complete hands-on airway management skills training and assessment administered by pediatric anesthesiologists. Physicians must demonstrate competency with a minimum of 10 cases each of the following: deep sedation cases with propofol, inhalational induction with bag-mask ventilation, endotracheal intubations, peripheral IV insertions, oral airway insertions with bag-mask ventilation, and laryngeal mask airway (LMA) insertions. Minimum requirements for re-credentialing include a minimum of 50 cases over a 6-month period and two full sedation shifts per month averaged over 6 months. If individuals do not meet the above requirements, they are required to repeat the training and credentialing process over again. Newly credentialed sedationists work in radiology procedure areas (e.g., MRI, nuclear medicine) for the initial 6–12 months before advancing to sedate in the procedure suite during more invasive procedures, such as EGDs and colonoscopies.

RESULTS

A total of 1,030 cases were initially reviewed, with 8 cases later excluded for not meeting procedure criteria and 93 cases excluded for patient age <5 or >21 years. Children under age 5 years were excluded from the study as they do not qualify for hospitalist sedation at our institution. Of the 929 included cases, there included a total of 864 patients, with 65 patients that underwent repeat procedures during the review period (see **Appendix 2**). There were 10 patients who underwent both propofol-based deep sedation and general anesthesia (GA) in separate procedures during the review period. For all 10 patients, no explanation was documented for switching from general anesthesia to deep sedation or vice versa. A total of 496 (53.4%) included cases underwent propofol-based deep sedation administered by pediatric hospitalists with training and experience to administer propofol as part of a hospital-supported sedation team (NAAP). A total of 433 (46.6%) cases underwent general anesthesia (GA). Baseline demographic data for the two groups is shown in **Table 1**. While there is a slight female predominance in the NAAP group, the gender differences between the two groups are not significant ($p = 0.066$). The two groups also had comparable numbers of each type of procedure ($p = 0.08$). The NAAP group was older in age and had a lower mean BMI percentile, although both groups had similar age and BMI percentile ranges. While both groups had comparable numbers of patients with comorbid conditions, the NAAP group was predominantly ASA 2, while the general anesthesia group had more patients categorized as ASA 3 and 4. The most common comorbid condition in both groups was asthma. The NAAP group had overall shorter average procedure times, as well as anesthesia, room, and PACU stay duration times.

Adverse events comparison between both groups is found in **Table 2**. Overall, the general anesthesia group had a higher rate of hypoxia and desaturations that lasted longer than 60 s. The NAAP group had nine patients who received positive-pressure ventilation, two patients who received bag mask ventilation, and higher rates of bronchospasm and laryngospasm, although the difference was not significant ($p = 1.000$, $p = 0.052$). One out of the 12 patients in the NAAP group with hypoxia had an LMA placed electively after laryngospasm. The NAAP group had two cardiac adverse events, in the form of a self-resolving wide-complex tachycardia to a heart rate of 205 and one case of syncope shortly after the patient arrived home. The GA group had one cardiac adverse event in the form of PVCs noted during induction. The two groups had comparable rates of cardiac adverse events, and the GA group had slightly more gastrointestinal events. The NAAP group had two patients requiring treatment with antiemetics, and one patient who presented to the emergency room with hematemesis several hours after the procedure. The GA group had seven patients with nausea and emesis receiving treatment with antiemetics, with three emergency room visits for emesis, and one hospital admission for IV fluids in the setting of intractable nausea and vomiting.

The NAAP group had 17 overall adverse events, giving a rate of 3.4%, and the GA group had 62 total adverse events, with an adverse event rate of 14.4% (**Appendix 1**). The difference between the overall adverse event rate of the two groups is significant ($p < 0.0004$). The overall respiratory adverse event rate between the two groups was also significant ($p = 0.034$), with the NAAP group having a respiratory adverse event rate of 2.4% and the GA group 12.5%. There was no significant difference between the cardiac, gastrointestinal, and other adverse event rates. A logistic regression shows that there is a significant difference between NAAP and GA, favoring the NAAP group ($p < 0.0004$) (**Table 3**). The age of the patients is also significant with younger patients having fewer adverse events, especially in the NAAP group. The weight and BMI percentile of the patient, ASA score, presence of a comorbid condition, presence of a trainee, whether the patient was inpatient or outpatient for the procedure, and the total procedure time all did not significantly contribute to the overall adverse event rate (**Table 3**).

The adverse events in both groups were classified as pre-, intra-, or post-procedure (**Supplementary Table 2**). The NAAP group had 13 intra-procedural adverse events including 12 cases of hypoxia and 1 case of arrhythmia; 4 post-procedural adverse events including 1 case of syncope, 2 cases of nausea/vomiting, and 1 case of hematemesis; and no pre-procedural events. The GA group had 1 pre-procedural adverse event (a case of arrhythmia during induction), 54 intra-procedural adverse events (all cases of hypoxia), and 8 post-procedural events in the form of 7 cases of nausea/vomiting and 1 case of urinary retention.

The adverse events were further classified using the common terminology criteria for adverse events (11) (**Supplementary Table 2**). This system grades events by severity with grade 1 being mild, grade 3 being severe, and grade 5 being death (11). Overall, the majority of the adverse events in both groups were grade 1 or mild. There was one grade 3 event in the general anesthesia group, in the form of an admission to the hospital lasting longer than 24 h for intractable vomiting requiring IV fluids.

The post-procedural events were classified using a system developed by Kramer and Narkewicz (12) (**Supplementary Table 2**). Grade 1 is a mild event requiring supportive care or telephone management, grade 2 is an adverse

TABLE 1 | Demographics of the NAAP and general anesthesia groups for all data and ASA 2-only sub-analysis.

Demographics for all data				Demographics for ASA 2 Only			
	NAAP (*n* = 496)	**General anesthesia (*n* = 433)**	***p*-Value**		**NAAP (*n* = 470)**	**General anesthesia (*n* = 290)**	***p*-Value**
Gender			0.066	Gender			0.445
Male	230	227		Male	220	144	
Female	266	206		Female	250	146	
Age				Age			
Mean	13.06 ± 3.6	12.10 ± 3.96	0.002	Mean	13.07 ± 3.5	12.08	
Median	14	12		Median	14	12	
Range	5–20	5–20		Range	5–20	5–20	
IQR	6	6		IQR	6	6	
BMI percentile (%)			0.000	BMI percentile (%)			
Mean	47.8 ± 29.8	54.9 ± 34.2		Mean	47.8 ± 29.7	55.8 ± 33	
Median	45.9	60.4		Median	46.3	61	
Range	0–99.38	0–99.99		Range	0–99.4	0–99.9	
IQR	50.6	65.7		IQR	64.4	60.9	
ASA score			0.000				
ASA 1	5	38					
ASA 2	470	290					
ASA 3	21	103					
ASA 4	0	2					
Comorbid conditions			0.004				
Present	310	309					
None	186	124					
Patient status			0.000	Patient status			0.000
Inpatient	16	49		Inpatient	9	23	
Outpatient	480	384		Outpatient	461	267	
Presence of a trainee			0.000	Presence of a trainee			0.000
Trainee present	86	126		Trainee present	78	86	
No trainee	410	307		No trainee	392	204	
Procedure type			0.080	Procedure type			0.062
EGD	284	223		EGD	275	151	
Colonoscopy	60	57		Colonoscopy	57	30	
EGD/colonoscopy	152	163		EGD/colonoscopy	138	109	
Time (minutes)				Time (minutes)			
Total procedure				Total procedure			
Mean	25.76 ± 21.8	37.2 ± 29.1	0.0004	Mean	24.9 ± 20.5	37.3 ± 29.7	0.0004
Median	15	26		Median	15	24	
Range	4–132	3–140		Range	4–106	3–140	
IQR	30	42		IQR	29	42	
EGD				EGD			
Mean	10.68 ± 7.3	15.7 ± 26.3	0.0004	Mean	10.5 ± 7.1	15.7 ± 11.8	0.0004
Median	11	16		Median	11	16	
Range	4–46	3–140		Range	4–46	3–140	
IQR	8	10		IQR	7	9	
Colon				Colon			
Mean	13.53 ± 19.7	20.2 ± 26.3	0.0004	Mean	12.7 ± 18.7	20.7 ± 27.1	0.0004
Median	31	37		Median	31	39	
Range	11–115	8–124		Range	12–97	12–124	
IQR	19	25		IQR	17	26	

(Continued)

TABLE 1 | Continued

	Demographics for all data				Demographics for ASA 2 Only		
	NAAP (*n* = 496)	**General anesthesia** (*n* = 433)	***p*-Value**		**NAAP** (*n* = 470)	**General anesthesia** (*n* = 290)	***p*-Value**
Anesthesia time				Anesthesia time			
Mean	42.3 ± 24.8	61.1 ± 31.9	0.0004	Mean	41.5 ± 23.8	60.7 ± 32.2	0.0004
Median	32	51		Median	32	48	
Range	10–162	14–202		Range	10–162	14–202	
IQR	34.3	44		IQR	34	43	
Total room time				Total room time			
Mean	41.2 ± 24.3	56.31 ± 31.9	0.0004	Mean	40.4 ± 23.2	56.4 ± 32.2	0.0004
Median	32	46		Median	31	45	
Range	13–158	12–200		Range	13–158	12–200	
IQR	34	43		IQR	33	44	
PACU stay duration				PACU stay duration			
Mean	50.7 ± 24.9	55.4 ± 26.3	0.151	Mean	50.8 ± 25.2	55.1 ± 20.6	0.153
Median	46	51		Median	46	52	
Range	17–337	25–358		Range	17–337	25–145	
IQR	19	24		IQR	19	24	

TABLE 2 | Characterization of adverse events for all data and ASA 2-only sub-analysis.

Adverse events for all data				Adverse events for ASA 2 only			
	NAAP (*n* = 496)	**GA** (*n* = 433)	***p*-Value**		**NAAP** (*n* = 470)	**GA** (*n* = 290)	***p*-Value**
Respiratory				**Respiratory**			
Hypoxia	12	54	0.0004	Hypoxia	12	26	0.0001
Lowest O_2 sat	85%	50%		Lowest O_2 sat (%)	85	62	
Desaturation <90% lasting longer than 1 min	0	11	0.0004	Desaturation <90% lasting longer than 1 min	0	5	0.007
Positive pressure ventilation	9	0	0.005	Positive pressure ventilation	9	0	0.005
Bag mask ventilation	2	0	0.502	Bag mask ventilation			
Bronchospasm	1	0	1.000	Bronchospasm			
Laryngospasm	7	1	0.052	Laryngospasm	7	0	0.037
Cardiac				**Cardiac**			
Arrhythmia	1	1	1.000	Arrhythmia	1	1	1.000
Syncope	1	0		Syncope	1	0	
Gacardiacstrointestinal				**Gastrointestinal**			
Treatment with antiemetics	2	7	0.06	Treatment with antiemetics	2	6	0.031
Hematemesis	1	0	1.000	Hematemesis	0	0	
Other				**Other**			
Urinary retention	0	1	0.466	Urinary retention	0	0	1.000
ER visit	1	3	0.253	ER visit	1	2	
Admission	0	1	0.466	Admission	0	1	

event requiring ER visit or unanticipated evaluation by a physician, and grade 3 is an admission (12). The majority of the post-endoscopy events in the general anesthesia group were grade 1, while the deep sedation group was evenly distributed between grade 1 and grade 2.

A sub-analysis was conducted comparing only ASA level 2 patients between the two groups, as the NAAP group was predominantly ASA level 2 (**Table 1**). The NAAP group has a slightly higher mean and median age and shorter procedure, anesthesia, room, and PACU times. The number of patients who are inpatient vs. outpatient, as well as the presence of a trainee, remains significantly different between the two groups. The number of adverse events in the NAAP group remains unchanged (**Table 2**), indicating that all the adverse events took place in ASA level 2 patients in that group. The GA group had fewer cases of hypoxia ($n = 26$), however still significantly

TABLE 3 | (A) Logistic regression using all data; **(B)** logistic regression with only ASA level 2 patients.

	B	Sig	Exp(*B*)	95% CI
A. Logistic regression using all data				
NAAP vs. GA	−1.112	0.000	0.329	0.179–0.603
Age at time of scope	−0.119	0.000	0.888	0.832–0.948
Weight %	0.000	0.977	1.00	0.985–1.016
BMI %	0.007	0.417	1.007	0.991–1.023
Presence of comorbid conditions	−0.466	0.164	0.627	0.325–1.210
Presence of trainee	0.514	0.127	1.672	0.864–3.235
ASA score		0.056		
ASA 1	−21.391	0.999	0.000	
ASA 2	−22.292	0.999	0.000	
ASA 3	−21.582	0.999	0.000	
Total procedure time	0.009	0.053	1.009	1.00–1.018
Patient status	−0.589	0.268	0.555	0.196–1.574
Nagelkerke R^2	0.175			
B. Logistic regression with only ASA level 2 patients				
NAAP vs. GA	−0.857	0.012	0.424	0.217–0.830
Age at time of scope	−0.137	0.001	0.872	0.804–0.945
Weight %	−0.005	0.598	0.995	0.976–1.014
BMI %	0.013	0.206	1.013	0.993–1.033
Presence of comorbid conditions	−0.459	0.208	0.632	0.309–1.291
Presence of trainee	0.263	0.507	1.3	0.599–2.823
Total procedure time	0.014	0.011	1.014	1.003–1.025
Patient status	−0.589	0.268	0.555	0.304–4.189
Nagelkerke R^2	0.129			

more than the NAAP group ($p < 0.0004$). There is one less gastrointestinal event in the GA group. The number of cardiac events in both groups is unchanged. The overall adverse event rate of the NAAP group remains at 3.4%, and the overall adverse event rate of the GA group using only ASA 2 patients is 11% ($p < 0.0004$, **Appendix 1**). The difference in the respiratory adverse event rates of the two groups is still significant ($p < 0.0004$), with the respiratory adverse event rate of the NAAP group being 1.7% while the respiratory adverse event rate of the GA group is 9.0%. The difference in the gastrointestinal event rates between the two groups is now significant ($p = 0.031$) while the rates of cardiac adverse events remain insignificant. The logistic regression with only ASA 2 patients continues to favor the NAAP group over the GA group ($p = 0.012$), with age being significant and favoring the NAAP group ($p = 0.001$). The total procedure time is significant with longer procedure times having fewer adverse events ($p = 0.011$). The weight and BMI percentile of the patient, ASA score, presence of a comorbid condition, presence of a trainee, whether the patient was inpatient or outpatient for the procedure did not significantly contribute to the overall adverse event rate (**Table 3**).

We conducted propensity score matching in SPSS for age, BMI, weight, ASA, presence of a comorbid condition, presence of a trainee, total procedure time, and patient status (inpatient vs. outpatient). This resulted in 158 patients, with 87 in the deep sedation group and 71 in the GA group. Differences in gender ($p = 0.523$), presence of a comorbid condition ($p = 0.576$), presence of a trainee ($p = 0.062$), weight ($p = 0.352$), and gender ($p = 0.523$) were not statistically significant. ASA score ($p < 0.001$) and patient status ($p = 0.017$) remained significantly different between the two groups. Logistic regression of this data set had a Nagelkerke R^2 of 0.582, and only the method of sedation was significant ($p < 0.001$, $B = -3.686$, 95% CI 0.008–0.084) favoring deep sedation over GA.

DISCUSSION

Sedation is integral to the success of pediatric endoscopies, as it ensures patient comfort and cooperation. However, in pediatric endoscopy procedures, complications that arise from sedation can occur more frequently than complications from the endoscopic procedure itself (13). Propofol-based sedation is on the rise, as is the use of NAAP. NAAP by pediatric hospitalists has not been widely studied or characterized in pediatric endoscopy. To our knowledge, our study is the first to examine the safety and efficacy of NAAP by pediatric hospitalists in pediatric endoscopy. We found that NAAP by pediatric hospitalists (vs. general anesthesia) for pediatric endoscopy resulted in fewer adverse events. This difference in adverse events between NAAP and general anesthesia persisted even when accounting for known risk factors such as age and ASA classification. These findings suggest NAAP for pediatric endoscopy has an acceptable safety profile.

Our NAAP pediatric endoscopy findings appear to complement other available pediatric non-anesthesiologist-administered anesthesia studies—the majority of which were completed in other hospital settings. Khalila et al. (14) examined 1,190 pediatric endoscopic procedures (all ASA 1 or 2), with NAAP by the pediatric gastroenterologist performing the procedure, and found a 0.7% adverse event rate, comparable to adult studies in which sedation is performed by the adult gastroenterologist. A study by Hertzog et al. examined rates of adverse events of non-anesthesiologist-provided sedation in pediatric procedural sedation, including approximately 2,100 cases by pediatricians (15). The study, which was not limited to propofol-based sedation and included 6.1% GI procedures, found an overall adverse event rate of 5.3% (15), but did not specify adverse event rate by type of provider, as that was not the goal of their study.

Jain et al. (8) compared propofol-based deep sedation by pediatric critical care or emergency medicine providers to general anesthesia for children undergoing cardiac MRI. They had a 3.4% adverse event rate in their deep sedation group (compared to a 4.7% adverse event rate in the general anesthesia group), with adverse events including airway obstruction requiring nasopharyngeal or oral airway, hypotension requiring IV fluids, desaturations requiring PPV, and excessive secretions requiring suctioning (8). A study conducted by Rajasekaran et al. (1) examined the safety of deep sedation in pediatric EGDs performed by an intensivist-run sedation program. The study found a 3% overall complication rate for propofol-based sedation in 2,325 pediatric EGDs over the course of 4 years (1).

We found respiratory adverse events to be most common in both the NAAP and general anesthesia groups. Similar to the study by Hertzog et al., the most common adverse events in both the NAAP and GA group in our study was hypoxia as measured by pulse oximetry (15). The NAAP group had a lower rate of respiratory adverse events when compared to the GA group. This is significant as hypoxemia is thought to be a significant contributor to cardiopulmonary complications during endoscopy (16). It is possible that the differences in respiratory adverse events between the two groups are due to the use of airway devices (intubation or LMA) that can be associated with increased risk of respiratory events by the GA group. Other considerations include differences in equipment in the GA room and hospitalist sedation rooms and the method of data collection, which may have included artifactual data (such as false pulse oximetry readings due to patient movement or probe misplacement) in addition to adverse events. The adverse event rate of the general anesthesia group in our study was 14.3%, which is higher than other similar studies in the past. This is most likely due to the differences in study parameters, such as the definition of hypoxia (the SpO_2 reading cut-off), and the inclusion of post-procedure events.

Our study also found that procedure times were lower in those undergoing NAAP. Rajasekaran et al. also compared procedure times of 549 deep sedation patients to 13 general anesthesia patients and found that deep sedation had shorter length of sedation times (22.1 min) when compared to anesthesia patients (38.3) (1). However, the difference was not significant. In our study, the mean total procedure, EGD, colonoscopy, and total anesthesia times for the deep sedation group were significantly shorter in the deep sedation group compared to the anesthesia group. The difference in total procedure times between the two groups may be influenced by the presence of trainees, who are more likely to be assigned to general anesthesia procedures. There was no difference in the PACU stay times between the two groups; however, the PACU stay duration was highly affected by factors such as the availability of transportation for the patient's families or the availability of an inpatient bed for patients who are being admitted to the hospital post-procedure. Notably, in our study, the total procedure time in the sub-analysis with only ASA 2 patients becomes significant with longer procedure times having fewer adverse events ($p = 0.011$), favoring the GA group. Likely, this is secondary to adverse events leading to abbreviated procedures or the hastened completion of those procedures.

Limitations to this study include its retrospective nature, and as such, adverse event reporting was at the discretion of the medical team. However, we note that certain events such as hypoxia are uniformly captured prospectively during procedures, and all care was documented per standard medical care in our medical system. Another limitation includes differences in the age and ASA scores between NAAP and general anesthesia groups of patients. We accounted for this difference both by focusing on patients with ASA 2 in a sub-analysis and by accounting for both age and ASA status in our regression analyses. Both the sub-analysis and regression analyses continued to demonstrate higher adverse events in those with general anesthesia. We also note the possibility of bias in the referral process in which patients are assigned to general anesthesia or hospitalist sedation. This bias occurs at the level of the gastroenterologist, who is referring patients for hospitalist sedation or anesthesia, as well as the anesthesiologist/sedationist's discretion as to the method of sedation that they deem most appropriate for the patient. This may lead to healthier patients being selected for hospitalist sedation over general anesthesia. Patients with higher ASA scores and who were inpatient were more likely to receive general anesthesia. This was reflected in the propensity score matching calculations.

Future studies in this area are needed. Future directions can include the investigation of differences in cost between NAAP and general anesthesia. Rajasekaran et al. found that deep sedation was significantly more cost effective than general anesthesia; however, the study was only able to directly compare 13 general anesthesia cases to 549 deep sedation cases due to the majority of the general anesthesia cases being combined procedures. Other areas of investigation could include patient satisfaction, evaluating the difference between the length of time off work or school post-procedure between the two groups of patients, as well as direct comparison of outcomes between propofol-based deep sedation by pediatric hospitalists and anesthesiologists.

The pediatric hospitalists who provided the propofol-based deep sedation in this study were all trained in accordance to ASGE recommendations (7). The overall adverse event rate of NAAP in our study is comparable to the results of adult studies and similar pediatric studies. In our study, NAAP had a lower overall adverse event rate than general anesthesia cases and a lower overall respiratory adverse event rate. The rates of cardiac and gastrointestinal adverse events between the two groups are similar. Patients who are ASA 3 and above, or otherwise at high risk for anesthesia complications, should still be referred for general anesthesia. The results of our study suggest that NAAP deep sedation by a pediatric hospitalist during pediatric EGD, colonoscopy, and EGD/colonoscopy is safe and effective. NAAP by a pediatric hospitalist-run sedation team is an example of multidisciplinary collaboration to produce high-quality care for pediatric patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Baylor College of Medicine. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FL: data collection, data analysis, and manuscript writing. KQ: data collection and manuscript editing. BC: data analysis and manuscript editing. AR: experimental design and manuscript editing. CS: manuscript editing. DF: experimental design, data analysis, manuscript writing, and manuscript editing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

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MINI REVIEW
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Evolution in the Practice of Pediatric Endoscopy and Sedation

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The fields of pediatric gastrointestinal endoscopy and sedation are critically important to the diagnosis and treatment of gastrointestinal (GI) disease in children. Since its inception in the 1970s, pediatric endoscopy has benefitted from tremendous technological innovation related to the design of the endoscope and its associated equipment. Not only that, but expertise among pediatric gastroenterologists has moved the field forward to include a full complement of diagnostic and therapeutic endoscopic procedures in children. In this review, we discuss the remarkable history of pediatric endoscopy and highlight current limitations and future advances in the practice and technology of pediatric endoscopy and sedation.

Keywords: gastrointestinal endoscopy, sedation administration, artificial intelligence, pediatric, history, ERCP

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INTRODUCTION

Pediatric endoscopy came into existence nearly 170 years after Dr. Phillip Bozzini developed the first "endoscope" in 1805 known as the "Lichleiter" candle (1). At that time and throughout the 1800s, endoscopy was plagued by inadequate and even dangerous methods of combustible lighting, but Thomas Edison's electric light bulb quickly resolved this issue in the 1880s. Despite improved illumination, endoscopes remained limited by poor visualization and rigidity which prevented access to deep body cavities like the proximal colon and duodenum (2). Then, in 1958, Dr. Hirschowitz famously described his clinical experience with the first fiberscope (3). This technology paved the way to modern flexible endoscopes by incorporating bundled glass fibers to transmit light and images. By the 1970s fiberscopes had become widely available, but their use in small children remained limited because of the problem of miniaturizing the equipment. During this time, smaller 5.2 mm fiber bronchoscopes were being used in children, but these were not suitable for examination of the gastrointestinal tract because of poor image quality, limited angulation, and lack of suction or insufflation (4).

In 1969 the Hopkins rod-lens system permitted miniaturization of the endoscope. This revolutionary system paved the way for development of the pediatric specific fiber endoscope (5, 6). In the ensuing two decades fiberoptics gave way to the charge-coupled device (CCD) video endoscope which was introduced by Welch Allyn in 1983 (7). A CCD allowed real time image display on video monitors which transformed the field and art of endoscopy. Over the past 40 years, advances in biomedical technologies have led to real-time visualization of the luminal features through high-definition images, the current industry standard. The obstacles of lighting, optics, and maneuverability have been mostly conquered with today's technology, but the design of the gastrointestinal endoscope remains relatively unchanged leaving multiple problems yet unsolved including procedural discomfort, loop related perforation, difficult sterilization, and subtotal examination of the GI tract (8). Because of the inherent risks and discomfort associated with the current endoscope design, deep sedation or general anesthesia are essential.

SEDATION IN CHILDREN UNDERGOING GASTROINTESTINAL ENDOSCOPY

Sedation for pediatric gastrointestinal endoscopy is an important component for patient comfort and procedural success. Pediatric developmental and physiologic considerations, however, require a specialized approach to avoid serious complications. Although the occurrence of serious complications from pediatric procedural sedation performed by experienced practitioners in a culture of safety is <2% (9), life-threatening events during sedation still occur (10). The trend of increasing use of sedation for diagnostic and therapeutic procedures by a wider array of providers, including pediatric hospitalists (9), underscores the need for continued vigilance around sedation safety.

Cardiopulmonary and sedation-related adverse events may account for up to 60% of periprocedural complications from pediatric endoscopy (11). Patient groups at elevated risk for cardiopulmonary and sedation-related adverse events have been identified through analysis of large pediatric outcomes databases (12, 13). These high-risk groups include infants younger than 1 year and children with significant congenital comorbidities, such as congenital heart disease, cystic fibrosis, muscular dystrophy, or acquired comorbidities, such as obesity and acute upper respiratory tract infection (11). Preprocedural assessment for these and other conditions affecting hemodynamic stability, airway management and aspiration risk and assigning an American Society of Anesthesiologists (ASA) physical status score are a standard recommendation of the American Academy of Pediatrics (10).

Given the anxiety and discomfort associated with pediatric endoscopy, deep sedation or general anesthesia administered by a dedicated provider or anesthesiologist are typically required (14). Sedation is often achieved with a combination of fentanyl, meperidine, midazolam, or ketamine. Endoscopist performed sedation is technically difficult, time consuming, and may increase the risk for adverse cardiopulmonary events. Therefore, multiple authors suggest dedicated anesthesiologists or carefully selected sedation teams in line with national legislation and institutional regulations to perform endoscopic sedation (15, 16). In the interest of patient safety, current guidelines for deep sedation and/or general anesthesia continue to require at least two individuals present including a skilled observer independent of the procedure itself with training and credentialing in sedation and advanced airway skills capable of patient rescue during life-threatening emergencies (10).

Increased attention has focused on expanding options for non-anesthesiologist-administered sedation including with propofol. Propofol is a potent amnestic and hypnotic agent with rapid onset and short duration allowing for rapid titration to a targeted depth of sedation without gastrointestinal side effects. Its primary disadvantage its narrow therapeutic window and ease of moving quickly between levels of sedation into general anesthesia with potential airway, respiratory and hemodynamic compromise. With proper training and institutional support, usually aligned with practice recommendations from the ASA (15), credentialing pathways have emerged for deep sedation using propofol in adult gastroenterology practice based on high-level evidence (16). Building on reports of propofol administration by non-anesthesiologists for pediatric procedural sedation (17), researchers have continued to establish a favorable safety profile for a team-based approach to sedation with propofol in pediatric endoscopy even compared with general anesthesia (18). This issue remains unresolved, however, and safety considerations when using propofol remain significant as the largest database of pediatric procedural sedation outcomes reported increased risk of adverse events, especially airway events, in sedation using propofol alone or in combination with other agents (9).

Putting It Into Practice

- Pediatric sedation for gastrointestinal endoscopy results in rare but sometimes serious adverse events and requires a specialized approach. It is important to determine sedation risk based on the patient's profile and their ASA physical status score.
- Pediatric sedation is technically challenging and requires the expertise of pediatric anesthesiologists or an approved hospitalist led sedation team in accordance with ASA guidelines, institutional regulation, and applicable legislation. Endoscopist performed sedation is not advised as it results in decreased patient satisfaction, increased procedure time, and leads to higher risk for cardiopulmonary adverse events.

COMMON ENDOSCOPIC PROCEDURES IN CHILDREN

As with anesthesia, selection of the proper endoscopic tools in pediatric endoscopy is necessary for procedural success and patient safety. Endoscopes are presently manufactured in a range of sizes to permit access into the gastrointestinal tract of children. Diagnostic endoscopy includes the acquisition of endoscopic images and sampling of mucosal tissue and includes both esophagogastroduodenoscopy (EGD), and colonoscopy. These procedures can be performed by an adequately trained pediatric gastroenterologist with an appropriately sized endoscope.

Depending upon the pathology, therapeutic procedures are sometimes indicated. A range of endoscopic therapies are available but only a handful are typically employed by general pediatric gastroenterologists. Some of these procedures include stricture dilation, variceal ablation, polypectomy, foreign body management, hemostatic therapy, and transnasal endoscopy. However, options for some of these remain limited in ultrathin pediatric gastroscopes. These scopes, including trans-nasal endoscopes, range from 4.9 to 5.9 mm in diameter, contain a single 2.0–2.4 mm working channel and are requisite in children weighing <5 kg. Due to these size restrictions some therapies like endoscopic balloon dilation, use of large retrieval devices, and application of topical hemostatic agents are not possible (17, 18).

Slim gastroscopes have an insertion diameter of 7.8–9.0 mm and are typically used in children weighing <10–15 kg. Standard gastroscopes range from 9.0 to 10.0 mm in diameter and are useful in children weighing more than 20 kg (18). The primary advantage of these endoscopes compared with ultrathin models is the 2.8 mm working channel which supports most therapeutic instruments including balloon dilators, retrieval devices, polypectomy snares, and hemostatic therapies.

Esophageal stricture dilation is an important procedure for pediatric endoscopists (19). Balloon dilators come in various sizes and are important tools because of their ability to create an even distribution of circumferential pressure on a stricture. Balloon dilation is often advantageous over bouginage because of several key features including endoscopic and fluoroscopic real-time evaluation of balloon placement and stricture reduction, wire guided balloon placement in difficult-to-reach locations, and lower rates of post-procedural pain, although both have similar safety profiles (20, 21). This therapy is only available when using endoscopes with 2.8 mm working channels so alternative methods must be employed in smaller patients (22).

Management of gastrointestinal foreign bodies in children is a unique and important aspect of pediatric gastroenterology. Some solid ingestions like esophageal button battery, multiple magnets, or sharps necessitate rapid resolution (23). In addition to emergent ingestions, other objects requiring endoscopic retrieval may simply be too large to pass a child's lower esophageal sphincter or pylorus. Various retrieval devices are manufactured to fit in standard gastroscopes, and it is important for endoscopy units to maintain a stocked armamentarium of this equipment.

Significant gastrointestinal bleeding is rare in the pediatric population, but this represents an important indication for endoscopy. Appropriate endoscopy unit planning and stocking is required to manage these events effectively. Hemostatic therapies broadly include, mechanical, thermal, topical, and injection methods (24). Ultrathin pediatric scopes are unable to support the use of topically applied powders including Hemospray (TC-325, Cook Medical, Bloomington, Indiana, United States) and Endoclot (EC, Micro-Tech Europe, Düsseldorf, Germany), as well as mechanical clips (18, 25). Available hemostatic therapies for ultrathin scopes include 22–25 g injection needles, argon plasma, and thermal contact devices. This again underscores the importance of maintaining a variety of endotherapies for use in both standard and ultrathin sized endoscopes.

TNE offers pediatric endoscopists the ability to perform non-sedated endoscopy in the clinic setting. However, free-standing gastroenterology offices may encounter logistical difficulties related to scope reprocessing. TNE has historically been used in adult patients but is garnering attention in pediatrics in part because of disorders like eosinophilic esophagitis (EOE) which require serial endoscopies. A major benefit of TNE is that it overcomes the need for sedation and can be performed within the clinic setting (26) thereby reducing cost, time, and sedation related adverse events. Anxiety surrounding non-sedated TNE may be mitigated by the novel use of virtual reality video goggles, a strategy that has been successful in children as young as 6 years (27).

Putting It Into Practice

- The smaller working channel found in ultrathin endoscopes can present therapeutic challenges for certain disease states.
- Pediatric endoscopy centers should maintain appropriate quantities of endoscopic tools for foreign body management and hemostasis in both standard and ultrathin pediatric scopes.
- Limit accidental unpackaging of inappropriate sized equipment by clearly designating scope size requirements.
- To successfully employ TNE within the gastroenterology clinic it is important to consider the logistics of daily scope reprocessing. TNE is beneficial for patients who require serial esophagoscopy and it can be helpful to utilize non-pharmacologic methods for anxiolysis such as virtual reality goggles.

ADVANCED ENDOSCOPIC PROCEDURES IN CHILDREN

Advanced endoscopic procedures including endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and per-oral endoscopic myotomy (POEM) are becoming more widely available to children, but many pediatric centers still cannot offer these therapies. These therapies provide minimally invasive solutions for patients with illnesses that previously would have been surgically managed (28, 29). A recent published survey of North American pediatric gastroenterologists showed that 72% of respondents believed their institutions' arrangement for advanced endoscopic procedures was inadequate (30). This discrepancy is the result of an historically low supply of advanced pediatric endoscopists and pediatric case load in addition to scare training options (31).

ERCP in pediatrics has been increasing steadily over the past 20–30 years and has shifted from a diagnostic to a therapeutic procedure. For most patients weighting >10 kg a standard adult duodenoscope can be utilized. However, for smaller patients a pediatric duodenoscope must be used (32). ERCP is technically demanding with higher complication rates than standard endoscopy and proper patient selection is key in preventing complications. Increasing evidence continues to demonstrate its safety and efficacy in pediatrics (33–36). ERCP is performed in pediatrics primarily for pancreaticobiliary indications such as: biliary obstruction, pancreatic ductal stones, acute recurrent and chronic pancreatitis, pancreas divisum, choledochal cysts, trauma, and sphincter of Oddi dysfunction. The major limitations of pediatric ERCP continue to be duodenoscope size, lack of pediatric specific instruments and endoscopes and lack of adequate training.

Endoscopic ultrasound (EUS) has diagnostic and therapeutic relevance in pediatrics along with promising patient safety data (37–39). EUS is used in idiopathic recurrent pancreatitis, pancreatic pseudocysts, walled-off necrosis, cyst-gastrostomy creation, cyst-duodenoscopy, fine needle aspiration and biopsy, suspected choledocholithiasis, celiac plexus block, submucosal lesions, and congenital malformations (40, 41). An advantage of EUS compared with other radiologic exams is its ability for precision tissue sampling. EUS can further discriminate the appropriateness of ERCP in patients whom the diagnosis of choledocholithiasis is unclear (42). Patient-scope size mismatch can again present challenges in pediatrics as the weight cut-off for EUS is typically >15 kg.

POEM has become an important procedure for the management of pediatric achalasia and is being performed by both surgeons and gastroenterologists. Achalasia has long been managed with pneumatic balloon dilation and surgical correction but a meta-analysis from 2019 demonstrated the superiority of POEM for all three achalasia subtypes (43). POEM was first performed by Dr. Haruhiro Inoue in 2008 (44) and since then, several pediatric case series have reported clinical success rates of 90–100% with only minor complications (45, 46).

The future of pediatric advanced endoscopy is bright with new advances in training, pediatric specific endoscopes, and instrument development. However, to continue to advance the field of pediatric advanced endoscopy it is crucial to maintain a collegial relationship with our adult GI colleagues (30).

Putting It Into Practice

- Pediatric centers are frequently unable to provide advanced endoscopic procedures, however, adult advanced gastroenterologists may be able to help manage some patients. Establish and maintain a collegial relationship with local advanced endoscopists who are willing and able to care for pediatric patients.
- Pediatric endoscopists may acquire advanced endoscopic skills through formal or informal training programs in the United States and globally. This will help meet needs at institutions where advanced procedures are limited.
- EUS should be performed in cases where choledocholithiasis is uncertain as it frequently avoids unnecessary ERCP.
- POEM has become an important treatment option for pediatric achalasia and is being offered at numerous centers. POEM can be considered for first line treatment but may also be considered after unsuccessful surgical myotomy.

COMPLICATIONS RELATED TO ENDOSCOPIC PROCEDURES IN CHILDREN

Adverse events (AEs) related to pediatric endoscopy are rare but high-quality large-scale data remains scant. However, recent publications and clinical practice guidelines have helped inform practicing gastroenterologists and guide quality improvement measures within endoscopy units.

Until recently, the largest studies detailing AEs in pediatric endoscopy came from retrospective multi-center datasets. The 2006 PEDS-CORI report acquired data during or immediately following pediatric gastroduodenoscopies and cited a 2.3% (1.6% anesthesia related and 0.7% endoscopy related) overall AE rate with no deaths or perforations (47). This study likely missed late presenting AEs. A report from the Pediatric Hospital Information System (PHIS) in 2017 described a 0.7% 5-day readmission rate following diagnostic EGD and colonoscopy. However, only 6.6% of these cases required inpatient treatment. Despite its inability to describe specific AEs, this report importantly noted that minority race, female sex, and complex chronic conditions were factors more commonly associated with readmission (48). PHIS data revealed an overall therapeutic procedure complication frequency (0.74%) and mortality rate (0.1%) and identified higher risk for readmission following variceal ablation and stricture dilation compared with other procedures (49).

A more recent study prospectively evaluated AEs within the 72 h following endoscopy over 4 years and reported a 2.6% cumulative AE rate from all diagnostic and therapeutic endoscopies. Medically significant AEs related to infection, bleeding, and perforation were encountered in only 0.28%, and therapeutic procedures accounted for most of these cases (50). This study improved our understanding of the adverse event profile following endoscopy by defining specific events within the 72 h following endoscopy.

Despite the low rate of serious AEs, these remain a concern and warrant attention. A review from 2018 cited various studies which identified endoscopist experience, pre-procedural assessment, identification of appropriate equipment, and CO_2 insufflation as the most frequently proposed counter measures to reduce procedural complications (51). The North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) endoscopy committee made formal quality improvements recommendations for endoscopy units to include a preoperative assessment designed to identify high risk patients (11) and for individual institutions to track AEs (52). It is imperative that pediatric gastroenterology fellows receive adequate hands-on experience during training to develop proper technique, but also that they readily understand the indications and proper use of all endoscopic equipment.

Finally, it is important that post-procedural complications including fever and abdominal pain are handled appropriately. In most cases these symptoms are unrelated to serious AEs and providing reassurance can help allay caregiver anxiety. Recently, data from a clinical care guideline aimed at improving post-endoscopy fever management showed a reduction in health care overutilization by nearly 40% (53). The guideline appropriately instructed a small subset of patients with clinically significant fever to seek medical evaluation. Abdominal pain represents another important post procedural complication and reducing discomfort with carbon dioxide insufflation has gained popularity in recent years. This technique significantly reduces post endoscopy abdominal pain within the 6 h following the procedure (54, 55) and could lead to reduced healthcare overutilization.

Putting It Into Practice

- Endoscopy centers should develop ways to systematically record adverse events during and within the 72 h following

procedures. AE data may reveal unique challenges for individual centers, and these should be used to inform quality improvement efforts.
- CO2 should be considered for pediatric endoscopy because it reduces post-procedural discomfort. This may reduce caregiver anxiety and lead to reduced emergency department overutilization.
- Institutions should develop post-procedural guidelines to triage and advise patients who develop post-procedural fever or pain as this can reduce emergency department overutilization.

FUTURE DIRECTIONS

The future of pediatric endoscopy and endoscopy in general involves technological developments that will advance the field of gastroenterology and may gradually shift the role of an endoscopist. Artificial intelligence, robotic assistance, and disposable endoscopes are being developed to improve efficiency, diagnostic accuracy, increase procedure tolerability, and reduce the transmission of infectious disease.

AI is revolutionizing most industries because of its ability for complex data processing. Though it has been a "hot topic" for decades, AI in medicine is now taking shape largely because of the robust technological infrastructure currently in place (56). Medical education is incorporating AI into its curriculum and manufacturers are adding AI to endoscopy software (57–59). Commercially available AI software for gastroenterologists now exists through multiple manufacturers but is limited to polyp detection during endoscopy. It is reasonable to assume that with future software updates these platforms will begin to include more robust features such as identification of inflammatory lesions, and population of critical elements on a procedure report. With AI steadily on the rise, endoscopy centers interested in cutting edge technology should consider pioneering these systems within the pediatric population. AI has already been used to differentiate inflammatory lesions of the colon and diagnose celiac disease with surprising accuracy (60, 61) and to differentiate Crohn's from ulcerative colitis in pediatric patients (62). These reports indicate that AI may eventually assist physicians with real-time endoscopic diagnostic and therapeutic decision making.

AI has also shown the potential to improve the sensitivity of pill endoscopy while saving time for gastroenterologists. Recent studies involving convolutional neural networks demonstrate how computer assisted diagnosis using pill endoscopy outperforms human readers in the detection rate of pathology 88.39–99.98% vs. 74.57% and in exam completion time: 5.9 vs. 96.6 min, respectively (63, 64). AI for pill endoscopy will soon be commercially available.

Improving efficiency for clinicians is one of the most exciting improvements, but AI is not limited to high-skill tasks such as diagnostics. Documentation consumes substantial amounts of physician time and some have proposed incorporating AI into generation of procedure reports. Investigators have trained systems to recognize anatomic location, endoscopic tools, and the goodness of cleanout (65–67). Leveraging machines to generate scope report data would be a welcome opportunity for many gastroenterologists.

To address the growing concerns of exogenous infection using reprocessed endoscopes, including Carbapenem-resistant Enterobacteriaceae (68), the American Society for Gastrointestinal Endoscopy has called for enhanced endoscope reprocessing and the development of effective, environmentally friendly, disposable endoscopes (69). The first example of this is the EXALT^{TM} Model D (Boston Scientific Corporation, Marlborough, Massachusetts, USA) which achieved equal cannulation compared with standard reusable duodenoscopes in low complexity ERCPs (70). Multidrug resistant (MDR) infection is an uncommon problem in pediatrics in general. However, it is important to consider that pediatric patients undergoing ERCP within adult hospitals are at increased risk for nosocomial MDR infection spread from adult patients. Because of this risk, we suggest that adult hospitals prioritize use of disposable endoscopes in pediatric patients.

Finally, robotically assisted magnetic capsule endoscopy is an emerging technology that represents a potential paradigm shift in the way endoscopy may be performed in the future. This novel strategy employs a robotic arm wielding an electromagnet, which guides a tethered, pill-shaped endoscope through the intestine. An important patient advantage of this machine is the reduction in shearing forces on the bowel wall (71, 72). For pediatric purposes, this technology represents further miniaturization of the endoscope and could allow for the expansion of therapeutic options in very small children. This machine improves upon other magnetically guided capsules in that the tether and working channel allows for utilization of routine endoscopic tools to perform traditional diagnostic and therapeutic procedures.

Putting It Into Practice

- Commercially available AI for endoscopy is available through multiple major manufacturers but has not been studied in pediatrics. AI for pill endoscopy will soon be available. These technologies represent an important area for future pediatric research.
- Disposable duodenoscopes are commercially available and should be considered for use in pediatric patients undergoing ERCP at adult hospitals to limit exposure to multidrug resistant bacteria.

CONCLUSION

The practice of endoscopy is a cornerstone in the field of pediatric gastroenterology and has evolved over the last 50 years to include an array of advanced diagnostic and therapeutic procedures. However, despite a host of improvements, limitations related to patient safety, procedure tolerability, and diagnostic accuracy still exist. While it is not possible to know exactly how the field of pediatric endoscopy will evolve in the ensuing decades, the ongoing surge in innovation offers hope that many of today's limitations will become tomorrow's history.

AUTHOR CONTRIBUTIONS

CC, TL, and JK co-wrote the first draft of the manuscript and performed the literature review. GH conceived the manuscript, made significant contributions, and revised the final manuscript. All authors contributed to the article and approved the submitted version.

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Variation in Pediatric Anesthesiologist Sedation Practices for Pediatric Gastrointestinal Endoscopy

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Background: Despite a worldwide shift toward anesthesiologist-administered sedation for gastrointestinal endoscopy in children, ideal sedation regimens remain unclear and best practices undefined.

Aim: The aim of our study was to document variation in anesthesiologist-administered sedation for pediatric endoscopy. Outcomes of interest included coefficients of variation, procedural efficiency, as well as adverse events.

Methods: IRB approval was obtained to review electronic health records of children undergoing routine endoscopy at our medical center during a recent calendar year. Descriptive and multivariate analyses were used to examine predictors of sedation practices.

Results: 258 healthy children [2–21 years (median 15, (Q1–Q3 = 10–17)] underwent either upper and/or lower endoscopies with sedation administered by anesthesiologists (n = 21), using different sedation regimens (29) that ranged from a single drug administered to 6 sedatives in combination. Most patients did not undergo endotracheal tube intubation for the procedure (208, 81%), and received propofol (255, 89%) either alone or in combination with other sedatives. A total of 10 (3.8%) adverse events (9 sedation related) were documented to occur. The coefficient of variation (CV) for sedation times was high at 64.2%, with regression analysis suggesting 8% was unexplained by procedure time. Multivariable model suggested that longer procedure time ($p < 0.0001$), younger age ($p < 0.0001$), and use of endotracheal tube intubation ($p = 0.02$) were associated with longer sedation time.

Discussion: We found great variation in anesthesiologist administered regimens for pediatric endoscopy at our institution that may be unwarranted, presenting may opportunities for minimizing patient risk, as well as for optimizing procedural efficiency.

Keywords: sedation, endoscopy, anesthesiologist, pediatrics, variation in care, coefficient of variability, efficiency, pediatric anesthesiology

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KEY POINTS

1. To date, there is no single sedative or combined regimen that has been established as ideal for pediatric gastrointestinal procedures, regardless of whether procedural sedation is being administered by endoscopists or anesthesiologists.
2. Over the past two decades, pediatric endoscopy is increasingly being performed with anesthesiologist-administered sedation regimens that use propofol.
3. Broadly speaking, sedation plans that call for general anesthesia with endotracheal intubation are not necessary for routine pediatric endoscopy or colonoscopy and may decrease procedural efficiency and value.
4. It is becoming increasingly important for pediatric endoscopists to engage in a dialogue with anesthesiologists, with the goal of determining best sedation practices for children undergoing gastrointestinal procedures.

INTRODUCTION

Over the past 2 decades, the landscape of sedation practices for pediatric endoscopy has shifted toward anesthesiologist-administration, despite no single sedative or regimen yet to be established as ideal (1–3). Historically, pediatric endoscopic sedation has been administered by endoscopists or anesthesiologists, and is generally considered necessary for children to undergo procedures (4). The trend toward anesthesiologist-administration has evolved from increasing interest in ensuring patient safety and comfort, (5, 6) as well as the ability of propofol to target a spectrum of sedation levels with rapid induction and recovery times (7). However, it is not clear that these and other anticipated benefits of anesthesiologist-administration for pediatric endoscopy have been fully realized, perhaps due to wide variations in care that have yet to be systematically documented or examined (1, 8–11).

Multiple studies have shown propofol, either as a total intravenous anesthetic (TIVA) or in combination with inhalational agents, to be highly effective for endoscopic sedation in children (12–16). Generally speaking, anesthesiologists differ from endoscopists in their regulatory license to use propofol and inhalational anesthetics, as well as to aim for deep levels of sedation or general anesthesia (17, 18). Anesthesiologists may therefore be more equipped to administer sedation regimens that can assure children will tolerate endoscopic procedures, without exhibiting agitation, vocalization and disruptive movements (6). Nevertheless, anesthesiologist-administration has not decreased the occurrence of sedation related adverse events in children undergoing upper and lower endoscopy (19, 20). Adverse events associated with sedation, such as apnea, laryngospasm and bradycardia- even when sedation practices involve anesthesiologists - continue to occur more often during pediatric endoscopy than procedural complications, such as mucosal bleeding or perforation (1, 12, 19–22).

Abbreviations: GI, Gastrointestinal; IV, Intravenous; ASA, American Society of Anesthesiology.

Another important concern regarding use of anesthesiologists during pediatric endoscopy is the potential for inefficient use of healthcare resources (2, 8, 9, 23). For example, unnecessary use of endotracheal intubation for routine diagnostic endoscopy in children has been shown to increase endoscopy room times and costs (11). While many endoscopists acknowledge increased patient comfort when anesthesiologists provide sedation, it has also been true that variability in anesthesiologist practices can lead to a mismatch between sedation provided and the procedure performed (8). For example, provider variation in the use of rapid sequence intubation has been associated with much longer sedation times relative to procedural duration, as well as patient paralysis when immobility is not required for endoscopy (24). Ultimately, reducing unwarranted variation in pediatric anesthesiologist sedation for endoscopy will likely be necessary to improve patient safety, as well as to ensure procedural efficiency and value (19).

We believe the intersection between gastrointestinal procedures in children, patient safety, efficiency and sedation regimens remains of great importance to study in the current era of anesthesiologist-administration – particularly because unwarranted variation in anesthesiology sedation practices has been speculated to exist and best practices have yet to be identified (1, 12). As a first step in examining this topic, we undertook to systematically document variation in anesthesiology sedation practices for pediatric endoscopy at our institution. We were specifically interested in examining how various sedative regimens, anesthesiology and endoscopy providers, provider staffing models, and use of endotracheal intubation might interrelate with procedure and patient factors, including procedure type, age, and medical complexity. Outcomes of interest included sedation and procedural efficiency, as well as both sedation and non-sedation related adverse events.

METHODS

Institutional approval (Protocol # H00013675) was granted to develop and analyze a complete retrospective database of all endoscopic procedures performed by pediatric gastroenterologists with anesthesiologist-administered sedation at our academic medical center during calendar year 2018. An endoscopy reporting database (ProVation MD) was used to identify all children who underwent upper and/or lower endoscopic procedures performed during the study period for routine, diagnostic purposes. Two independent investigators (KH, TD) codified and abstracted information about each case from components of the electronic medical record (Epic) onto an institutionally approved separate case report form, including from the endoscopists' procedure reports, endoscopy technician and nurse peri-procedure documentation forms, as well as from the anesthesiologists' records. Patient descriptive data was recorded, including sex, age, height, weight, medication allergies and American Society of Anesthesiology (ASA) patient complexity status, as documented by the anesthesiologist. Type of procedure performed (upper endoscopy, lower endoscopy, both upper and lower endoscopy), time first sedative administered, time out of room, time of endoscope insertion, and time of endoscope removal were recorded, as well as the indication for the procedure, whether the patient underwent endotracheal intubation as part of the sedation plan with or without paralytic agents, and/or documented adverse events. We also noted the names and doses for all oral and intravenous sedatives that were administered during the sedation time, including midazolam, fentanyl, propofol, ketamine; as well as names of all inhalational anesthetics, including sevoflurane, isoflurane, and nitrous oxide. In addition, we recorded and coded the identities of all endoscopists who performed procedures, anesthesiologists of record for administration of the sedation, and any certified registered nurse anesthetists (CRNAs) who were documented to have delivered sedation with anesthesiologist supervision, during each case.

The first sedative administered was defined as any oral, intravenous (IV) or inhalational agent administered for the purposes of anxiolysis, analgesia or inducing sedation, and included oral midazolam if administered in the pre-operative area for anxiolysis prior to transport to the endoscopy room. We excluded any sedatives administered in the recovery area for agitation, delirium, or other adverse sedation events, although these events were recorded as below. We defined sedation time as first sedative administered to patient time out of room, and procedure time as scope in to scope out.

Adverse events are predefined at our institution and include apnea, disordered respiration, laryngospasm, vomiting, aspiration, delirium, agitation, inadequate sedation for a procedure, as well as airway management issues, intravenous line infiltration, patient pain or discomfort, bleeding, procedural complications, unanticipated admission to the hospital, and death. Any adverse event that was recorded as such in the endoscopy report or the anesthesia record was abstracted to the study case report form. For the purposes of analysis, adverse events were categorized to be either sedation-related or other.

Patients and Procedures

We included all patients ages 1–21 years old who underwent routine, diagnostic upper and/or lower endoscopy at UMASS Medical Center with anesthesiologist-administered sedation during the study period. We excluded pregnant patients, as well as patients undergoing emergency or add-on procedures, including for gastrointestinal bleeding, foreign body, or caustic ingestions. We also excluded patients undergoing procedures that were performed in combination under the same sedation with non-gastrointestinal procedures performed by other subspecialists – including otolaryngologists performing laryngoscopies or pulmonologists performing bronchoscopies. We also excluded procedures that involved endoscopic interventions, including dilations and polypectomies. All endoscopic procedures were performed in a hospital-based operating room setting by an American Board of Pediatric (ABP) certified pediatric gastroenterologist attending. All patients received anesthesiologist-administered sedation regimens that was either provided or overseen by an attending anesthesiologist with pediatric training, who at times was assigned a CRNA to assist in providing sedation care. The targeted depth level of sedation for all patients was at least deep sedation. We defined all patients who underwent endotracheal intubation in our study to have received general anesthesia.

Study Outcomes

Our primary outcome of interest was variation in sedation regimens. We sought to characterize this in terms of sedative names and types (oral vs. IV vs. inhalational), as well as number of sedatives employed. Secondary outcomes included total anesthesiologist- administered sedation time, and sedation or non-sedation related adverse events.

Statistical Analysis

We described continuous variables representing provider experience (e.g., number of endoscopist sedations administered during the study period; number of procedures performed during the study period), patient's characteristics (e.g., age, weight), sedation (e.g., sedative doses), and procedure characteristics (e.g., anesthesiologist-administered sedation time, procedure time) using medians, lower (Q1) and upper (Q3) quartiles. Categorical variables, including whether patients underwent endotracheal intubation or experienced an adverse event, were tabulated using proportions. Box and whisker plot was drawn to display the distribution of anesthesiologist-administered sedation time by procedure type. To identify predictors for length of anesthesiologist-administered sedation time, we performed multivariable generalized linear regression model with potential predictors including patient's age and sex, ASA level, length of procedure, procedure type, adverse events, and use of endotracheal intubation and CRNA. To identify predictors for use of endotracheal intubation, which was dichotomized as yes vs. no, we performed multivariable logistic regression model which yielded odds ratio (OR) of using the tube for each predictor. Both regression models were incorporated with generalized estimating equation (GEE) to account for potential correlations between repeated measures by anesthesiologists. Statistical analyses were performed using SAS v9.4 (SAS Institute, NC) and S-Plus 7 for Windows (Insightful, USA).

RESULTS

A total of 258 upper and lower routine, diagnostic, endoscopic procedures were performed at our institution in patients ages 2–20 years of age with median age of 15 years (Q1-Q3 = 10–17, **Table 1**). Most patients were older than 9 years of age (n = 197, 76%), and were healthy with an ASA status of $\leq$ 2 (249, 97%). The number of cases that each anesthesiologist (n = 21) staffed during the study period varied widely, ranging from 1–71 (**Figure 1**). Anesthesiologists were assigned a certified registered nurse anesthetist (CRNA) to work with them for 205 (80%) of the cases. Most anesthesiologists (11, 52%), and CRNAs (15, 60%) provided sedation care for <5 endoscopic cases over the study period. Five anesthesiologists administered endoscopic sedation for a single case each, while 4 staffed at least 30 cases over the calendar year.

TABLE 1 | Descriptive characteristics of patients, providers and procedures.

	Summary statistics
Patients (*N* = 258)	
Age (years), *median (Q1, Q3)*	15 (10, 17)
Weight (Kg), *median (Q1,Q3)*	52.3 (35, 63)
Gender (male), *n (%)*	126 (49)
ASA, *n (%)*	
ASA 1	77 (30)
ASA 2	172 (67)
ASA 3	8 (3)
ASA 4	1 (<1%)
ETT intubation for sedation, *n (%)*	50 (19)
Providers	
Total number of endoscopists, *n*	6
Total number of endoscopies per Endoscopist, *Median (Q1, Q3)*	32 (20.3, 60.3)
Total number of attending anesthesiologists, n	21
Total number of cases per anesthesiologist, *Median (Q1, Q3)*	4 (1.5, 12.5)
Total number of CRNAs, n	26
Total number of cases per CRNA, *Median*, *(Q1, Q3)*	3.5 (1,11.25)
Procedures (*N* = 258)	
Procedure time (minutes), *median (Q1,Q3)*	14 (8, 35)
Anesthetic Time (minutes), *median (Q1,Q3)*	25 (17, 41)
Type of Procedure, *n (%)*	
Upper endoscopy	147 (57)
Lower endoscopy	28 (11)
Upper and lower endoscopy	83 (33)
Procedure Indication, *n* (%)	
Abdominal pain	85 (33)
Positive celiac serologies	34 (13)
Hematochezia	25 (10)
Diarrhea	18 (7)
Reflux symptoms	23 (9)
Known inflammatory bowel disease	22 (9)
Dysphagia	21 (8)
Known Eosinophilic esophagitis	16 (6)
Other	14 (5)
Adverse events, *n* (%)	
Sedation-related	9 (3.5)
Other	1 (<1)

Q1 = 25th percentile; Q3 = 75th percentile; ASA, American Society of Anesthesiology (ASA) Patient Classification; ETT, endotracheal tube.
Mean anesthetic time = 31.8 mins, SD = 20.4, coefficient of variation (CV) = 64.2%.

Sedation Practices

A total of 29 sedation regimens, ranging from a single drug administered to 6 sedatives in combination, were administered to patients at our institutions during the study period (**Table 2**). Most patients (n = 192, 74%) did not receive pre-operative oral midazolam or undergo endotracheal intubation for the procedure (208, 81%). Patients who underwent endotracheal intubation had a greater number of sedative agents administered during cases, with 15/50 (30%) patients who had endotracheal intubation receiving a regimen that involved ≥5, compared with 7/208 (3%) of patients who were not intubated for the procedure ($p < 0.0001$ by Chi-square test of proportions).

Most patients (255, 89%) received infused propofol either alone or in combination with other medications, with the most common regimen (TIVA with propofol and midazolam) used in 47 (18%) patients. Among patients who did not receive propofol, 1 received an infusion of midazolam as a single drug regimen, and 2 received sevoflurane with intravenous midazolam and fentanyl. Use of inhalational anesthetics also varied, with many patients receiving more than 1 volatile gas during the case.

Adverse Events

A total of 10 (3.8%) institutionally defined adverse events were documented to occur. These included 9 that were categorized for study purposes as related to sedation [bradycardia (1), laryngospasm (3), inappropriately woke during procedure (1), use of reversal agent (1), post-op delirium (2), and stridor (1)], as well as 1 adverse event (IV infiltration) that was categorized for study purposes as not related to sedation. We could not find any pattern regarding patient demographics, procedure characteristics and sedation regimens among patients who experienced adverse events (data not shown), although endotracheal intubation in univariate analysis was noted to be weakly associated with adverse events (OR 2.93, 95% CI: 0.89, 9.60, $p = 0.08$). By grouping anesthesiologists into those who staffed >5 endoscopic cases vs. those ≤5 during the study period, mean number of adverse events between two groups was not significantly different ($p = 0.23$ by two-sample t test).

Efficiency

Mean anesthesiologist-administered sedation time was 31.8 (±20.4 SD) minutes, with median 25 (17–41) minutes. The coefficient of variation (CV) for sedation time was 64.2%, indicating a wide variation across all procedures. Highly skewed sedation time was seen for upper endoscopic procedures, and for combined upper and lower endoscopic procedures (**Figure 2**).

Furthermore, regression analysis showed that 92% of variation in anesthesiologist-administered sedation time was explained by procedure time (**Figure 3**). In other words, 8% was unexplained by procedure time.

Multivariable model suggested that longer procedure time ($p < 0.0001$), younger age ($p < 0.0001$), and use of endotracheal intubation ($p = 0.02$) were associated with longer sedation time (**Table 3**). Endotracheal tube intubation was performed for procedures in 50 (19%) patients and was associated with longer sedation time (OR = 1.02, 95% CL 1.00–1.04, $p = 0.04$) and patient's younger age (OR = 0.93, 95% CL 0.88–0.98, $p = 0.0047$), higher ASA level (level 2 OR = 1.90, $p < 0.0001$, and level 3&4 OR = 3.61, $p = 0.005$, respectively when compared to level 1, **Table 4**). Endotracheal tube intubation also varied by procedure type. When compared to lower endoscopic procedures, upper procedures were more than 3 times likely to have patients

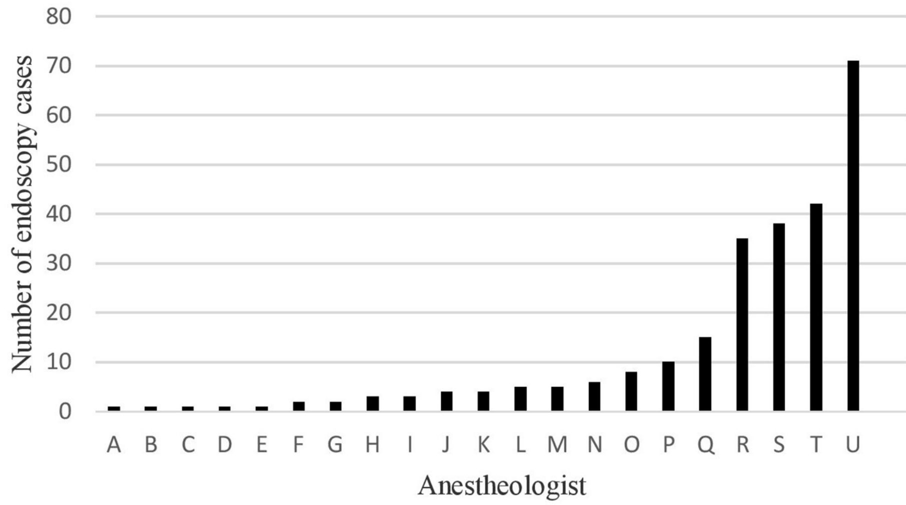

FIGURE 1 | Number of endoscopy cases performed by each anestheologist ($N = 21$).

undergo endotracheal tube intubation (OR = 4.33, 95% CL 2.23–8.44, $p < 0.0001$).

DISCUSSION

The results of our study show great variation in sedation regimens used by staff anesthesiologists caring for children undergoing gastrointestinal endoscopy at our hospital. Indeed, so many drugs were used in different combinations, it was difficult to determine any predictive factors or patterns and no dominant regimen was identified. We believe this variation in anesthesiologist-administered regimens for pediatric endoscopy reflects a paucity of evidence-based or consensus best practices that leads anesthesiologists at our institution and elsewhere to determine their own preferences.

Our results suggest provider-driven variation may have an impact on quality and safety outcomes. While procedural times were a primary factor in variation of sedation efficiency, about 8% of variation remained unexplained. This may be particularly the case for upper endoscopy, where provider decision to perform endotracheal intubation may affect procedural efficiency. Although multivariate analysis of our single-institution sample suggests some association for sedation decision making around endotracheal intubation with procedure type and patient characteristics, the dramatic spectrum of sedation practices that was documented across anesthesiology providers raises the specter that at least some variation in anesthesiologist sedation practices may be unwarranted. Our results also affirm that adverse events occur with anesthesiologist-administered sedation more commonly than non-sedation related events and continues to suggest that even when anesthesiologists are administering the sedation, improving child safety during endoscopy is highly dependent upon seeking improvements in sedation regimens.

We suspect the magnitude of variation in sedation protocols used at any institution likely reflects local preferences and the number of anesthesiologists who may be involved with staffing cases (25). Few guidelines exist that address anesthesiologist-administered sedation for pediatric gastrointestinal procedures, (2, 18, 25) and none directly identify regimens that may be ideal. All agree that the primary purpose of sedation for children undergoing upper and lower endoscopies is to perform procedures safely, with a minimal amount of emotional and physical discomfort. Although many sedatives have been shown to be safe and effective for endoscopic sedation, all have the potential to significantly depress the central nervous system, airway protective reflexes, and ventilation (1, 12, 26). Those with narrow therapeutic windows such as propofol may be even more likely to be associated respiratory events (7, 15). Kaddu et al. reported that 20% of pediatric patients receiving anesthesiologist administered propofol for upper endoscopy experienced transient apnea (14).

Rates of adverse events in our study mirror those published for endoscopist-administered sedation for pediatrics (14, 25), as well as for anesthesiologist administered rates at other institutions (19, 26, 27). In terms of safety, both the American Society of Gastrointestinal Endoscopy (ASGE) (2) and the American Academy of Pediatrics (AAP) (25) advise tailoring sedation plans according to a patient's physical status, as classified by the American Society of Anesthesiology (ASA). (28) Considering a patient's age and developmental status may also be of importance. Larger studies have suggested that generally speaking, the smallest and youngest pediatric patients with the highest ASA classifications are at greatest risk for complications during gastrointestinal procedures (19, 21, 22).

Adverse events and prolonged sedations are more common with deeper levels, which are considered to stretch along a continuum without clear boundaries and are defined by a patient's response to verbal, light tactile or painful stimuli,

TABLE 2 | Descriptive information about sedatives, as well as single and combination drug regimens, including frequency of use and PO/IV doses used.

Sedative	N° of Patients/ Cases (%) (*N* = 258)	Dose Median (Q1, Q3)
Fentanyl (mcg/kg)	100 (39)	0.823 (0.48, 1.24)
Ketamine (mg/kg)	3 (1)	0.21 (0.16, 0.67)
Midazolam PO (mg/kg)	67 (26)	0.39 (0.32, 0.49)
Midazolam IV (mg/kg)	117 (45)	0.033 (0.03, 0.04)
Propofol (mg/kg)	255 (89)	5.53 (3.64, 9.35)
Nitrous Oxide	112 (43)	–
Sevoflurane	122 (47)	–
Isoflurane	2 (<1)	–
Sedative Regimens		
Single Drug, *n* (%)	**13 (5)**	
Propofol only	12 (4.5)	10.3 (5.84, 13.31)
Midazolam IV	1 (<1%)	0.03
Double drug, *n* (%)	**66 (26)**	
Propofol + Fentanyl	5 (2)	4.58 (3.5, 11.97) + 0.75 (0.48, 1.51)
Propofol + Midazolam PO	6 (2)	8.83 (6.89, 10.9) + 0.27 (0.13, 0.38)
Propofol + Midazolam IV	47 (18)	5.94 (4.53, 11.76) + 0.03 (0.03, 0.04)
Propofol + Nitrous Oxide	3 (1)	6.8 (6.49, 7.39) + IA
Propofol + Sevoflurane	4 (2)	7.93 (6.25, 9.41) + IA
Other[1]	1 (<1)	
Triple drug, *n* (%)	**106 (41)**	
Propofol + Midazolam IV + Fentanyl	42 (16)	6.74 (4.28, 10.44) + 0.035 (0.03, 0.04) + 0.62 (0.45, 0.89)
Propofol + Nitrous oxide + Sevoflurane	39 (15)	5.12 (3.57, 10.48) + IA + IA
Propofol + Midazolam PO + Sevoflurane	6 (3)	4.47 (3.62, 7.54) + 0.25 (0.70, 0.52) + IA
Propofol + Midazolam PO + Fentanyl	8 (3)	5.15 (3.03, 12.16)+ 0.03 (0.03, 0.38) + 0.90 (0.4, 1.14)
Propofol + Midazolam PO + Nitrous oxide	5 (2)	11.53 (4.35 + 13.15)+ 0.29 (0.23, 0.42) + IA
Other[1]	6 (2)	
Quadruple drug, *n* (%)	**51 (20)**	
Propofol + Midazolam PO + Nitrous oxide + Sevoflurane	25 (10)	3.75 (2.8 + 5.7) + 0.45 (0.36, 0.50) + IA + IA
Propofol + Fentanyl +Nitrous oxide + Sevoflurane	10 (4)	3.93 (1.94, 7.41) + 0.72 (0.53 + 1.1) + IA + IA
Propofol + Midazolam IV + Fentanyl + Sevoflurane	6 (2)	3.5 (2.69, 4.31) + 0.03 (0.02 + 0.04) + 0.89 (0.64, 1.77) + IA
Other[1]	10 (4)	
Five drugs or more, *n* (%)[1]	**22 (9)**	

Q1 = 25th percentile; Q3 = 75th percentile; IV, intravenous; PO, oral; IA, inhalational anesthetic.

[1]The other double drug regimen was midazolam IV + fentanyl (1 case). Other triple drug regimens included midazolam IV + propofol and either nitrous oxide (2 cases) or sevoflurane (1 case) or ketamine (1 case). Another triple drug regimen consitented of midazolam IV + fentanyl and sevofluance (1 case) and another regimen of propofol + fentanyl + nitrous oxide (1 case). Other quadruple drug regimens included propofol + sevoflurane in combination with either nitrous oxide + midazolam IV (4 cases) or midazolam PO + fentanyl (4 cases) or midazolam PO + ketamine (1 case); and nitrous oxide + midazolam PO + fentanyl + propofol (1 case). Five drug regimens include: nitrous oxide + sevoflurane + fentanyl + propofol in combination with either midazolam IV (9 cases) or midazolam PO (11 cases). Six drug regimens included: nitrous oxide + isoflurane + midazolam IV + fentanyl + propofol with either sevoflurane (1 case) or ketamine (1 case).

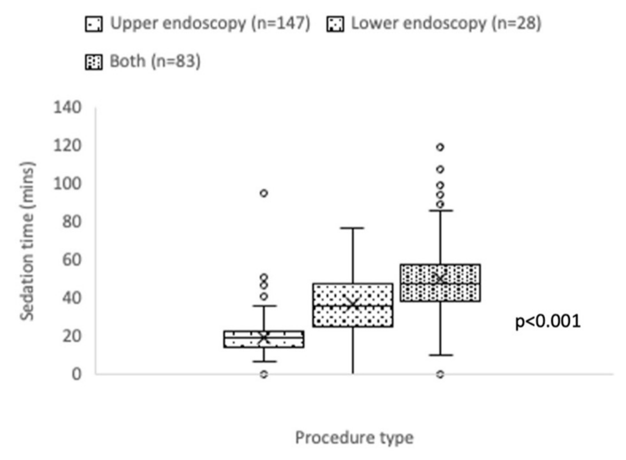

FIGURE 2 | Sedation time (minutes) by procedure type.

as well as their vital signs (29). Deep sedation implies a medically controlled state of depressed consciousness from which the patient is not easily aroused but may respond purposefully to painful stimulation. General anesthesia describes the deepest level of sedation where the patient is unconscious, with reduced responses to stimuli, and with an airway that may require support. Of course, optimal levels of sedation may vary depending upon the procedure, and may be tricky to maintain during routine maneuvers intrinsic to endoscopy that can affect the fine line between lighter and deeper levels of sedation (1, 30). In upper endoscopy, a major overall goal of sedation may be to avoid gagging and increase patient cooperation, and it is reasonable to anticipate that the few seconds it takes to insert the endoscope will typically be the most stimulating part of the procedure, while colonoscopy sedation planning should anticipate visceral pain associated with looping (31). It is important to know that deep sedation may develop during patients undergoing longer procedures (i.e., combined endoscopy and colonoscopy), or after a decrease in painful stimuli (i.e., after successful navigation of the hepatic flexure) (30).

In our study, patients who underwent endotracheal intubation for the procedure had more sedatives given in combination regimens and had more adverse events. These results are also unsurprising. Patients who receive multiple doses and/or different sedatives have been shown to be at increased risk for deeper sedation than planned, and may be more likely to have adverse events (6). Child anxiety levels can also affect sedation and have been demonstrated to be reduced in randomized controlled trials of pre-operative medication with oral midazolam (6, 25). We noted <20% of patients at our institution received a regimen that included this evidenced-based approach to improving patient satisfaction and tolerability (27, 32).

In 2002, Wennberg defined "unwarranted variations" in care as those that cannot be explained by patient factors, including illness severity, indication for treatment or patient preference (33). More recent publications have examined variation among

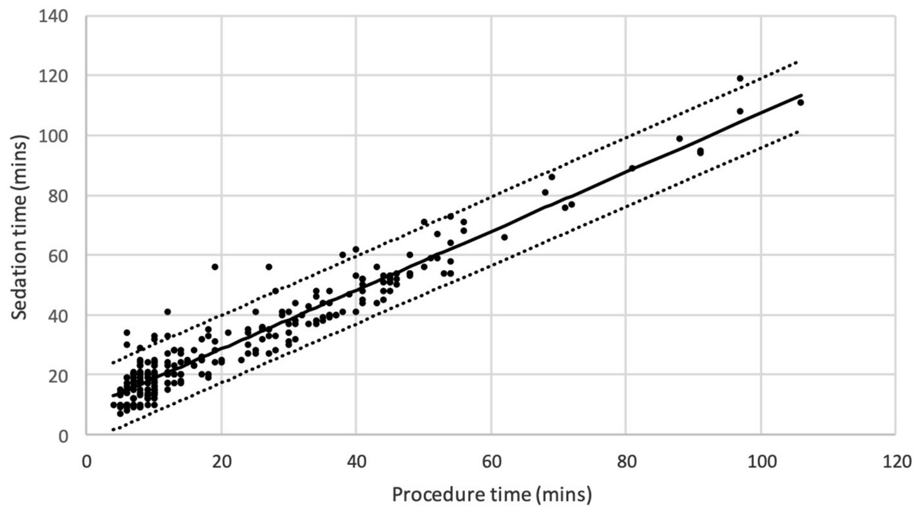

FIGURE 3 | Scatter plot for sedation time vs. procedure time with prediction line and 95% prediction limits ($N = 258$, R-square = 92%).

TABLE 3 | Multivariate normal regression model on sedation time (mins).

Predictor	Category	Estimate	SE	95% Confidence Limits		*p* value
Age (years)	Continuous	−0.53	0.09	−0.70	−0.36	<0.0001
Male	Vs female	0.63	0.74	−0.81	2.08	0.39
ASA level	2 vs. 1	0.0	0.7	−1.4	1.3	0.95
	3 & 4 vs. 1	3.8	2.3	−0.7	8.3	0.10
Procedure time (mins)	Continuous	0.98	0.03	0.93	1.03	<0.0001
Procedure type	Lower endoscopy vs. Upper endoscopy	0.2	1.2	−2.2	2.6	0.88
	Both vs. Upper endoscopy	2.2	1.3	−0.4	4.7	0.10
Adverse events	Yes vs. No	3.1	2.0	−0.9	7.0	0.13
Endotracheal intubation	Yes vs. No	1.8	0.8	0.2	3.3	0.0229
CRNA	Yes vs. No	−1.3	1.3	−3.8	1.2	0.31

Total procedure cases = 258, performed by 21 anesthesiologists.
The model was multivariate normal regression, incorporated with generalized estimating equation (GEE) to account for potential correlations between repeapted measures by anesthesiologists.

anesthesiologists terms of regional differences, as well as "professional uncertainty," (34, 35) which may both contribute to variation in anesthesiologist sedation regimens for pediatric endoscopy. Our study was limited to a single institution. Ideally, future studies will examine how the variation we found at our relatively small children's medical center within a larger university hospital compares with similarly sized groups of either anesthesiologists or endoscopists, or with variation that may happen at larger children's hospitals with higher volume of pediatric endoscopy.

Our study was further limited by its design as a retrospective review of electronic medical records, which precluded a prospective understanding of variation in sedation practices which may have been warranted. We did not prospectively survey our anesthesiologists as they planned sedation regimens pre-operatively, nor collect data on why or how sedation plans may have been adjusted once the procedure was underway. Furthermore, the retrospective nature of our investigation also ensured heterogeneity in our patient population (i.e., a wide variety of patient ages), and a lack of comparative data so that we are unable to comment on benefits and risks of specific regimens that were used. Fortunately, we did find the range and mean ages of children undergoing endoscopy at our center to be similar that reported in other multicenter studies that have examined outcomes of endoscopy and sedation (21, 22), which lends credence to the generalizability of our population to pediatric gastroenterology centers.

Nevertheless, we believe the variation in sedation practices found in our study resulted from uneven anesthesiologist familiarity with upper and lower endoscopy as brief, non-surgical procedures that do not require strict patient immobility. While some anesthesiologists may specialize in endoscopic sedation for children and have developed preferred regimens, others may only be asked to provide it on rare occasions. Our study was not powered to examine patient safety, and our data did not show an inverse relationship between the number of anesthesiologist cases in our database and adverse events, nor with variation in sedation time. From our perspective as pediatric gastroenterologists, it

TABLE 4 | Multivariate logistic regression model on endotracheal tube intubation.

Predictor	Category	OR	95% Confidence Limits		*p* value
Age (years)	Continuous	0.93	0.88	0.98	0.0047
Male	Vs. female	1.25	0.92	1.69	0.15
ASA level	2 vs. 1	1.90	1.43	2.51	<0.0001
	3 & 4 vs. 1	3.61	1.47	8.85	0.0050
Sedation time (mins)	Continuous	1.02	1.00	1.04	0.0413
Procedure type	Upper vs. lower endoscopy	4.33	2.23	8.44	<0.0001
	Upper & lower vs. lower endoscopy	3.33	2.20	5.04	<0.0001
Adverse events	Yes vs. no	1.95	0.59	6.50	0.27
CRNA	Yes vs. no	1.12	0.64	1.98	0.69

Total procedure cases = 258, performed by 21 anesthesiologists.
The model was multivariate logistic regression, incorporated with generalized estimating equation (GEE) to account for potential correlations between repeapted measures by anesthesiologists.

is reasonable to assume that anesthesiologist familiarity with endoscopy is desirable.

We also believe anesthesiologist familiarity with routine gastrointestinal procedures in children is likely associated with more confidence in recognizing that it is possible, and even preferable, to employ a propofol-based regimen for most pediatric endoscopy without performing endotracheal intubation. The practice of avoiding unnecessary endotracheal intubation may be important to assuring secondary and desirable goals of endoscopic sedation, including maximizing procedural efficiency, minimizing recovery times, and maintaining cost-effectiveness (1, 12, 15, 25, 28). Although it has been suggested that shorter induction times associated with propofol should lead to improved procedural efficiency in pediatric endoscopy units, variations in anesthesiology practices may explain why this has not been found to be true (1, 8, 12, 23). Currently, routine endotracheal intubation of all children undergoing upper GI procedures is not supported in the anesthesia literature (23). It is also important to recognize that there is no consensus for medical indications or an age cut-off, and that the decision to intubate pediatric patients should be weighed against issues that may occur with instrumenting the airway, as well as with increasing depth and prolonging sedation time unnecessarily (36).

In our study, patients were less likely to undergo endotracheal intubation for colonoscopy. This was expected as a spontaneously breathing, propofol based regimen is particularly considered to be well suited for colonoscopy, where the risk of airway compromise is greatly reduced compared to upper endoscopy that stimulates the airway (37). On the other hand, propofol does not have analgesic properties and loop formation of the scope as well as maneuvers performed to reduce this (i.e., the application of external abdominal pressure) may cause pain and patient movement, leading to increased sedation requirements (38). As was seen in the few (∼5%) patients in our study that received such a regimen, higher doses of a single-drug propofol TIVA may ensue, which in turn can increase patient risks (39, 40). Future studies should focus on identifying best practices for balancing propofol with analgesics for pediatric colonoscopy.

In conclusion, we believe the findings of our study contribute to the literature by illustrating striking variation in anesthesiologist-provided sedation care for children undergoing gastrointestinal endoscopy that likely extends beyond our institution to many others. In this way, our findings provide a mandate for all pediatric gastroenterologists to engage in a dialogue with our anesthesiology colleagues about the need to identify best practices for endoscopy sedation. While it has become standard in many ways for endoscopic sedation in children to administered by anesthesiologists, the number, doses, and combinations of sedatives may vary greatly, as does the use of endotracheal tube intubation. Unwarranted provider variation may explain why the trend toward anesthesiologist-administered sedation has not necessarily reduced the rate of adverse events related to sedation for endoscopy or improved procedural efficiency. Moving forward, we call upon all anesthesiologists who are providing endoscopic sedation for children to ensure that they are knowledgeable about routine gastrointestinal procedures, and that they are actively seeking to avoid unwarranted variations in care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by H00013675. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JL: responsibility for the integrity of the data, accuracy of the data analysis, and writing first draft of the manuscript. JL, TD, KH, and AL: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content, and approval of final version. AL: analysis. All authors contributed to the article and approved the submitted version.

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REVIEW
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Capsule Endoscopy in Children

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Since its clearance for use throughout the world, capsule endoscopy (CE) has become an important diagnostic tool, helping us to understand and document both normal and abnormal findings in the small intestine, especially in children, since CE usually can be employed without sedation or radiation. The indications in children and adults are similar, though their relative frequencies are different, with evaluation of potential and known inflammatory bowel disease the most common in the pediatric population, with CE also yielding increased diagnostic certainty compared to radiographic studies and surrogate biomarkers. Newer capsules now create opportunities to expand that understanding and our practices so that we can learn when and how to employ CE and pan-enteric CE to better monitor and guide therapy. It will take further studies to determine the best uses for CE and how to select the appropriate candidates, especially with ongoing concern about capsule ingestion vs. placement, the potential for capsule retention (particularly in known Crohn's disease), still elusive optimal methods for bowel cleansing, and the most meaningful scoring for research and clinical use.

Keywords: capsule endoscopy, pan-enteric capsule endoscopy, Crohn's disease, inflammatory bowel disease, small intestine, occult intestinal bleeding, capsule retention

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INTRODUCTION

Consider that a swallowable video capsule, based on miniaturization technology applied to its electronic components, allows us to visualize and photograph the entire small intestine (1). That seemed like pure science fiction, based on old movie scripts, until the beginning of the twenty-first century, when the fantasy turned into a logical, startling reality. Introduced in 2001, the pill camera (Given Imaging, Yoqneam, Israel) received North American and European marketing clearance for patients of 10 years of age and older in 2003, and expanded to 2 years of age and older in 2009, with patency capsule use approved the same year, expanding the possibility of wide pediatric use (2).

Upgrading CE's technical aspects (dual or rotational cameras, wider field of vision, longer battery life), the software (dynamic imaging speed, real-time viewing), and better bowel cleansing have all improved diagnostic accuracy. However, these features differ on the six currently available CE systems that are available internationally (PillCam, Medtronic, formerly Given, US; Endoscapsule, Olympus, Japan; Mirocam, Intromedic, Korea; CapsoCam, Capso Vision, US; NaviCam, Ankon Technologies, China; and OMOM, Chongqing, China), though not all are available in every country.

The ability to visualize the small intestine, the only portion of the gastrointestinal tract previously outside the visual limits of traditional endoscopy, was particularly appealing because capsule endoscopy (CE) can usually be performed without anesthesia or radiation and discomfort of other imaging procedures. Those same benefits, as well as CE's sensitivity, drove a desire to make CE a less invasive, initial diagnostic study and one to monitor the mucosa both in the small intestine and beyond. A slightly larger colon capsule (Medtronic) and a pan-enteric capsule (dubbed the

TABLE 1 | Indications, outcomes, and adverse events in capsule endoscopy procedures on pediatric and adult patients (8).

Indications (%)	Pediatric	Under 8 years of age	Adult
Bleeding and / or anemia	15	36	66
Inflammatory bowel disease	63	24	10
Abdominal pain	10	14	11
Polyps / neoplasms	8	-	3
Other	4	25	10
Positive findings (%)	61	67	59
Adverse events (%)			
Retained capsule	2.6	0.5	1.4
Incomplete procedures	13	7	16
Other	0.9	-	1.1

FIGURE 1 | Polyp in the jejunum.

Crohn's capsule, Medtronic), to evaluate the small and large intestine in the same procedure, are already available in Europe. Additionally, an esophageal device (PillCam ESO2) was developed to evaluate Barrett's esophagus, but has found little use. With scant pediatric data available on the esophageal, colon, and Crohn's capsules, this review focuses on small intestinal CE and the newly emerging use of pan-enteric CE.

INDICATIONS

American and European endoscopic societies have promulgated guidelines on the indications for CE (3–5). While both recommend CE for evaluation of obscure gastrointestinal bleeding and anemia (OGIBA) and suspicion of Crohn's disease (CD), they also suggest doing so after negative gastroscopy and ileocolonoscopy.

Of note, the relative frequency of those indications differs substantially in adults and children, and even within the pediatric population when stratified by age. OGIBA in adults accounts for 66% of the indications for CE, with evaluation of CD accounting for 10%, and 11% of CE performed for clinical symptoms of pain, diarrhea, and /or weight loss (6). According to a pediatric meta-analysis, the evaluation of suspected or known small intestinal CD is the most common pediatric indication for CE in children, accounting for 63% of the total (7). Over half of the procedures for inflammatory bowel disease (IBD) indications, and 44% of the total, relate to suspicion of CD, while 16% of the total CE were to monitor those with known CD (16% of total). The evaluation of abdominal pain, particularly in combination with diarrhea represents another 10% of the procedures (8–28) (**Table 1**).

However, these clinical indications vary with age (25). Among children aged 1.5–7.9 years who underwent CE, OGIB, accounted for 30 (36%) of the 83 patients in the cohort. Suspected CD was the indication for 20 patients (24%) of CEs with 11 (55%) having positive findings; while three patients had CE to monitor their CD. Evaluation of abdominal pain, malabsorption, and protein loss each prompted CE for 12, 12, and nine patients (14, 14, and 11%), respectively; those with suspected CD or recurrent abdominal pain are typically older than those with protein losing enteropathy and / or malabsorption. In contrast, OGIB and CD in older children and teens accounts for only 13–24 and 40–86%, respectively, of the indications in those of 10–18 years of age (29).

Polyposis

Assessment of polyposis syndromes in the SB demonstrates positive findings in 80.2% of CE in children, the highest diagnostic yield of any indication (18, 26). Considered "feasible, safe, and accurate" for the detection of small bowel polyps (**Figure 1**), CE allows for screening and surveillance of Peutz-Jeghers (PJS) and similar syndromes (familial adenomatous polyposis, Gardner's syndrome). While clinical guidelines generally recommend beginning to screen asymptomatic symptoms in those with PJS at 8 years of age, the frequency of repeating the exams every 1–5 years thereafter, and whether to do so with CE and then obtain an MRE or to directly proceed with deep enteroscopy for management are still debated (CE can miss proximal polyps, but CE and MRE are less invasive and together detect large and small polyps with accuracy equal to enteroscopy) (29, 30). Of note, screening the SB in cases of juvenile polyposis has shown no benefit (31).

Inflammatory Bowel Disease

Since pediatric patients with CD will have small bowel (SB) involvement up to 70% of the time, with 40% estimated to have active disease exclusively in the SB, guidelines of European and North American societies suggest full evaluation of the gastrointestinal tract at the approximate time of CD diagnosis in pediatric patients to assess the extent/severity of CD and to clarify a classification of indeterminate colitis (30, 32–34) (**Figures 2–7**).

Repeated studies have shown the superiority of CE to accomplish that task, especially early onset or more proximal SB disease, either alone or following magnetic resonance imaging with oral contrast (MR enterography, MRE), which also can also detect strictures that would be a contraindication for CE (35–40).

A number of studies have now demonstrated the feasibility of sequential CE as a minimally invasive method to evaluate the mucosal response to treatment (41–45). Subsequently, pan-enteric capsule endoscopy (PCE) has been adapted to guide a treat-to-target therapeutic modifications strategy using a modified colon capsule to perform pan-enteric capsule endoscopy (PCE). In a cohort of 48 pediatric patients with CD,

FIGURE 2 | Moderate Crohn's with superficial and deepening ulcers.

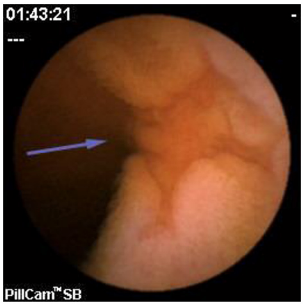

FIGURE 3 | Deep erosion (presumably Crohn's).

FIGURE 4 | Severe Crohn's with ulceration and stenosis.

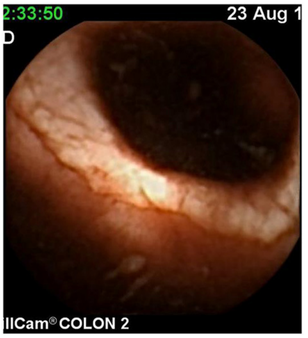

FIGURE 5 | Crohn's small bowel stricture.

FIGURE 6 | UC-like mucosa in jejunum (of a girl with prior colectomy).

FIGURE 7 | Apthous ulcers in the colon.

inflammation was present in 34 (71%) patients at baseline, 22 (46%) patients at 24 weeks, and 18 (39%) patients at 52 weeks ($P < 0.05$) (46). These findings resulted in therapeutic adjustment for 34 (71%) patients at baseline and 11 (23%) patients at 24 weeks based on PCE, while only 2 (4%) patients with PCE-negative results changed therapy based on their imaging studies. The treat-to-target strategy increased mucosal healing (MH) and deep remission (clinical and mucosal normality; DR) from 21% at baseline to 54% at 24 weeks and 58% at 52 weeks ($P < 0.05$ compared to baseline); whereas two patients (4%) did not respond to treatment.

Using an ITT analysis, complete MH at 52 weeks was associated with a decreased relapse rate clinically ($p < 0.003$), reduced steroid use ($p < 0.0005$), less treatment escalation ($p < 0.0003$), and decreased hospitalization ($p < 0.0001$). The decreased need for surgery was not statistically significant ($p = 0.065$). From the initial cohort, PCE was performed on 42 patients at 104 weeks (two developed an ileo-cecal valve stricture at 52 weeks; four were lost to follow-up) (47). MH decreased by 7% compared to their year 1 results.

At each assessment, PCE was compared to the other tested modalities. At 52 weeks, PCE showed DR in 28 (58%), complete MH in 6 (who had partial MH at 24 weeks), and new lesions detected in four subjects. MRE and SICUS had good concordance in evaluating DR (24/28, 86%), but they did not identify the

TABLE 2 | Simple endoscopic score for Crohn's disease (CE-CD) (51).

Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers (0.1–0.5 cm)	Large ulcers (0.5–2 cm)	Very large ulcers (>2 cm)
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	Unaffected segment	<50%	50–75%	>75%
Presence of narrowing (stenosis)	None	Single, can be passed	Multiple, can be passed	Cannot be passed

new lesions in the four patients or mucosal improvements after therapy ($p < 0.05$). C-reactive protein and fecal calprotectin were not able to evaluate DR as well at 24 or 52 weeks (BR in 65 and 69%, respectively). The overall diagnostic yield of PCE, MRE, and biomarkers were 54, 37, and 33%, respectively ($p < 0.05$) (46).

However, to make these advances more effective, a challenge remains: to standardize CE interpretation in order to consistently diagnose and monitor CD findings. Two main CE scores exist for CD: the Lewis score (LS) and the CE Crohn's Disease Activity Index (CECDAI) (47, 48). While the LS is currently the most widespread CE score, the score is largely driven by stenosis and also includes villous edema, which is not considered a major feature of CD and it leads to the risk of errors in the assessment of mucosal healing (MH). Both indices have been used in small pediatric series, but remarkable discrepancies between the two were reported, with CECDAI better reflecting intestinal inflammation than LS (49). A new method, the Capsule Endoscopy - Crohn's Disease (CE-CD) index was devised adapting the Simple Endoscopic Score for Crohn's Disease (SES-CD), which is well-validated and widely used for ileocolonoscopy (50). Similar to SES-CD, CE-CD considers ulcers as elemental lesions of CD and takes into account the number of ulcers, size of the largest ulcer, the affected surface (as a percentage), and the presence or absence of stenosis in both the small and large intestine (**Table 2**). To date, the CE-CD has proven to be simple, reliable, and reproducible in the evaluation of SB inflammation in 312 pediatric patients with CD. This score seems also predictive of disease outcomes over time. The Pediatric Crohn's Disease Activity Index (PCDAI) appears to be correlated reasonably well (CE-CD $\geq$ 9; the area under the curve or AUC: 0.779) with a high specificity (90.1% for PCDAI $\geq$ 15) and low sensitivity (60.5%). Of particular note, 35 out 132 (26.5%) patients in clinical remission (PCDAI $<$ 10) had surprisingly severe endoscopic patterns (CE-CD $>$ 13), suggesting that CE-CD might be a useful pre-clinical predictor of CD exacerbations rather than overestimating disease severity (52).

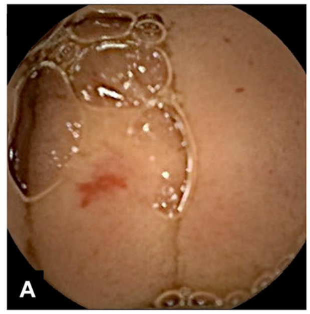

FIGURE 8 | Arteriovenous malformation.

FIGURE 9 | Vascular malformation.

Symptom-Based Evaluation

In children, the diagnostic yield of CE for evaluation of OGIB is estimated to be 42% (7). In a study of 72 patients, positive findings in the assessment of abdominal pain with negative inflammatory markers were apparent in 21%, rising to 67% when inflammatory markers were present (51). However, the range of positive findings includes angioectasia and other vascular lesions (**Figures 8**, **9**), Crohn's disease or other ulcers, gastritis, eosinophilic or other gastroenteropathy, polyps, graft-vs.-host disease, lymphangiectasia (**Figures 10**, **11**), Meckel's diverticuli, scalloping or villous atrophy typical of celiac disease (**Figure 12**), and active bleeding without any source (29). Of note as well, CE has been used to acutely evaluate and re-evaluate graft-vs.-host disease after stem cell transplantation, and other protein-losing enteropathies. However, it also important to recognize that some findings are entirely normal (**Figures 13–15**).

Pan-Enteric Capsule Endoscopy

The development of a slightly larger colon capsule (11.6 × 31.5 mm) with a 12-h battery life, two cameras with wider angles enabling nearly 360°, with a second iteration with higher resolution imaging of greater magnification than the first, and an "adaptive image acquisition rate" depending on the capsule's speed (53) has been able to be adapted and released in Europe, where it is termed a Crohn's capsule (Medtronic) PCE to evaluate both the small and large intestine in a single procedure.

FIGURE 10 | Lymphangiectasia (patchy).

FIGURE 11 | Lymphangiectasia (extensive).

FIGURE 12 | Celiac scalloping distally (with normal EGD).

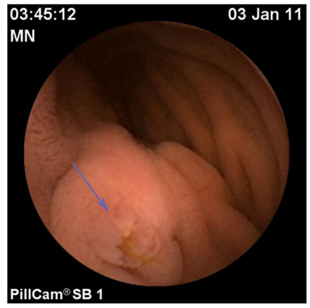

FIGURE 13 | Ampulla of vater.

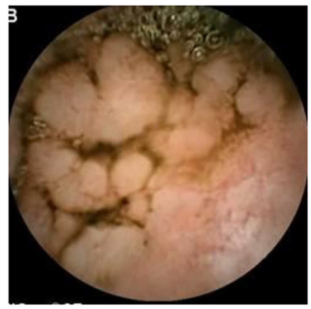

FIGURE 14 | Lymphoid hyperplasia.

While it has a few disadvantages: its larger size (though the same size as the colon capsule); bowel cleansing resembles that for a colonoscopy, with an additional booster dose during the actual procedure; and the procedure and reading times are longer, its utility has been shown in several studies.

The first published study evaluated the adapted devise in 40 pediatric subjects (age 13.1 ± 3.1 years) with known CD who underwent protocolized, comparative procedures in the course of disease re-evaluation. PCE demonstrated 90% sensitivity, 94% specificity in the SB, with PPV and NPV of 95 and 90%, respectively. PCE sensitivity was 89% in detecting colonic inflammation, while specificity was 100%. The positive predictive value (PPV) was 100% and negative predictive value (NPV) was 91% for colonic inflammation compared to MRE (sensitivity 85%, specificity 89%) and small intestine contrast ultrasonography (SICUS) (sensitivity 90%, specificity 83%). There were no serious adverse events related to the PCE procedure or the preparation reported (54).

Subsequently, the commercially available PCE and ileocolonoscopy (IC) were studied in 66 adult subjects with known CD and bowel patency. The diagnostic yield for active CD lesions was 83.3% for PCE and 69.7% for IC [95% confidence interval (CI), 2.6–24.7%]; with both modalities identifying active CD lesions in 65% of subjects. Of the 12 subjects where only PCE showed active CD, five had their lesions in the terminal ileum. Of note, IC, but not PCE, demonstrated active CD in three subjects (55). Two other larger studies of 99 and 93 adult patients subsequently reached similar conclusions, also showing the superiority of PCE over MRE, the latter study finding that C-reactive protein and fecal calprotectin were insensitive in recognizing active CD (0.48 and 0.59, respectively) (56, 57).

OVERCOMING CAPSULE ISSUES

As with any procedure, even a minimally invasive one like CE, some capsule issues continue to present challenges, especially in children (28).

- Swallowing the capsule
- Endoscopic placement
- Capsule retention
- Bowel cleansing

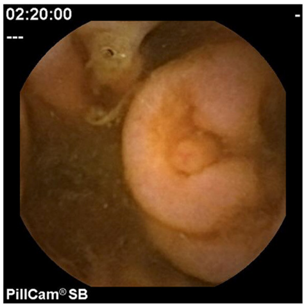

FIGURE 15 | Intussusception.

Swallowing the Capsule/Placement for Those Who Cannot Swallow

Swallowing the capsule may be difficult for some patients at any age (in the same way that some individuals are unable or unwilling to ingest pills). A technique called *stimulus fading* has been used to teach swallowing small, then progressively larger gelatin capsules or candies, with water, other liquids or even a small amount of yogurt, pudding, or apple sauce (58).

For those unable or unwilling to swallow a capsule, those with motility disorders or a tight esophageal sphincter, a capsule can be placed directly into the stomach, or preferably, the duodenum, during an endoscopy. This should be performed under general anesthesia, since capsules have been placed in the trachea when deep sedation was used (18). A front-loading capsule delivery devise (AdvanCE TM, US Endoscopy) can be used for older SB2 capsules. However, the newer SB3 and PCE capsules have cameras at each end, so that launching them with the extruder that pushes them out may mar the lens cover, interfering with interpretation. The alternative, a Roth Net (US Endoscopy), an extrudable fabric basket, has been shown to cause 50% more mucosal trauma, and may be difficult to use to launch a capsule in the small intestine (25).

A pediatric study compared the success rates and the differences in 51 CEs that were swallowed and 53 where it was placed. The median age was 12.8 (range: 1.6–18.5) years. Endoscopic placement was needed for children who were significantly younger (9.8 vs. 14.2 years; $P < 0.001$), lighter (34.5 vs. 54.9 kg; $P < 0.0001$), and had a longer small intestinal transit time (308 vs. 229 min; $P < 0.0001$). Children who ingested the capsule were more likely to have positive findings (50 vs. 30%, $P = 0.017$). Biopsies at the time of the endoscopy resulted in Iatrogenic bleeding and decreased visibility in 30% (16/53) of those who had CE placement, but that was not thought to change the outcome or subsequent patient management (59).

Capsule Retention

Of note, prokinetics have made CE possible for those with esophageal or gastric motility disorders; however, intestinal dysmotility remains a contraindication similar to known stenosis or obstruction of the gastrointestinal tract, which would be most common in those with CD, those who have had intestinal resection, or undergone radiation to the abdomen. Furthermore, clinical signs of obstruction are a contraindication unless the passage of a self-dissolving patency capsule within timed guidelines (discussed below) or radiographic evidence proves that patency or surgery is considered a pre-procedure, as above. The potential for retention can also be discussed as being potentially therapeutic, in that it may identify a stricture. In at least one case, CE was performed specifically to help the surgeon identify the stricture intraoperatively (8).

A meta-analysis of 1,013 pediatric CE procedures documented gastric retention in four and SB retention in 18, a pooled retention rate of 2.3% (95%CI: 1.5–3.4%) (7). Endoscopy removed five capsules, four from the stomach and one from an ileal pouch with 13 surgically retrieved, simultaneously mitigating the cause of the retention. In one case, a bowel cleanout at 22 days post-ingestion evacuated a retained capsule.

Retention rates in children were 1.2% (95%CI: 0.9–1.6%), 2.6% (95%CI: 1.6–3.9%), and 2.1% (95%CI: 0.7–4.3%) for evaluation of occult gastrointestinal bleeding (OGIB), CD, and neoplastic lesions, respectively, with a pooled rate of 1.4% (95%CI: 1.2–1.6%) (8). On a per-procedure basis, this pattern is similar in adults, where capsule retention occurs at rate of 1.4, 2.2, and 1.2% in evaluation of OGIB, CD, and polyps, respectively (6).

The greatest risk factors for capsule retention overall is known IBD (5.2% risk), with that increasing when a previous small bowel follow-through (SBFT) demonstrated small bowel CD (35.7% risk) or if a body mass index below the fifth percentile is combined with known IBD (43% risk). However, retention has occurred despite the absence of strictures on SBFT (17). Among four patients with CD where the capsule passage lasted > 5 days (with three continuing on to retention), age was significant (18.8 ± 0.9 vs. 14.6 ± 3.5), but not height or weight, compared to patients who did not experience retention (17). Thus, it appears that the risk of retention is dependent on the clinical indication, and higher risk in patients with suspected chronic small bowel obstruction (60). No perforations, aspirations, or small bowel obstructions have been reported in children though rare cases have been reported in adults.

In a recent meta-analysis of 35 papers with 4,219 adult and pediatric patients with CD, 3.32% suffered from retention [95% confidence interval (CI), 2.62–4.2%]: this broke down to 4.63% (95% CI, 3.42–6.25%) in established CD and 2.35% (95% CI, 1.31–4.19%) in suspected CD. Retention rates were 3.49% (95% CI, 2.73–4.46%) in adults and 1.64% (95% CI, 0.68–3.89%) in those <18 years of age. Retention risk in established CD was 3.4 times higher than suspected CD in adults, but no difference existed in pediatric retention risk for established CD compared with suspected CD. In established CD, retention decreased if a patency capsule (2.88%; 95% CI, 1.74–4.74%) was used or MR/CT enterography (2.32%; 95% CI, 0.87–6.03%) was performed (61).

The majority of retentions have occurred despite normal SB radiographic studies, while radiologically documented strictures do not preclude functional patency allowing CE performance. A patency capsule (PC), identical in size to the SB capsule with a radiofrequency identity tag, was developed to address these concerns. The currently available version has barium, lactose, and dual timer plugs that gradually dissolve and disintegrate after 30 h.

Both a retrospective (9) and a prospective study (62) have been performed in pediatric IBD undergoing CE after using the first iteration of the PC (which had a 40-h time limit). In the retrospective analysis, CE was performed successfully in all but one of the 19 patients where patency was established. The prospective trial of 10–16-year-olds who ingested the PC found that 15 of 18 excreted an intact PC (mean 34.5 h) without any PC or CE retentions or adverse events (62). CD was eventually diagnosed in all patients having PC transit of more than 40 h and in nine of 12 who passed the patency capsule in 40 h or less. There were no capsule retentions or adverse events. Thus, the PC can serve as a useful guide and may lessen the likelihood of CE retention, particularly in known CD where the risk of retention is greatest.

Other Contraindications

In pregnant women, CE should be restricted to urgent cases where diagnosis cannot be postponed, since safety data are not available. There is still an existing contraindication by manufacturers that those with an implanted cardio-assistive device should not have CE performed, though theoretical and clinical evidence suggest that VCE can be performed safely. Of note, patients undergoing an MRI with a capsule in the abdomen show susceptibility artifacts on their scans but show no evidence of clinical harm (63).

Bowel Cleansing

Because of the inability to flush or suction fluids or gas during CE, adequate bowel cleaning is essential. Debris, bubbles, bile, and blood, particularly in the distal small bowel, limit CE's diagnostic ability (64). Various cleansing regimens have been tested in adults (65, 66). The only pediatric prospective study evaluated 198 patients with five different preparations (67). Of these, polyethylene glycol (PEG) solution, 1.75 g/25 mL per kg (up to 70 g/1,000 mL) the night prior the procedure with 20 mL (376 mg) of oral simethicone given 30 min was the most successful, lessening discomfort and improving visualization significantly in the distal ileum, the portion most often impaired by debris.

A specific score to evaluate cleansing in the SB for CE has recently been developed and validated by 20 readers who independently read 1,233 duplicate images 4 weeks apart. Each image was scored on two parameters: visualized mucosa and the degree of the image obscured by debris, bubbles, and bile. Almost perfect inter-rater and intra-rater reliability was observed for what is to be known as the KODA score and can be used for clinical trials (68).

A similar effort has been occurring for colon capsule cleansing. In that grading scale (CC-CLEAR), the colon is divided into three segments: right, transverse, and left colon. Each is classified by an estimation of the mucosa visualized clearly with the overall cleansing classification a sum of the segment scores, grading between inappropriate and excellent, although an inappropriate classification in any segment renders the entire score as inappropriate. That scale was considered superior to a previously developed score, the Leighton scale, on 58 consecutive colon capsules, with excellent inter and intra observer agreement (69).

The regimen devised for pediatric pan-enteric cleansing is based on what was used for the treat-to-target studies, getting an adequate cleaning level in >80% of cases (46, 47). This regimen primarily uses polyethylene glycol (PEG), includes domperidone, though metoclopramide can be substituted, and sodium phosphate (NaP) as a booster to speed up the capsule during the exam. This scheme was able to obtain completion and excretion rates higher than 95 and 84%, respectively.

CONCLUSION

Over the two decades since its inception, CE has become part of our diagnostic armamentarium, helping us to understand and document both normal and abnormal findings in the small intestine. Newer capsules now create opportunities to expand that understanding and our practices so that we can learn when and how to employ CE and PCE to better monitor and guide therapy. This will take further studies to determine the best uses for CE and how to select the appropriate candidates.

AUTHOR CONTRIBUTIONS

Both authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Endoscopy in Pediatric Eosinophilic Esophagitis

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Endoscopy and mucosal biopsies are essential to the diagnosis of EoE. Together they either confirm or exclude mucosal eosinophilia and provide a visual inspection of the esophagus that may be consistent with EoE or suggest other underlying etiologies. Endoscopy also plays an important therapeutic role in the management of EoE including the assessment of treatment response and treatment of associated complications including esophageal stricture and food impaction. Assessment of treatment response largely depends on endoscopy and mucosal biopsies although less invasive strategies may eventually provide alternative means to assess mucosal inflammation. Herein we will review current use of endoscopy in EoE, including recently developed technologies and their role in the management of EoE.

Keywords: eosinophilic oesophagitis, endoscopy, dilation, pediatric, children, esophagogastroduodenoscopy

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INTRODUCTION

During the last two decades, an emerging body of clinical experiences and research studies have identified eosinophilic esophagitis (EoE) as the most common cause of food impaction and a common cause of dysphagia and esophagitis in children and adults. The incidence of EoE ranges from 5 to 10 cases per 100,000 (1) and it has been reported to occur worldwide (1). Eosinophilic esophagitis is a chronic immune antigen-mediated disease characterized by symptoms of esophageal dysfunction and inflammatory changes in esophageal mucosa including >15 eosinophils per high power field on biopsy (2, 3). Endoscopy and mucosal biopsies are essential to the diagnosis of EoE by either confirming or excluding mucosal eosinophilia and providing a visual inspection of the esophagus that may be consistent with EoE or suggest other underlying etiologies (4, 5). Endoscopy also plays an important therapeutic role in the management of EoE including the assessment of treatment response and treatment of associated complications including esophageal stricture and food impaction. Assessment of treatment response largely depends on endoscopy and mucosal biopsies although less invasive strategies may eventually provide alternative means to assess mucosal inflammation. Herein we will review current use of endoscopy in EoE, including recently developed technologies and their role in the management of EoE.

ROLE OF ENDOSCOPY IN EOSINOPHILIC ESOPHAGITIS

Obtaining Mucosal Biopsies

The gold standard for diagnosis of EoE requires mucosal biopsy for histological assessment to evaluate for its characteristic eosinophil predominant inflammation of the esophageal epithelium (defined by >15 eosinophils per high power field) (2). Visual inspection of the esophagus alone is not sufficient as a reliable marker of tissue involvement in EoE (6). Esophageal biopsies should be obtained from multiple locations along the esophageal length including the distal, mid and/or proximal esophagus. Two previous studies in adults and children have suggested that obtaining a total of six biopsies from at least two sites increases the probability of establishing the diagnosis of EoE to over 95% (7, 8). The normal esophagus is devoid of eosinophils and eosinophil enumeration is most often used to describe the severity of inflammation. However, several other histologic features have been described in eosinophilic esophagitis, including basal cell hyperplasia, dilated intercellular spaces, rete-peg elongation, lamina propria fibrosis, eosinophilic microabscesses and eosinophil layering of the surface epithelium and collectively are used in the EoE Histologic Severity Score (EoEHSS) (9, 10). The EoEHSS is a validated histologic measure for EoE that provides a broad assessment of epithelial inflammation beyond eosinophil density.

Identification of Endoscopic Findings

Several endoscopic findings are associated with EoE including esophageal edema (decreased vascularity or pallor of the esophageal mucosa), esophageal rings (concentric rings or trachealization in the esophagus), white exudate (white spots or plaques), longitudinal furrows, esophageal strictures, narrow caliber esophagus (reduced caliber of the majority of the esophagus), and crepe paper esophagus (mucosal fragility of the esophagus). See **Figure 1**. Studies have identified that more than 90% of patients with EoE will have at least one abnormal endoscopic feature of EoE (4). The Endoscopic Reference Score (EREFS Score) is a numerical scoring system that grades both the presence and severity of endoscopic features including edema, rings, exudate, furrows and stricture (4). The EREFS score provides a standard method of assessing the endoscopic appearance of EoE and can assist in identifying patients as having only inflammatory findings (e.g., white plaques, linear furrows, edema) as compared to fibrotic features (e.g., esophageal rings or stricture) (4). Although not a universal conclusion, studies in both adult and pediatric subjects concluded that the EREFS score accurately identified patients with EoE and can be used as an endoscopic outcome measure of response to treatment (5, 11, 12). Biopsies and histologic inflammation remain the primary marker of disease activity but endoscopic appearance provides a practical adjunct assessment of disease activity at diagnosis and of treatment response.

Visual inspection of the esophagus is also helpful in patients to assess for alternate etiologies of esophageal symptoms (candida esophagitis, herpes esophagitis, or erosive esophagitis).

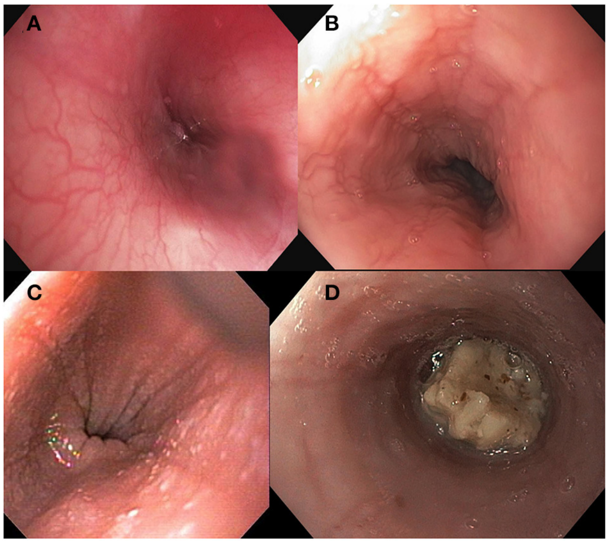

FIGURE 1 | Endoscopic findings in Eosinophilic Esophagitis including **(A)** normal esophageal mucosa **(B)** longitudinal furrows, **(C)** white exudate, and **(D)** food bolus impaction.

Assessment of Treatment Response

Treatment of inflammation is important to improving the natural history of disease, preventing complications including food impaction and esophageal stricture (13, 14). Endoscopy with biopsy remains an essential tool in the assessment of treatment response. It has been recognized that patient reported symptoms do not necessarily correlate well with histology, particularly in those treated or partially treated for EoE. Patient reported symptom assessment tools have been developed for both adult and pediatric population which provide a standard means of assessing symptom severity; however there continues to be only a moderate level of association in symptom and histologic response to treatment (15–17). Therefore, tissue assessment has been and continues to be an important tool to assess treatment response. Most studies to date have evaluated response to treatment by endoscopy at 6–16 weeks after initiation of treatment and this time frame, while broad, generally is accepted practice. Results from ongoing and future studies will help us determine what time frame is optimal.

The downside of assessing histologic response to treatment is the increased need for invasive procedures along with associated patient and health care costs. In addition, there has been increasing attention on repeated use of anesthesia in young children, particularly after the US Food and Drug Administration issued a "Drug and Safety Communication" warning that repeated use of anesthetics may affect development of children's brains (https://www.fda.gov/Drugs/DrugSafety/ucm532356.htm). This has motivated the search for a biomarker of tissue inflammation. However, to date no specific serum, blood, breath, or urine biomarkers has been validated to differentiate between active and inactive esophageal eosinophilia. Less invasive means of esophageal sampling without the need for anesthesia have begun to show promise and are described below.

Therapeutic Endoscopy in EoE

Patients with EoE can have esophageal complications including food impaction and esophageal stricture and endoscopy is an important tool in the management of both.

Food Bolus Impaction

Food bolus impaction is often a presenting symptom of EoE and occurs in 33–55% of children and adults with EoE. When a presenting symptom, obtaining esophageal biopsies is recommended during endoscopy for food impaction removal in order to assist in making a timely diagnosis (18, 19). Gastroenterologists, surgeons and otolaryngologists may all be asked to assist in the removal of esophageal food impaction. When located in the proximal esophagus, rigid endoscopy may be considered but flexible endoscopy is more often utilized. Methods to remove food range from using either single or multiple devices, including snare, net retriever, tripod grasper, rat tooth forceps, biopsy forceps, and suction. Suction using a transparent suction cap secured to the end of the endoscope or bander can be effective and may reduce procedure time compared to other pull removal techniques (20). Often, difficult impactions require the use of multiple tools as they are rarely removed as a single piece. Due to the frequent need for multiple passes of the endoscope to fully remove an impaction, use of an overtube should be considered in children large enough to accommodate them to minimize the potential trauma of repeated esophageal intubation. While gentle pressure to "push" the impaction into the stomach can be considered, extreme caution should be exercised as it often unknown if there may be a more distal stricture and longitudinal tearing of the mucosa or perforation may occur.

Timing of this procedure is urgent if there is drooling or other evidence of complete esophageal obstruction that puts the patient at risk for aspiration. For this reason, as well as the likelihood of repeated passes of the endoscope, use of an endotracheal intubation should be strongly considered. With complete obstruction urgent endoscopy (<8 h) should be performed regardless of *nil per os* (NPO) status. If the patient is able to manage their own secretions, removal of the impacted food bolus should nevertheless be performed within 24 h from the onset of symptoms to avoid tissue necrosis and the risk of perforation during the procedure.

Esophageal Stricture

Focal stricture or long segment narrowing occur in a subset of children and adults with EoE. Stricture severity is typically characterized as mild, moderate, or severe based on the ability to pass either a standard or pediatric sized endoscope. Strictures may occur with or without presence of esophageal rings. Mild strictures can be detected by endoscopy but diffuse or long strictures often require a high index of suspicion and complete esophageal insufflation. Studies in both children and adults demonstrate that narrowing can be missed in up to 55% of patients if endoscopy alone is used as a diagnostic tool, as compared to barium esophagram and endoscopy together (21, 22). If a patient has solid food dysphagia, performance of a barium esophagram, often with a barium pill, can be helpful in assessing for the presence of luminal narrowing (23). More frequently, EoE related strictures are long segment or diffuse making them more amenable to bougie dilation with either Maloney or wire guided Savary dilators rather than balloon dilation. When focal strictures exist, balloon dilation is a reasonable approach and has the benefit of offering direct visualization during dilation as well as directing all of the force radially. A balloon pull-through technique has also been described for adults in the management of EoE narrowing (24). Complications include bleeding and esophageal perforation however, several studies in adults and children including a systemic review have found these complications to be rare and no more frequent than in esophageal dilations for other underlying etiologies (25, 26). Additionally, a meta-analysis comparing dilation method found no evidence to suggest a significant difference in perforation risk related to dilator type (27). Post-operative chest pain; however, is expected in 15–74% of patients and can be preemptively managed by providing anticipatory guidance and symptomatic pain relief if needed with non-narcotic pain medications (25, 26). With the presence of stricture, longitudinal "rents" in the mucosa are often seen with passage of the endoscope even before dedicated dilation is performed. This is expected and should not be necessarily interpreted as a result of undue trauma or an adverse event. Though the "rule of three" standard dilation practice advises against dilation of more than 3 mm within a single session, single center data in pediatric EoE patients has not shown an association with the final dilator size and risk of perforation, with a mean increase of 4.5 mm per dilation (26).

More than half of patients necessitating dilation will require repeat dilation in their symptom management. In adults, repeat dilation was often needed within a year of initial dilation (26, 28). While dilation can improve dysphagia when used in the appropriate patient, it should not be viewed as an alternative to therapies directed at treating inflammation. When inflammation is controlled patients require fewer dilations to achieve a similar improvement in esophageal diameter (29).

EMERGING ENDOSCOPIC AND LESS INVASIVE TOOLS IN EOE

Transnasal Endoscopy

Over the last few years, unsedated transnasal endoscopy (TNE) has been performed successfully in children as an alternative to EGD for surveillance of EoE (30, 31). In an outpatient clinic room, children wear video or virtual reality goggles for distraction and TNE is performed using an ultrathin bronchoscope (with an outer diameter of 2.8–4.2 mm). This allows for direct visualization of the esophagus and esophageal biopsies are obtained (31). Endoscopic features such as white plaques are readily visible and, with adequate insufflation, other features such as linear furrows and edema are possible however how a standardized endoscopic score obtained during TNE compares to one during standard endoscopy has not yet been evaluated. See **Figure 2**. In the largest study in pediatrics, of 300 attempts, 294 TNEs were successfully performed (98% success rate) in 190 children and young adults, with ages ranging from 3 to 22 years (31). The biopsy specimens obtained by TNE were all adequate for assessment of EoE (30, 31). There were no major adverse events and TNE reduced costs by over 50% compared with EGD under anesthesia (31). In addition, qualitative studies

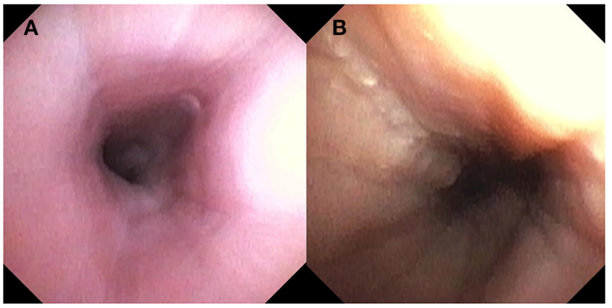

FIGURE 2 | Endoscopic findings with Transnasal Endoscopy including **(A)** normal esophageal mucosa and **(B)** longitudinal furrows and scant white plaques.

show that the overall perception and satisfaction of TNE for parents and patients was positive (30, 32). Unsedated TNE has advantages because it can be performed in an outpatient clinic room and reduces the risk and cost associated with anesthesia. This is particularly relevant to children with EoE, who often require serial endoscopy.

Endoscopic Functional Lumen Imaging Probe

Endoscopic functional lumen imaging probe (FLIP) is a novel endoscopic assessment tool to measure caliber and distensibility of the esophageal lumen. It uses impedance planimetry during volume-controlled distention of the esophagus to provide measurements of pressure and dimensions of the esophagus and gastroesophageal junction (33). Studies in adults and children have shown that esophageal distensibility is decreased in patients with EoE compared to non-EoE controls. Lower distensibility is associated with the occurrence of food impaction and the need for dilation, important patient outcomes in EoE, and distensibility has been shown to improve with treatment (34–37). In children and adolescents, lower distensibility was associated with active inflammation as compared to the distensibility in patients with inactive/treated EoE (36). FLIP is likely to be a useful and practical tool in the assessment of disease severity and disease phenotype assessment.

Less Invasive Methods to Assess Disease Activity

EoE management often requires frequent assessment of histologic changes in response to therapeutic adjustments particularly in the case of dietary management of EoE. TNE obviates the need for anesthesia but still allows for endoscopic and histologic assessment. Less invasive means of sampling the esophageal lumen without endoscopy are being developed and may eventually alter the way in which we assess disease response. Developed sampling methods include the cytosponge and the esophageal string test. The cytosponge consists of an ingestible gelatin capsule containing a compressed mesh sponge attached to a string developed initially for esophageal cancer screening. As the sponge passes back up through the esophagus, a tissue specimen is collected to create a tissue pellet that can then be evaluated for histologic assessment. In an adult study, eosinophil counts highly correlated between the biopsy and cytosponge (38). At the time of this writing, the cytosponge has yet to be studied in children or adolescents. Given the size of the mesh sponge, it may have limited use in pediatrics or in patients with esophageal narrowing.

The esophageal string test (EST) similarly calls for swallowing a gelatin capsule. In the EST, a weighted gelatin capsule containing 90 cm of nylon string is swallowed while one end is taped to the side of the face. The esophageal portion is analyzed for the presence of eotaxin-3 and eosinophil major basic protein-1 and an EoE score resulted. Combined, these two biomarkers strongly associated with eosinophil density and had AUC 0.86 for identifying active EoE (39).

Other technologies, such as mucosal impedance, have been studied in the assessment of mucosal inflammation in EoE. Real-time mucosal impedance measurements correlate with esophageal eosinophilia and treatment improves mucosal impedance (40–42). Mucosal impedance probes are placed at the time of endoscopy. As these and other techniques show promise in the research setting, clinical need will encourage the incorporation of these technologies in devices that do not require sedated endoscopy. The EST or other biomarkers are unlikely to take the place of initial diagnostic endoscopy, however less invasive means of sampling the esophageal lumen may allow for less burdensome longitudinal assessment in the management of this chronic disease; hopefully leading to fewer endoscopies for patients without sacrificing control of inflammation.

CONCLUSION

Endoscopy is essential to the diagnosis and management of EoE including the attainment of mucosal biopsies, visual inspection of the esophagus and, when needed, therapeutic intervention. Newer endoscopic tools such as FLIP allow for measurement of esophageal distensibility and esophageal remodeling that occurs in EoE. This can provide a complementary assessment of the esophagus together with mucosal inflammation and endoscopic appearance. TNE and novel less or non-invasive means of sampling the esophageal mucosa and/or lumen aim to lessen the burden of repeated endoscopy in this population. Ideally these tools will be able to provide practical assessment of disease activity in the longitudinal management of patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

NN, RK, and CM-K contributed to the concept development, writing and review of this manuscript, and provided final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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EUS in Pediatrics: A Multicenter Experience and Review

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Background/Aim: Endoscopic ultrasound (EUS) is a well-established tool used in the evaluation and treatment of a wide range of pathologies in adult medicine. EUS in pediatrics has been shown to be safe and technically effective, and its use continues to evolve. This article aims to describe the EUS experience at our tertiary-care centers with regard to safety, technical success, and its impact in clinical management. We also discuss the current and developing diagnostic and therapeutic uses for EUS in pediatrics such as in pancreaticobiliary disease, congenital anomalies, eosinophilic esophagitis, inflammatory bowel disease, and liver disease.

Methods: This is a retrospective review of EUS performed by two pediatric gastroenterologists trained as endosonographers between April 2017 and November 2020. Patient demographics, procedure indication, procedure characteristics, technical success, and complications were collected. Literature review was performed to describe current and future uses of EUS in pediatrics.

Results: Ninety-eight EUS were performed with 15 (15.3%) including fine needle aspiration/biopsy and 9 (9.2%) cases being therapeutic. Most common indications include choledocholithiasis ($n = 31$, 31.6%), pancreatic fluid collections ($n = 18$, 18.4%), chronic and acute recurrent pancreatitis ($n = 14$, 14.3%), and acute pancreatitis characterization ($n = 13$, 13.3%). Notable indications of pancreatic mass ($n = 6$, 6.1%) and luminal lesions/strictures ($n = 6$, 6.1%) were less common. Complications were limited with one instance of questionable GI bleeding after cystgastrostomy creation. Ninety-eight of 98 (100%) cases were technically successful.

Conclusion/Discussion: EUS has been shown to be performed safely and successfully in the pediatric population by pediatric endosonographers. This study and review support its use in pediatric practice and demonstrate the wide variety of indications for EUS such as pancreatic cystgastrostomy, celiac plexus neurolysis, and evaluation of chronic pancreatitis. This literature review also demonstrates areas of potential development for EUS within the practice of pediatric gastroenterology.

Keywords: endoscopic ultrasonography, pediatric, pediatric gastroenterologists, pancreatitis, pancreatic fluid collection

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INTRODUCTION

Endoscopic ultrasound (EUS) is a procedure that combines the direct intraluminal visualization of endoscopy with a sonographic exam of the GI tract and surrounding organs. This is most often accomplished with an echoendoscope, which has an ultrasound transducer built into the tip of a flexible endoscope. Since its introduction, EUS, followed by its combination with fine-needle aspiration/biopsy (FNA/B), has become a well-established tool in the evaluation and treatment of a wide range of pathologies in adult medicine (1, 2). Although it is used extensively in adult medicine, the use of EUS in pediatrics has been comparatively limited (3–9). Its use in pediatrics has been shown to be safe for patients >15 kg and continues to evolve (10–14). This article aims to describe the safe and successful use of EUS and its role in clinical management at two large academic referral centers. We will also discuss current and developing diagnostic and therapeutic uses for EUS in children.

EUS is performed commonly with two distinct types of echoendoscopes, a radial echoendoscope and curvilinear echoendoscope. The radial echoendoscope is used purely as a diagnostic tool with imaging produced in a 360° view, perpendicular to the scope. The curvilinear scope provides a ∼120°-180° view parallel to the scope and is equipped with a working channel suitable for both diagnostic and interventional maneuvers, such as FNA/B or stent placement. The working channel is positioned so needles and devices can be visualized sonographically. The primary downside to the use of these echoendoscopes in pediatrics is their relatively large size in small children. These echoendoscopes are limited to patients who can accommodate their large-diameter and long transducer tip. Esophageal intubation of a small child with a standard EUS scope carries an increased risk of cervical esophageal perforation. Nevertheless, there are studies reporting successful EUS in children <1 year of age, with echoendoscopes usually safely utilized in children as small as 15 kg (4, 5, 12). In our experience, we have successfully performed therapeutic EUS in children as small as 12 kg.

EUS can also be performed using high-resolution miniprobes placed through standard endoscopes. These have higher frequencies, increasing their resolution but limiting their ability to examine deeper structures. These probes are thus well-suited to examine the mucosa or immediate vasculature of the GI tract but have limited view beyond this level and thus have limited use to evaluate surrounding anatomy such as the pancreas and biliary tract.

EUS has traditionally been most often used to evaluate pancreaticobiliary and GI lumen pathology in adult gastroenterology (3, 4, 6, 8, 9, 11, 15). In pediatrics, this continues to be the main indication for EUS (10). The benefits of using EUS for this pathology include the lack of ionizing radiation, the ability to combine with therapeutic/interventional procedures, and the dynamic and high-resolution images produced. EUS compares favorably to other imaging modalities such as CT and MRI for these reasons. Although its use in pediatrics is increasing, it is limited by patient size and the need for anesthesia. Additionally, there continues to be a dearth of training opportunities for pediatric gastroenterologists to learn this skill and thus a lack of skilled endosonographers still exists in many communities (8). Despite these limitations, our paper aims to discuss the safety, technical success, and clinical impact of EUS performed by pediatric gastroenterologists in our large patient experience, as well as the current and future role for EUS in children.

METHODS

After approval from the Institutional Review Boards of Children's Hospital Los Angeles (CHLA), Los Angeles, CA, USA, and Cedars Sinai Medical Center (CSMC), Los Angeles, CA, USA, we performed a retrospective review to identify all patients ≤18 years of age who underwent EUS and associated interventions between April 2017 and December 2020. The study was exempt from obtaining the consent due to its retrospective and chart review nature. Procedures were performed by one of two pediatric gastroenterology-trained endosonographers (TLP or QYL). EUS examinations were performed using the Olympus radial echoendoscope (GF-UE160), the Olympus curvilinear array echoendoscope (GF-UCT180 or GF-UC140P-AL5), or the Olympus miniprobe system (Olympus America, Inc., Center Valley, PA, USA). FNB was performed using the 22-G or 25-G Boston Acquire needle (Boston Scientific, Marlborough, MA, USA) or the SharkCore FNB Biopsy system (Medtronic, Minneapolis, MN, USA). FNA was performed using the 22-G or 25-G Boston Expect FNA needle (Boston Scientific, Marlborough, MA, USA), or the 19-G, 22-G, or 25-G Cook EchoTip FNA needle (Cook Medical, Indianapolis, IN, USA). Lumen apposing metal stent placement was performed using the AXIOS system (Boston Scientific, Marlborough, MA, USA). Although the majority of the procedures were performed under general anesthesia, some were performed under monitored anesthesia care. The type of anesthesia was deferred to the anesthesiologist, unless the EUS procedure was for pseudocyst drainage and cyst-gastrostomy creation in which general anesthesia was recommended and performed. Decision to perform EUS was made by the performing endosonographer based on the clinical management decision of each patient.

Patient demographics such as age, weight, and sex were collected. Also, procedure indication, procedure characteristics, technical success, and complications were collected. Procedures were defined to be diagnostic if the primary outcome of the procedure was for obtaining information used in diagnosis including the use of FNA/B. The procedure was defined as therapeutic if there was any associated intervention with the goal of treating or managing pathology. This includes cyst drainage, creation of a cystgastrostomy, or stent placement/removal.

We defined diagnostic success as the ability of EUS to sonographically evaluate the anatomy of interest (e.g., the bile duct or pancreas gland) or the ability to obtain diagnostic tissue by FNA/B. Therapeutic success was defined as the successful completion of the therapeutic maneuver as planned (e.g., creation of a cystgastrostomy). The EUS was defined to change management if the procedure directly leads to a treatment course

TABLE 1 | Procedure indications.

Indication category	Indication	Procedures, *n*	% of total procedures
Pancreatic		54	55.1%
	Pancreatic fluid collection	18	18.4%
	Acute pancreatitis	13	13.3%
	Chronic pancreatitis	8	8.2%
	Pancreatic mass	7	7.1%
	Acute recurrent pancreatitis	6	6.1%
	Autoimmune pancreatitis	6	6.1%
	Biliary obstruction of suspected pancreatic origin	3	3.1%
Biliary		34	34.7%
	Choledocholithiasis evaluation	31	31.6%
	Biliary stricture	5	5.1%
Luminal		6	6.1%
	Esophageal	5	5.1%
	Small bowel lesion	1	1.0%
Other		4	4.1%
	Abdominal pain	3	3.1%
	Liver evaluation	1	1.0%

TABLE 2 | Procedural characteristics.

Procedure characteristic	Procedure number, *n*	Percentage of total	Notes
Diagnostic	89	90.80%	
Therapeutic	9	9.20%	All related to cystgastrostomy and management
FNA/FNB performed	15	15.30%	Pancreatic mass−5 Pancreatic fluid collection (PFC)−4 Autoimmune pancreatitis−2 Abdominal pain−1 Liver biopsy−1 Periampullary nodule−1 Chronic pancreatitis−1
Changed management	17	17.3%	Avoid unnecessary ERCP−9 Directly treat, to avoid surgery for PFC−4 Obtain histology to determine management−4
Complications	1	1.0%	Possible GI bleed−1
Procedure successful	98	100.00%	

(e.g., avoidance of ERCP, surgery, or chemotherapy), *via* either therapeutic maneuver or diagnostic information gained from the EUS.

Post procedure complication, as defined per ASGE guidelines, were recorded (16). Data were analyzed using descriptive statistics. Discussion of current practice was based on our findings, and wider/future indications were included to provide a more complete review of EUS in pediatrics.

RESULTS

From April 2017 through December 2020, 98 EUS procedures were performed on a total of 72 children, of which there were 34 males (42 procedures) and 38 females (56 procedures). Eighty-five cases (87%) were performed under general anesthesia with the remaining 13 cases (13%) performed under monitored anesthesia care. Patient age ranged 3–18 years with a mean age of 10.7 ± 4.5 years. Patient weight ranged 11.4–113 kg with a mean 49.9 ± 24.1 kg. Indications for the procedure were divided into pancreatic ($n = 54$, 55.1%), biliary ($n = 34$, 34.7%), luminal ($n = 6$, 6.1%), and other ($n = 4$, 4.1%) (**Table 1**). More specifically, the most common indications for EUS in this series were bile duct evaluation for choledocholithiasis ($n = 31$, 31.6%), pancreatitis ($n = 27$, 27.6%), pancreatic fluid collection (PFC) management ($n = 18$, 18.4%), and suspected pancreatic mass/biliary obstruction ($n = 16$, 16.3%). The majority of the EUS performed was diagnostic in nature ($n = 89$, 90.8%) with a minority ($n = 9$, 9.2%) being therapeutic (**Table 2**). Therapeutic cases represent the creation of cystgastrostomy and subsequent stent and PFC management. Seventeen of 98 procedures (17.3%) directly changed management. Nine cases ruled out the need for ERCP for choledocholithiasis. Four cases treated PFCs with the patient no longer requiring surgical intervention. Four cases made diagnoses that altered the expected clinical management (e.g., need for surgery or chemotherapy).

A complication was observed in one case. This was a suspected GI bleed after EUS with cystgastrostomy placement. It is unclear if this was related to the procedure as the patient had anemia but no overt signs of GI bleeding on repeat endoscopy or cross-sectional imaging. Overall, 98/98 (100%) of cases were deemed successful.

DISCUSSION

This series represents one of the largest studies on pediatric endosonography to date. We demonstrate that EUS is technically feasible and safe in the pediatric population, supporting previous case series. This study reflects the presence of pediatric gastroenterology-trained endosonographers within referral, academic practices, which may influence how EUS is used. In previous literature reviews, there is a variety of balances between diagnostic and therapeutic procedures, possibly reflecting varying accessibilities to an endosonographer for children (10, 11). In 2018, Bizzarri et al. (10) published a review of 19 articles describing a total of 634 EUS procedures in pediatrics. The Bizzarri review reflects differing practice patterns with several series being performed by adult gastroenterologists. Our series represents the highest concentration of patients reported to date (reporting 98 procedures in 3.75 years), reflecting a busy referral population, pediatric-trained endoscopists, and increasing use of EUS in pediatric centers. Compared to the Bizzarri review, our patient population was slightly younger (mean 10.7 vs. 12.7 years), with slightly more pancreaticobiliary indications (89.8 vs. 77.7%). Our series also showed similar use of FNA/B (15.3 vs. 15.5%). Since the Bizzarri review, there have been at least two series published on EUS in pediatrics. These series, despite having slightly different goals, continue to show similar indications and a positive clinical impact (17, 18).

EUS can impact the diagnosis and treatment course of pediatric diseases. Our series demonstrates the ability of EUS to change clinical management with diagnostic information that directly dictates treatment decisions or provide therapeutic interventions that avoid further surgical interventions in 17.3% of cases. This included cases of EUS ± FNA/B guiding treatment for congenital esophageal stricture and pancreatic pathology, EUS to exclude choledocholithiasis for unnecessary ERCP and intraoperative cholangiogram, and therapeutic EUS to manage PFC which avoids the need for external drains or surgical intervention (19).

Limitations of our study include its retrospective nature and lack of long-term follow up. Future goals would be to conduct long-term follow-up on these patients to better evaluate the impact of our series.

As illustrated in this series, EUS in pediatrics currently has the most use in the evaluation and treatment of pancreaticobiliary disorders. In addition, there are several other uses for EUS that have been used in pediatrics. The future of EUS in pediatrics will likely evolve from its current use in adult medicine as well as developing improvements to EUS such as elastography and contrast-enhanced EUS. These current and future uses of EUS in pediatrics warrant discussion here.

Pancreaticobiliary

Use of EUS in pediatric pancreaticobiliary pathology includes the endosonographic evaluation and treatment of pancreatitis and PFC, the evaluation of the biliary tree most often to assess for choledocholithiasis, and the evaluation of pancreatic masses (**Figure 1**) (including autoimmune pancreatitis) which can present with biliary obstruction.

The incidence of pancreatitis in children is increasing (20, 21). EUS for pancreatitis is traditionally used in a diagnostic capacity to evaluate for potential etiologies for idiopathic acute recurrent pancreatitis (ARP) as well as to characterize changes associated with chronic pancreatitis (CP) (12). EUS has been shown to offer increased sensitivity for microlithiasis and gallstones that may explain ARP (22). Cross-sectional, non-invasive imaging has been used to evaluate for late findings of CP parenchymal changes such as pancreatic calcifications and dilated or obstructed pancreatic ducts (23). EUS offers the capacity to demonstrate more subtle changes in pancreatic parenchyma and ductal structures that are often not appreciated on non-invasive cross-sectional imaging or lab work (24–29). In the adult patient population, CP diagnosis with EUS is made by utilizing the Rosemont or conventional criteria which evaluate for changes

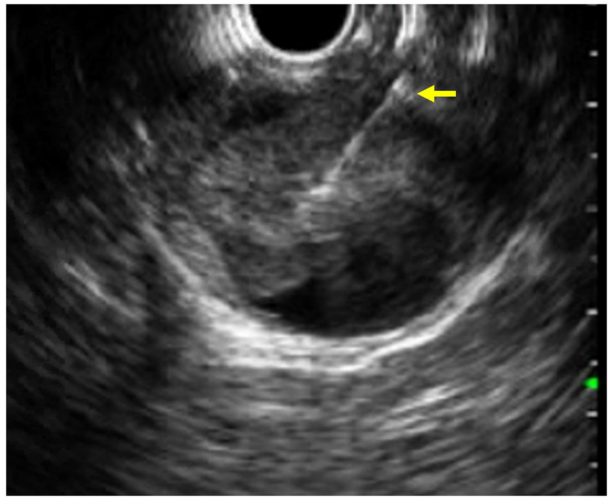

FIGURE 1 | EUS image of a fine needle biopsy (yellow arrow) performed on a solid pseudopapillary tumor of the pancreas.

such as parenchymal lobularity, hyperechoic foci/stranding, and ductal abnormalities (30–36). Although used in pediatrics, these criteria were derived utilizing adult patients, and to date, no validated EUS criteria exist for diagnosing CP in children. It should be noted that though these adult criteria are used in pediatrics, there are known age-related changes in the pancreas that can affect the sonographic appearance and it is well-described that pediatric CP has a much different etiology profile than adult cases (34, 37).

Much of pancreatic therapeutic EUS is for the management of PFC. These PFCs are often secondary to severe acute pancreatitis and categorized according to the revised Atlanta classification of 2012 (38). In cases where a symptomatic PFC has become mature enough, EUS-guided drainage and creation of cystgastrostomy/cystoduodenostomy can be considered (**Figure 2**) (39, 40). This is accomplished by using EUS with FNA to aspirate fluid from the fluid collection for cytology, fluid culture, and amylase levels. Cystgastrostomy and cystoduodenostomy were traditionally created *via* the Seldinger technique to ultimately place plastic stents from the lumen to the cyst. This has mostly been replaced with fully covered metal stents (FCMS), specifically the lumen apposing metal stent system, which places a large-bore, FCMS from the lumen to the cyst. Although commonly used in practice, the use of FCMS in pediatrics has been described but not widely studied (8, 41–44). In these cases, EUS visualization allows for vessel-free paths to be identified and confirmation of fluid characteristics. EUS can also be used therapeutically to perform celiac plexus block where an analgesic and steroid (or sclerosing agent) are injected at the celiac plexus. Unfortunately, this has shown limited benefit in adult patients with chronic pancreatitis and is also not widely studied in pediatrics (45, 46).

Pancreatic masses in children are rare but do occasionally present with signs and symptoms of biliary obstruction and/or

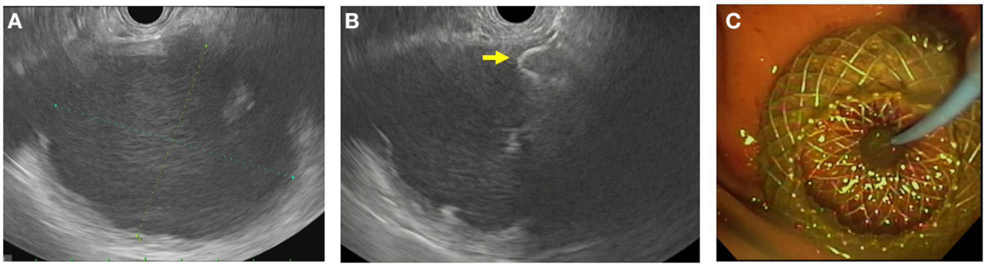

FIGURE 2 | EUS-guided cystgastrostomy. **(A)** EUS image of a pancreatic pseudocyst. **(B)** Luminal apposing metal stent with a flange (yellow arrow) deployed in the pseudocyst. **(C)** Endoscopic image of the cystgastrostomy with the luminal apposing metal stent.

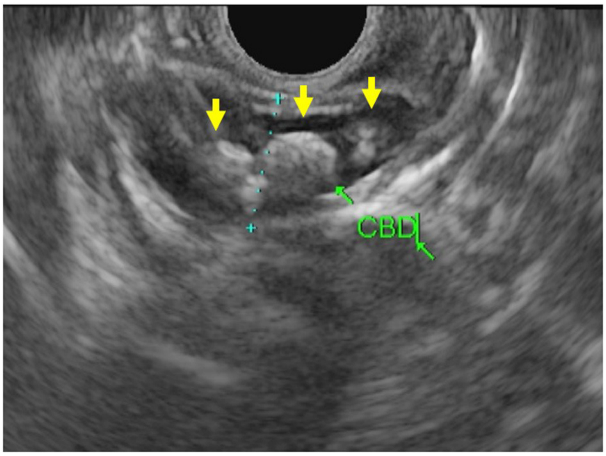

FIGURE 3 | EUS images of the common bile duct with multiple choledocholithiasis (yellow arrows).

vague symptoms such as abdominal pain. Like its use in adults, EUS for pancreatic lesions can evaluate the lesion size, location, and relationship to surrounding structures, which helps stage malignancies. Most importantly, EUS can aid in obtaining a tissue diagnosis using FNA/B. In addition to true pancreatic masses, autoimmune pancreatitis (AIP) can also present as a pancreatic mass (47). Tissue diagnosis is crucial for these patients to determine the correct treatment course and avoid erroneous surgical resection of an AIP lesion.

Biliary Tree/Choledocholithiasis

The biliary tree is visualized well with EUS. For this reason, EUS offers an excellent modality to assess pathology of both the bile duct itself and the surrounding structures such as the liver, pancreatic head, and porta hepatis. As reflected in our series, EUS in pediatrics is commonly used to evaluate the biliary tree for choledocholithiasis (**Figure 3**). EUS can be employed directly before ERCP to avoid performing unnecessary ERCP with its associated risks. In adult patients, there is a well-delineated role for imaging (MRCP or EUS) in cases with intermediate risk by labs, risk factors, and abdominal ultrasound (48). Unfortunately, the adult risk stratification has not been as predictive for children who would benefit from ERCP in these cases (49). In practice, EUS has shown excellent sensitivity and specificity for choledocholithiasis and thus can be valuable in settings with equivocal laboratory or MRCP results (50).

Luminal EUS

EUS is well-suited to examine the gastrointestinal lumen because of the ability to differentiate between the five layers of the gastrointestinal wall: mucosa, muscularis mucosa, submucosa, muscularis propria, and serosa/adventitia. Because of this, it is often used in adults to stage GI malignancy and can be paired with FNA/B to help make tissue diagnosis during staging. In pediatrics, EUS can be used to evaluate luminal masses/lesions, but this is not as common as the adult population (51). EUS in pediatrics also has other uses. EUS can be used to evaluate congenital esophageal stenosis. This congenital malformation has three subtypes, and EUS is useful in determining if balloon dilatation is warranted or if surgical planning is needed (52). Eosinophilic esophagitis has been evaluated with EUS and shown to have significantly thicker portions of the luminal wall in two studies (53, 54). EUS has also been used in a variety of pathologies to evaluate the anorectal area. EUS can evaluate and treat varices, anal sphincter thickness/integrity, and postsurgical anatomy and monitor therapy in perianal IBD (55–59).

Evolving and Future Use

EUS in pediatrics continues to evolve, following the path of EUS in the adult patient population. Similarly in adult patients, endosonographers are performing EUS-guided liver biopsy, varix therapy, and EUS-guided biliary access in children (60). As techniques become more common for adult patients, we can expect these procedures to be used and studied in pediatric patients. Also, on the horizon are contrast-enhanced EUS and EUS elastography, novel techniques that can improve the resolution and utility of the EUS exam (61–64). Contrast-enhanced EUS uses gas-filled microbubbles injected peripherally during the EUS exam. It has been used in adults to help differentiate pancreatic lesions (65, 66). Contrast-enhanced EUS shows information about vascularity and blood flow in a lesion and can be used to reveal or differentiate early necrotic foci and AIP from neoplasms (63). Elastography can be paired with the

EUS to examine relative tissue stiffness and create a color map image. Early use of EUS elastography has been utilized in the evaluation pancreatic lesions and has been studied as a way to identify pancreatic fibrosis and predict risk of exocrine pancreatic insufficiency in CP (61, 62, 64, 67).

CONCLUSION

In summary, this large case series illustrates how EUS is currently utilized in tertiary referral pediatric GI centers. The data highlight the diagnostic role for EUS in both pancreaticobiliary and luminal pathology. EUS can be both interventional and therapeutic and alter clinical management in children. Our series also shows that currently the most common indications for EUS in pediatrics is for pancreaticobiliary indications, and that safety and technical success are comparable with previous reported series. Further larger multicenter prospective studies can continue to elucidate the technical success, safety, and role of EUS in the clinical management of children.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB of Children's Hospital LA and Cedars-Sinai Medical Center. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Bowel Preparation for Pediatric Colonoscopy

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Colonoscopy is an important diagnostic and therapeutic tool in evaluating and treating gastrointestinal tract pathologies. Adequate visualization of the intestinal lumen is necessary for detection of lesions, and thus bowel preparation is a key component of the process. It is estimated that over 25% percent of pediatric patients have sub-optimal bowel preparations, which can lead to longer procedure times, missed pathology, unsuccessful ileal intubation, and possibly repeat procedure/anesthesia. There is no universal protocol for bowel preparation in pediatrics and there is a wide variability of practices around the world. The purpose of this paper is to review the recent published literature regarding bowel preparations for pediatric colonoscopy with focus on published work in the last decade exploring a number of factors involved in bowel preparation including the role of patient education, types of bowel preparation, and their efficacy and safety.

Keywords: preparation, pediatric, laxative, colonoscopy, safety

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INTRODUCTION

Colonoscopy is an important diagnostic and therapeutic tool in evaluating and treating gastrointestinal (GI) tract pathologies. In pediatrics, common indications include abdominal pain, chronic diarrhea, and hematochezia, and a less common indication includes surveillance for polyposis syndromes. Adequate visualization of the intestinal lumen is necessary for detection of lesions, and thus bowel preparation is a key component of the process. It is estimated that over 25 percent of pediatric patients have sub-optimal bowel preparations (1). This can lead to longer procedure times, missed pathology, unsuccessful ileal intubation (2), and possibly repeat procedure/anesthesia.

There is no universal protocol for bowel preparation in pediatrics, and there is wide variability of practices around the world. These variations include differing laxative agents, duration of preparation, timing of administration, and dietary changes. The purpose of this paper is to review the recent published literature regarding bowel preparations for pediatric colonoscopy, with focus on published work in the last decade. Our group previously reviewed the literature leading up to 2010 and highlighted the vast differences in practices up until that point, and emphasized the need for larger, randomized controlled trials to elucidate a preferred protocol (3). For this current paper, we performed a PUBMED search of all English-language articles relating to pediatric colonoscopy preparation from 2010–2020. This search yielded 13 randomized controlled trials, 9 prospective studies, and 6 retrospective studies (**Supplementary Material**). These articles explore a number of factors involved in bowel preparation including the role of patient education, types of bowel preparation, and their efficacy and safety. In addition to this search, we reviewed publications relating to technological advances in colonoscopy preparation in adult patients.

PATIENT EDUCATION

Patient education is an integral part of the bowel preparatory process and lapses of which can impact the quality of the clean out. Identifying institutional risk factors that may lead to poor preparation and gaps in family and patient education should be an area of focus for all hospitals performing pediatric colonoscopy. These risk factors may differ from a center to center. Such risk factors can include poor communication, language barriers, low socio-economic status, and low health literacy. In a retrospective study exploring risk factors for suboptimal bowel preparations, identified risk factors in one center included Spanish-speaking patients and patients with Medicaid insurance coverage (1). In the Spanish-speaking group, one can deduce that the language barrier led to a lapse in patient communication and subsequent understanding of the preparation instructions.

Few pediatric studies have explored improving patient education as means to improving bowel preparation. It is important that patients and their families understand the importance of an adequate clean out and understand the goals of the bowel preparatory process (e.g., to achieve clear stools). A RCT evaluating the impact of an educational cartoon did not show improved Ottawa Bowel Preparation Scale (OBPS) scores in the 20 patients who received the cartoon, but the study did report a positive correlation with education level and quality of bowel preparation (4). A recent study of 42 patients applied the use a Smartphone App to deliver colonoscopy tutorial, instructions, and medication reminders (5). This study showed improved bowel clean out scores in the 20 patients who used the App. Many institutions, including ours, use a multi-pronged approach that employs phone call reminders, emailed instructions, and an animated video to relay instructions to patients and their families. In the current age of technological advances, it will be exciting to see how continued use of such technology can help improve patient education.

BOWEL PREPARATION ASSESSMENT

Reporting adequacy of bowel preparation is an important part of a colonoscopy documentation and allows endoscopists to communicate how well they visualized the bowel. Adequacy of bowel preparation can be assessed by indirect measures such as cecal/terminal intubation rates and procedure duration, but are more accurately assessed by formal scoring systems (6). A number of scales have been developed, with the three most commonly used scales being the Aronchik scale, Ottawa Bowel Preparation Scale, and the Boston Bowel Preparation Scale (BBPS) described in **Table 1**. The Aronchik scale provides a global assessment of bowel preparation and provides a rating of 1–5, with one indicating an excellent prep characterized by small volume liquid stool and 95% visible mucosa. The Aronchik score is assigned prior to any suctioning/cleaning during procedure. Unlike the Aronchik scale, the OBPS and BBPS rate the bowel preparation by colon segment. In the OBPS, each segment (right colon, mid-colon, and rectosigmoid colon) is given a score of 0–4 and the total colon is given a score of 0–2, with a summative score of 0–14. A score of 0 indicates an excellent prep. This score is also assigned prior to any suctioning. The Aronchik scale and BBPS do not specify what score equates an "adequate" clean out. Lastly, the BBPS provides an assessment of each colonic segment with a score of 0–3, with a summative score of 9. A score of 9 indicates an excellent prep, but a score of ≥ 6 indicates an adequate prep. Unlike the Aronchik scale and OBPS, the BBPS accounts for suctioning and washing. These scoring systems are not validated in pediatrics, but Tutar et al. showed that there is a close correlation ($r = -0.954$) between the OBPS and BBPS scores in a study of 123 pediatric patients (7).

The above scoring systems are prone to interpersonal variability, and thus a study in 2020 introduced the use of artificial intelligence (AI) in assessing bowel preparation with a program called ENDOANGEL (8). This AI software was "trained" by reviewing thousands of pre-scored colonoscopy images, using the BBPS. ENDOANGEL provides an assessment of the BBPS during the colonoscope withdrawal phase at an interval of every 30 s. This software was shown to achieve higher accuracy in assessing BPPS as compared to senior endoscopists (8). While this technology is still novel, it provides a promising new objective tool in the assessment of bowel preparation.

TYPES OF BOWEL PREPARATION

Historically, bowel preparation consisted of whole gut irrigation and lavage, which often resulted in fluid shifts, electrolyte changes, and overall patient discomfort and dissatisfaction. In recent decades, multiple laxative agents have been adapted for use in colonoscopy bowel preparation. Laxatives are categorized by their mechanism of action—osmotic laxatives or stimulant laxatives, but some can have combined effects. Osmotic laxatives are hyperosmolar solutions that typically require large volumes of fluid intake to be effective. Examples include polyethylene glycol (PEG), magnesium-based solutions, and sodium-based preparations. Stimulant laxatives such as sennasoids and bisacodyl are generally more palatable but may cause increased cramping and gastrointestinal discomfort. In this review, we will focus on the most commonly used agents—PEG, senna, and sodium picosulfate preparations (**Table 2**).

Polyethylene Glycol

Polyethylene glycol (PEG) is one of the most commonly used agents for bowel preparation in both adults and children worldwide. It is a synthetic water-soluble polymer which functions by drawing water into the gut and softening the stool. PEG exists in multiple formulations—with primary distinction being PEG with and without electrolytes. PEG may also have additives such as ascorbic acid and bisacodyl.

PEG with electrolytes (PEG-ELS) is a salty unpalatable solution that often requires administration via nasogastric tube in children (9). PEG-ELS is given in large volumes with doses up to 25 mL/kg/hr, with a maximum volume of 4 liters. PEG-ELS has been shown to be efficacious and safe and is widely used around the world. Studies have shown an adequate bowel cleansing rate of 88.4% (10). Oral intake of PEG-ELS has been falling out of favor in pediatrics due to difficulty of administration and taste. In a small study of 35 patients receiving PEG-ELS, up to 77.1% of

TABLE 1 | Bowel preparation assessment scales.

	Aronchik	Ottawa	Boston
Bowel Prep	Provides global assessment of bowel prep	Provides prep assessment by bowel segment	Provides prep assessment by bowel segment
Scoring	1 to 5 (1 = excellent prep)	0 to 14 (0 = excellent prep), 4 points assigned to each segment and 2 points assigned as a total score	0 to 3 (9 = excellent prep)
"Adequate" Prep Score	N/A	N/A	≥ 6
Accounts for Suctioning and Washing	No	No	Yes
Advantages	Easy to apply because it is a global assessment; global assessment may be more applicable in pediatrics where adenoma detection rate (ADR) is not as crucial	Provides assessment by bowel segment	Only scale to provide a defined score for "adequate" assessment. It is a comprehensive scale which provides assessment by bowel segment and accounts for suctioning and washing
Limitations	Does not account for suctioning and washing, does not define a cutoff score for adequate clean-out	Does not account for suctioning and washing, does not define a cutoff score for adequate clean-out, not as easy to apply as Aronchik	Not as easy to apply as Aronchik

patients rated the taste as "very bad" and 57.1% of patients rated the bowel preparation as "very difficult" (11). Similar results were shown in other studies (9, 10, 12). Newer PEG-ELS preparations now contain ascorbic acid; this is more palatable and has a higher osmotic effect, allowing for half the required volume. A pilot retrospective study showed this to be an effective regimen in pediatrics, though these patients also received a dose of sodium picosulfate (13).

PEG 3350 without electrolytes (e.g., Miralax®, Bayer Healthcare, Whippany, NJ), originally used for management of constipation and fecal impaction, is now the most commonly used bowel preparation. It has become increasingly popular as it comes in a tasteless powder form that can be dissolved in clear liquid or sports beverage. Similar to PEG-ELS, PEG without electrolytes also requires large volume of fluid intake. Thus, many protocols call for combination regimens with a stimulant such as senna or bisacodyl with lower volumes of liquid. Earlier regimens of PEG 3,350 without electrolytes called for protocols as long as 4 days, but shorter regimens of 1–2 days have been shown to be effective and tolerable (14–17). Phatak et al. showed that 92–93% of 111 pediatric patients receiving 2 days of PEG with bisacodyl achieved "good" or "excellent" bowel preparation (18). A large two-part retrospective and prospective study of 656 patients on 1 day of oral PEG-3350 monotherapy reported adequate clean out (defined as thin or thick liquids) in 79.5 and 15.8% of cases, respectively (19). While the safety of PEG without electrolytes has been questioned, two studies reviewing electrolytes pre and post PEG-3350 did not show clinically significant changes in potassium or bicarbonate (17, 20). However, Sahn et al. did report a risk of hypoglycemia in patients younger than 7 years old (20). Thus, it is our practice to obtain glucose serum levels for all patients immediately prior to undergoing colonoscopy.

A meta-analysis of randomized controlled trials (RCT) in adult cohorts showed that Miralax® and Gatorade® (PepsiCo, Chicago, IL) is inferior to PEG-ELS (21). While head-to-head data in pediatrics is limited, a study comparing PEG-ELS and PEG without electrolytes + bisacodyl showed similar efficacy in both groups (88.4 vs. 87.8% respectively) and importantly showed increased acceptability and tolerability in the latter group (10, 11). Nausea and vomiting are common adverse effects associated with both PEG-ELS and PEG without electrolytes, but these side effects can be ameliorated with anti-emetics. A RCT of 308 adult patients receiving PEG for bowel preparation found that D2 receptor antagonists (domperidone and sulpiride) were associated with less abdominal discomfort. Similar studies are needed in pediatrics cohorts, especially in the context of increasing use of PEG without electrolytes (22).

Sodium-Based Preparations

Sodium-based preparations are lower-volume osmotic laxative, introduced as gentler alternatives to PEG preparations. Earlier formulations with sodium phosphate were shown to be associated with hyperphosphatemia and higher risk of nephrotoxicity (acute kidney injury and chronic tubular injury). In fact, the Food and Drug Administration (FDA) has recommended avoidance of oral sodium phosphate in patients younger than 18 years and has issued a black box warning (23). Additionally, sodium phosphate was shown to distort colonic mucosa and cause aphthoid lesions, and is thus contraindicated in patients undergoing colonoscopy for IBD evaluation (24).

Subsequent sodium formulations such as sodium sulfate and sodium picosulfate have shown to be safe alternatives to sodium phosphate, and lower-volume, equally efficacious alternatives to PEG (10–12, 25, 26). Sodium picosulfate can be administered alone but is also given as a combination medication with magnesium oxide and citric acid. A randomized controlled trial (RCT) of 72 pediatric patients comparing PEG-ELS (25 mg/kg/h) with sodium picosulfate (100 g ×2 doses) showed no difference in bowel preparation between the two groups, but did show sodium picosulfate to be more tolerable in terms of taste and ease of administration (11). Eighty percent (28/35) of patients receiving sodium picosulfate regimen rated the taste as "good" or "very good" as opposed to none in the PEG group (11). Differences in tolerability are not as drastic when comparing sodium picosulfate

TABLE 2 | Commonly used bowel preparations.

Laxative	Sample brand names	Mechanism	Route of administration and dose	Advantages	Limitations
Polyethylene glycol (PEG)	Gialax, GaviLAX, GlycoLax, HealthyLax, MiraLax, PEGyLAX	• Osmotic laxative • Synthetic water-soluble polymer which draws water into the gut and softens the stool	• Comes in powder formulation that is mixed with a sports drink or other form of clear liquid • Dose is 4 g/kg with maximum of 238 g	• Palatable and well-accepted in children • Easily be administered at home	• Requires large volume of fluid • Associated with hypoglycemia in children <7 years of age
Polyethylene with electrolytes (PEG-ELS)	Colyte, GaviLyte, GoLYTELY, NuLYTELY, TriLyte	• Osmotic laxative • Synthetic water-soluble polymer which draws water into the gut and softens the stool	• Can be given by mouth but typically administered via nasogastric tube • Dose is 50–60 ml/kg with maximum of 4 L	• Safe and effective	• Requires large volume of fluid • Not palatable and often requires NG for administration
Polyethylene with electrolytes with ascorbic acid	MoviPrep, Plenvu	• Osmotic laxative • The added ascorbic acid increases the osmolarity of the formulation	• Available in powder and mixed with 50 m/kg of fluid with maximum of 2L • Can be given by mouth or administered via nasogastric tube	• Has higher osmotic effect compared to PEG-ELS, so requires less volume than PEG-ELS	• Limited data in children
Polyethylene with electrolytes with bisacodyl	GaviLyte-H and Bisacodyl	• Osmotic and stimulant properties • Bisacodyl stimulates the parasympathetic nervous system in the colon	• PO • Comes in 2L bottle of Gavilyte with one 5 mg Bisacodyl delayed-release tablet	• Requires less volume than standard PEG-ELS or PEG	• Not palatable
Sodium picosulfate/magnesium oxide/citric acid (SMPC)	Clenpiq, CitraFleet, PicoLax, Picoprep	• Combination medicine with stimulant and laxative properties • Sodium picosulfate is a prodrug that is metabolized into gut bacteria and causes peristalsis • Magnesium citrate and citric acid are osmotic agents	• Comes in 100 g powder sachets and ready-to-drink formulations. The powder is designed to be mixed in 150–250 ml of fluid. Most regimens call for 2 doses.	• Lowest volume preparation available • Palatable	• Not approved for children younger than 9 years old in many countries
Sodium sulfate/potassium sulfate/magnesium sulfate	Suprep	• Osmotic laxative • Sulfate salts are poorly absorbed and draw water into the gut	• Package comes in 2 liquid bottles, each of which is diluted in 360 mL	• Lower volume than PEG preparations	• Not approved in children younger than 12 years old
Senna	Sennakot, ExLax, Lax Pills	• Stimulant laxative • It is an anthraquinone plant derivative which increases colonic transit	• Comes in oral liquid, pills, or chewable tablets • Dose is 3 mg/kg/d in 2 divided doses, with maximum dose of 150 mg/d. • If used in conjunction with PEG, dose is typically 26.4 mg (15 ml) for children ages 6–12 or 52.8 mg (30 ml) for children > 12 years	• Easy to administer	• Not effective in bowel cleansing as monotherapy • Can cause cramping and abdominal pain

to PEG without electrolytes but were still statistically significant. A trial comparing three regimens: (1) PEG-ELS, (2) PEG without electrolytes, and (3) sodium picosulfate + magnesium oxide + citric acid (SMPC) showed the highest acceptability in the SMPC group, followed by PEG without electrolytes (10). Bowel preparation was equally efficacious in all three groups. A large RCT of 288 patients in Italy compared three different PEG regimens (PEG-ELS, PEG with citrate and bisacodyl, and PEG with ascorbic acid) with SMPC and recapitulated similar findings (26). Successful bowel preparation, defined as BBPS $\geq$ 6, was similar in all 4 groups (83.3–91.7%,) with no statistical difference. As in prior studies, the rate of children willing to repeat the same preparation was significantly higher in the SMPC group. Side effects including nausea, bloating, and abdominal pain were also significantly lower in the SMPC group. Lastly, it is important to note that this study included safety outcomes and found no significant differences in electrolyte levels (pre and post procedure) between all four groups.

Senna/Sennosides

Senna is anthraquinone plant derivative which acts as a stimulating laxative when orally ingested. It is not systemically absorbed and it is degraded into its active metabolite in the lower GI tract which subsequently increases colonic transit (27). Like other stimulant laxatives, side effects include abdominal cramping and nausea. Senna is typically used in combination with an osmotic laxative in bowel preparation, as studies have not shown it to be consistently efficacious as monotherapy. Our group conducted a RCT comparing 2 days of senna with oral PEG-3350 and showed that senna was far inferior, with only 29% of patients achieving adequate bowel clean out as opposed to 88% in the PEG group (28). This study was prematurely stopped as the senna regimen was insufficient for bowel preparation. Conversely, a recent RCT showed similar efficacy between pediatric patients receiving senna for 3 days and PEG3350 with bisacodyl (7). However, patients who received the Senna were less satisfied with the process and less willing to repeat the preparation (7). The Senna group was restricted to a full liquid diet for 2 days followed by 1 day of clear liquid diet (CLD), whereas the PEG group was only restricted to 1 day of CLD. Most recently, a study in India evaluated a combination product of senna and probiotic (Bacillus coagulans)(M Sip Lax® straws, Inzpera Healthsciences Ltd, Mumbai, India) with rectal enema and found that 93% (28/30) patients achieved an adequate bowel clean out, defined as BBPS of 3 in each segment (29). This group postulated that the probiotic provided a synergetic effect with the senna by promoting water absorption into the colon.

Other Stimulants

Other stimulant laxatives such as bisacodyl are often used as adjunctive agents to osmotic laxatives for bowel preparation. Bisacodyl works by stimulating the enteric neurons to generate peristalsis. Similarly, non-pharmacologic approaches such as gum chewing have been postulated to have similar effects on the parasympathetic pathway by stimulating the vagal nerve and subsequently promoting GI tract motility. There is limited data on gum chewing, although a RCT of 300 patients did not show any differences in bowel cleansing between the group who was instructed to chew gum vs. the control group (30). However, gum chewing improved patient satisfaction.

TIMING/ADMINISTRATION OF BOWEL PREPARATION

In addition to choosing an appropriate laxative agent, it is important to consider how timing and administration of such medications can impact bowel preparation. With respect to PEG 3350, it has been observed that consumption of bowel preparation over a shorter period of time is associated with a better bowel cleanout (17). In a prospective study of 45 patients receiving PEG3350 with Gatorade, patients who had "excellent" or "good" bowel preparations consumed the prescribed regimen in a shorter period of time, whereas the patient who had a "poor" preparation required 8.5 h to ingest the solution (17). This finding was not statistically significant but raises an interesting question regarding rapid administration of an osmotic laxative.

Split-dose PEG regimens, which have become a standard in many adult institutions, should also be taken into consideration. Under this regimen, half the prescribed volume of bowel preparation is given the evening prior to colonoscopy and the second half is given on the morning of the procedure. Split-dose PEG regimens have been shown to be more effective than single-dose regimens in adults (31, 32). This finding is attributed to the decreased duration between laxative and procedure time, and is attributed to improved compliance (32). Until very recently, split-dose regimens have not been attempted in pediatric patients, as there are limitations with NPO times and implementing split-dose regimens in the early morning. A trial of 179 pediatric patients comparing split-dose PEG with a single-dose PEG showed the split-dose to be more tolerable and more effective (33). The patients in the split-dose group received the first dose between 6:00–8:00 PM in the evening prior to colonoscopy and then at 6:00–8:00 AM in the morning of the procedure. Colonoscopy was scheduled in the afternoon. Surprisingly, patients reported less sleep disturbance with split-dose regimen. A second RCT of 45 pediatric patients also showed superior efficacy, acceptability, and decreased side effects in the split-dose group (34).

DIETARY CHANGES DURING BOWEL PREPARATION

Most pediatric bowel preparations recommend a clear liquid diet on the day prior to procedure. However, many groups are questioning the necessity of implementing a clear liquid diet, as opposed to a low residue/fiber diet. A low residue diet is more flexible and allows for consumption of dairy products, meats, pasta, and some breads. Multiple meta-analyses in adult cohorts have shown that the adequacy of bowel preparation is similar between patients on clear liquid diet and those on a low residue diet (35, 36). Based on this evidence, the European Society of Gastrointestinal Endoscopy (ESGE) 2019 guidelines strongly recommended the use of a low residue diet for bowel preparation (37). Though pediatric data on this subject is limited, a recent randomized controlled trial of 184 patients in Poland found no significant difference in BBPS between patients on a clear liquid diet and patients on low residue diet on the day prior to procedure. Both groups of patients received PEG-ELS (38). Further studies are needed to evaluate whether a low residue diet is appropriate with regimens other than PEG-ELS. This is especially important in pediatrics, where dietary restrictions are likely to cause greater disturbance in daily life and may lead to reduced compliance with the overall bowel regimen.

BOWEL CLEANSING DEVICES

In addition to optimizing oral preparations, there have been new efforts to develop bowel cleansing devices that can be used intra-procedurally or prior to procedure. The FDA recently cleared the Pure-Vu® system (Motus GI Holdings, Fort Lauderdale, FL) for use of bowel cleansing in poorly prepped colons. The Pure-Vu® system is a disposable sleeve that is attached to the colonoscope and uses a vortex mixture of water and air to break up fecal matter. Like a standard flush pump, the endoscopist uses a foot pedal to activate the device. Three recent studies have shown that the Pure-Vu system is successful in improving bowel preparation quality (39–41). Patients in these studies only received Bisacodyl prior to the procedure. It is important to note that these pilot studies excluded patients with inflammatory bowel disease, which is one of the more common indications for colonoscopy in children. Further studies are needed to assess safety of this device in patients with active inflammation.

Unlike the intra-procedural Pure-Vu system, the HyGIeaCare® (Lifestream Purification Systems, LLC) is a novel system designed to assist in bowel preparation prior to colonoscopy. Patients who undergo this preparation are seated in private sanitized basin and then have a disposable nozzle introduced in the rectum. This nozzle infuses a steady stream of warm water to help break up the stool. This process is intended to take less than an hour and eliminates the need for multiple bathroom trips. While this is less disruptive than traditional oral cleanout, we question whether children would be able to tolerate the process.

SUMMARY

An ideal bowel preparation is one that is efficacious, safe, palatable, and minimally disruptive to a patient's daily life. While no current bowel regimen meets all such criteria, there are multiple safe and efficacious one-day regimens in use. In the last decade, PEG without electrolytes has become increasingly popular in the United States; and more recently sodium picosulfate formulations have begun to gain traction around the world. The data suggests that both regimens are equally efficacious, but sodium picosulfate is more accepted and tolerable to patients. Larger randomized controlled trials are needed to compare efficacy and safety of these two preparations.

The wide variation in bowel cleansing regimens serves as an advantage to our patients and allows for an individualized approach based on a child's specific needs and abilities. PEG-ELS is an ideal option for patients with a nasogastric or gastrostomy tube at baseline, as the feeding tube eliminates the discomfort related to the large volume and poor palatability with PEG-ELS. Sodium picosulfate preparations are a good option for children who have trouble tolerating large volumes of fluid. PEG without electrolytes is a good option for children who are willing to drink larger volumes of liquid that is flavored with their beverage of choice. While most institutions implement a standard bowel cleansing protocol, practices may shift to involve a more patient-centered approach.

Other factors of bowel preparation such as split-dosing regimens, dietary restrictions, and use of technology in patient education remain an area that should be further explored in pediatrics. Exploring the role of a low residue diet may be especially impactful in pediatric patients as this will make the bowel cleansing process more tolerable.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.705624/full#supplementary-material

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Initial Esophageal Anastomosis Diameter Predicts Treatment Outcomes in Esophageal Atresia Patients With a High Risk for Stricture Development

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Background and Aims: Children with esophageal atresia (EA) who undergo surgical repair are at risk for anastomotic stricture, which may need multiple dilations or surgical resection if the stricture proves refractory to endoscopic therapy. To date, no studies have assessed the predictive value of anastomotic diameter on long-term treatment outcomes. Our aim was to evaluate the relationship between anastomotic diameter in the early postoperative period and need for frequent dilations and stricture resection within 1 year of surgical repair.

Methods: A retrospective chart review was performed of patients who had EA repair or stricture resection (SR). Medical records were reviewed to evaluate the diameter of the anastomosis at the first endoscopy after surgery, number and timing of dilations needed to treat the anastomotic stricture, and need for stricture resection. A generalized estimating equations (GEE) modeling with a logit link and binomial family was done to analyze the relationship between initial endoscopic anastomosis diameter and the outcome of needing a stricture resection. Median regression was implemented to estimate the association between number of dilations needed based on initial diameter.

Results: A total of 121 patients (56 females) with a history of EA (64% long-gap EA) were identified who either underwent Foker repair at 46% or stricture resection with end-to-end esophageal anastomosis at 54%. The first endoscopy occurred a median of 22 days after surgery. Among all cases, a narrower anastomoses were more likely to need stricture resection with an OR of 12.9 (95% CI, 3.52, 47; $p < 0.001$) in patients with an initial diameter of <3 mm. The number of dilations that patients underwent also decreased as anastomotic diameter increased. This observation showed a significant difference when comparing all diameter categories when looking at all surgeries taken as a whole ($p < 0.008$).

Conclusion: Initial anastomotic diameter as assessed *via* endoscopy performed after high-risk EA repair predicts which patients will require more esophageal dilations as well as the likelihood for stricture resection. This data may serve to stratify patients into different endoscopic treatment plans.

Keywords: endoscopy, esophageal atresia, anastomotic strictures, pediatrics gastroenterology, esophagus, esophageal diameter, esophageal dilatation, esophageal balloon

BACKGROUND

Children who undergo surgical repair of esophageal atresia (EA) are at risk for anastomotic stricture (AS) following surgical repair. Esophageal AS is one of the most common postoperative complications and occurs anywhere from 9 to 80% of EA patients (1–4). Esophageal AS can be treated with serial endoscopic dilation and adjunct therapies including steroid injections, incisional therapy, and stenting. However, treatment may require numerous dilations and may ultimately require surgical resection if the stricture proves refractory to therapy. Several risk factors have been reported for the development of an AS, including anastomotic leak, long-gap EA (LGEA), high-tension anastomosis, ischemic tissue ends, gastroesophageal reflux, and gestational age (5). To date, no evidence-based guidelines exist regarding screening children postoperatively for esophageal stricture. The recommended approach is endoscopy after a child exhibits symptoms of food and swallowing difficulties or failure to advance to a solid diet, at the appropriate age, after surgery (6). Also, there are no studies that have examined the relationship between anastomotic diameter assessed at time of initial postoperative endoscopy and treatment outcomes. This study examines the hypothesis that an anastomosis' initial diameter, when evaluated by endoscopy can predict the likelihood of requiring multiple AS dilations or require a stricture resection, in patients with risk factors for developing an AS.

METHODS

An institutional review board approved single-center retrospective chart review of patients with diagnosis of EA who underwent esophageal surgery and follow-up at our Esophageal and Airway Center between January 2016 and December 2019 was performed. Clinical data from patient charts particularly endoscopy/surgical and fluoroscopy reports were collected. Recorded patient information included type of EA, sex, gestational age, age at time of surgery, diagnosis of trisomy 21 and VACTERL association, number of days out from the surgery at the time of first endoscopy, initial anastomosis diameter, number of dilations in the first year after surgery, and stricture resection. LGEA was defined as any EA where the size of the gap length precluded the ability to complete a primary, one-stage surgical repair regardless of presence or absence of an associated tracheoesophageal fistula (TEF) (7–9).

It is our practice at the center that patients who have uncomplicated surgeries, non-LGEA with low anastomotic tension, and no leak or evidence of stricture on esophagram will be monitored for stricture based on clinical symptoms with repeat esophagram at ∼6 months of age. Patients who do not meet these criteria are considered more high risk for AS and have endoscopy performed 3–4 weeks postrepair. If a stricture is identified, dilation is performed, and a series of additional planned endoscopies with possible dilation would be scheduled as needed (8). The development of AS after the Foker procedure and after stricture resection has been previously described (5, 9–11). High-risk AS patients in this study were divided into two groups, LGEA patients who underwent a Foker procedure, for tension-induced esophageal growth (12) and patients who had undergone a surgical stricture resection (SR) for a known AS refractory to endoscopic treatment. All patients in the SR group underwent a complete resection of their prior AS with the creation of a new end-to-end esophageal anastomosis. Patients who had a Heineke-Mikulicz stricturoplasty or other type of stricturoplasty were excluded.

The initial diameter of the esophagus was determined by contrast esophagram, performed during the first endoscopy following EA/stricture repair, with a radiopaque ruler placed under the patient (**Figure 1**). The anastomotic diameter was measured using the fluoroscopic image with the greatest anastomotic diameter; the radiopaque ruler and known endoscope diameter were used as size references. Additionally, the known width of open and closed biopsy forceps and known scope diameter were used to determine the diameter of the anastomosis in cases with poor contrast distention (**Figure 2**). All procedures were done by two experienced endoscopists that use similar techniques. The endoscopes used were either the Olympus XP190N or Olympus GIF 190 series. In each patient group, the AS diameter measurements were divided into the following subgroups for comparison: 0 to <3, 3 to <6, 6 to <9, and ≥ 9 mm. Patients were followed up for 1 year after surgical repair or until resolution of stricture seen on follow-up endoscopy or esophagram.

Statistical Analysis

Demographics and patient characteristics were presented as median and interquartile range for continuous data and frequency and percentage for categorical data. The analysis of the relationship between anastomosis diameter at first endoscopy and the outcome of needing SR for refractory AS was performed using generalized estimating equations (GEE) modeling with a logit link and binomial family in order to account for multiple observations within the same patient. A two-tailed alpha level <0.05 was used to determine statistical significance, except for the analyses comparing between initial anastomosis diameter categories where a Bonferroni-adjusted $p < 0.008$ (0.05/6) was used to determine statistical significance to control for the risk of false-positive results (type I error) due to multiple group comparisons. All modeling results are presented using odds ratios (OR) with 95% confidence intervals (CI) and p-values. Stata

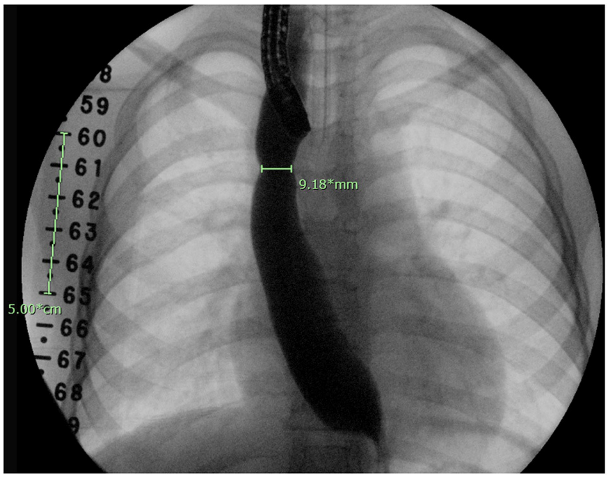

FIGURE 1 | Esophagram done at time of endoscopy. A fluoroscopic ruler is seen on the right side of the patient as a reference for calibration.

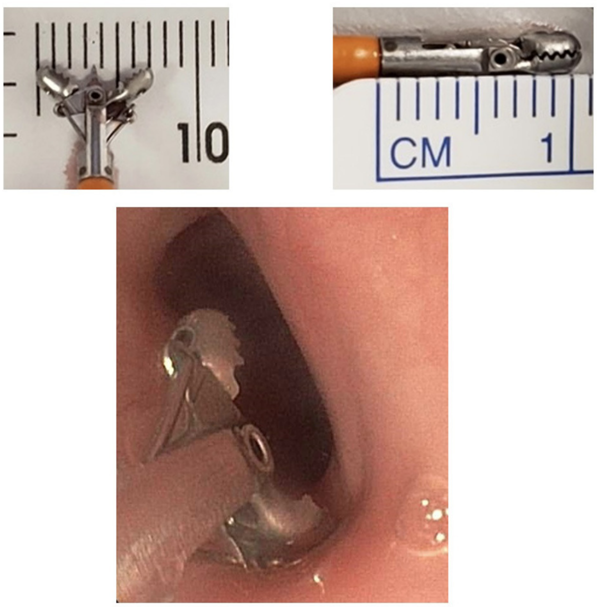

FIGURE 2 | Reference measurement of the biopsy forceps open and closed.

(version 15.0, StataCorp LLC., College Station, TX, USA) was used to perform all statistical analyses.

Median regression was implemented to estimate the association between number of dilations needed and initial diameter, with results shown as coefficients with 95% confidence intervals and *p*-values.

RESULTS

Demographics and Patients' Characteristics

We identified 121 patients with a history of EA who underwent a total of 141 surgeries (56 (46%) females, median age of 7 months (IQR, 4–14) at the time of surgical EA repair). There were 10 patients (8%) with Trisomy 21 and 25 (21%) with VACTERL association. From total surgeries, there were 65 (46%) Foker procedures for LGEA repair and 76 (54%) SR with end-to-end esophageal anastomosis. The first endoscopy occurred at a median of 22 days (IQR, 21–28) after surgery. Patients were noted to have three esophageal dilations (IQR, 2, 6) within 1 year following surgical repair (see **Table 1** for reference).

TABLE 1 | Demographic information.

Demographic data	
Patients	121
Female	56 (46%)
Gestational age (median weeks, IQR)	36 (33,38)
Age at surgery (median months, IQR)	7 (4, 14)
Trisomy 21	10 (8%)
VACTERL	25 (21%)
Diagnosis	
Long-gap esophageal atresia	78
Non-long-gap esophageal atresia	43
Endoscopy	
First endoscopy, postoperative day (median, IQR)	22 (21, 28)
Number of dilations 1 year from surgery (median, IQR)	3 (2, 6)
Surgical repair	141
Foker procedure (%)	65 (46%)
Stricture resection (%)	76 (54%)

Data are presented as n (%) or median (interquartile range).

Anastomotic Initial Endoscopic Diameter and Need for SR in All Surgeries

Looking at all surgeries combined ($N = 141$), 23 (16%) patients underwent a SR. A SR was more likely to occur in patients with a narrower initial diameter. The OR of requiring a SR was 12.9 (95% CI, 3.52, 47; $p < 0.001$) in patients with an initial diameter of <3 mm. When patients had a wider anastomosis diameter, 3 to <6 mm, the OR for requiring a SR decreased to 3.07 (95% CI, 0.97, 9.76; $p = 0.056$). Lastly, 25 cases had an initial diameter ≥9 mm, in which none underwent a SR (see **Table 2** for reference).

Anastomotic Initial Endoscopic Diameter and Need for SR Stratified by Type of Surgery

Sixty-five patients had undergone Foker repair for LGEA, and 14 (22%) underwent a stricture resection. When analyzing the diameter at initial endoscopy stratified by type of surgery, we noted a similar statistical pattern seen in the unstratified surgical group. The OR of requiring SR was 24 (95% CI, 2.41, 238.9; $p = 0.007$) in patients with a diameter of <3 mm. The OR decreased to 9.88 (95% CI, 1.11, 87.9; $p = 0.04$) when the diameter was wider measuring 3 to <6 mm. Four patients had an anastomotic diameter ≥9 mm, which did not require a SR (see **Table 2** for reference).

TABLE 2 | Analysis of need for stricture resection by anastomosis diameter at initial postoperative endoscopy among all cases and stratified by type of surgery.

All surgeries (N = 141)					
Anastomosis diameter at first endoscopy	**Needed stricture resection (N = 23)**	**Did not need stricture resection (N = 118)**	**Odds ratio**	**95% CI**	***p*-value**
0 to <3 mm (N = 16), n (row %)	9 (56%)	7 (44%)	12.9	(3.52, 47.0)	**<0.001***
3 to <6 mm (N = 34), n (row %)	8 (24%)	26 (76%)	3.07	(0.97, 9.76)	0.056
6 to <9 mm (N = 66), n (row %)	6 (9%)	60 (91%)	Reference		
≥9 mm (N = 25), n (row %)	0 (0%)	25 (100%)	Omitted—no patients with stricture resection.		
Foker (N = 65)					
Anastomosis diameter at first endoscopy	**Needed stricture resection (N = 14)**	**Did not need stricture resection (N = 51)**	**Odds ratio**	**95% CI**	***p*-value**
0 to <3 mm (N = 12), n (row %)	6 (50%)	6 (50%)	24	(2.41, 238.9)	**0.007***
3 to <6 mm (N = 24), n (row %)	7 (29%)	17 (71%)	9.88	(1.11, 87.9)	**0.04***
6 to <9 mm (N = 25), n (row %)	1 (4%)	24 (96%)	Reference		
≥9 mm (N = 4), n (row %)	0 (0%)	4 (100%)	Omitted—no patients with stricture resection.		
Stricture resection (N = 76)					
Anastomosis diameter at first endoscopy	**Needed stricture resection (N = 9)**	**Did not need stricture resection (N = 67)**	**Odds ratio**	**95% CI**	***p*-value**
0 to <3 mm (N = 4), n (row %)	3 (75%)	1 (25%)	21.6	(1.87, 250.0)	**0.014***
3 to <6 mm (N = 10), n (row %)	1 (10%)	9 (90%)	0.8	(0.08, 7.73)	0.847
6 to <9 mm (N = 41), n (row %)	5 (12%)	36 (88%)	Reference		
≥9 mm (N = 21), n (row %)	0 (0%)	21 (100%)	Omitted—no patients with stricture resection.		

Odds ratios (OR), 95% confidence intervals, and p-values are derived from regression analysis. CI, confidence interval.
**Statistically significant. Astrix under the table defines the bolded values.*

Similarly, in the stricture resection group, patients (N = 76) with an initial diameter <3 mm on endoscopy had a 21.6 increased likelihood of another stricture resection (95% CI, 1.87, 250; p = 0.014). By comparison, no patients N = 21 with anastomosis ≥9 mm had another stricture. One patient (10%) required a stricture diameter with an anastomosis diameter of 3 to <6 mm (OR, 0.8; 95% CI, 0.08, 7.73; p = 0.847) resection (see **Table 2** for reference).

Anastomotic Initial Endoscopic Diameter and Need for Esophageal Dilation in the First Year

The number of esophageal dilations that patients underwent decreased significantly as the initial anastomosis diameter increased in size seen on the first endoscopy following surgical repair. This observation showed a significant difference when comparing all diameter categories when looking at all surgeries taken as a whole (p < 0.008) (see **Figure 3A**). This was also illustrated in the median regression analysis. An increase in the initial diameter by 1 mm had coefficient of −0.67 dilations [95% CI, −0.85, −0.48; p < 0.001 (see **Figure 4A**)].

When stratifying surgeries, the Foker repair group reached statistically significant differences in the number of dilations when the initial diameter of 6 to <9 mm is compared with the initial diameters of <3 and 3–6 mm (p < 0.008) (see **Figure 3B**). A gain by 1 mm in initial diameter had a coefficient of −1 dilations (95% CI, −1.41, −0.59; p < 0.001) in the median regression analysis (see **Figure 4B**). However, the stricture resection group showed a statistically significant decrease in number of dilations between all initial diameter ranges when compared with an initial diameter ≥9 mm (p = 0.008) (see **Figure 3C**). Here, an increase by 1 mm in diameter had a coefficient of −0.5 dilations (95% CI, −0.78, −0.22; p < 0.001) (see **Figure 4C**).

DISCUSSION

This is the first study to look at anastomosis diameter, measured on initial endoscopic assessment after surgery in EA patients, as

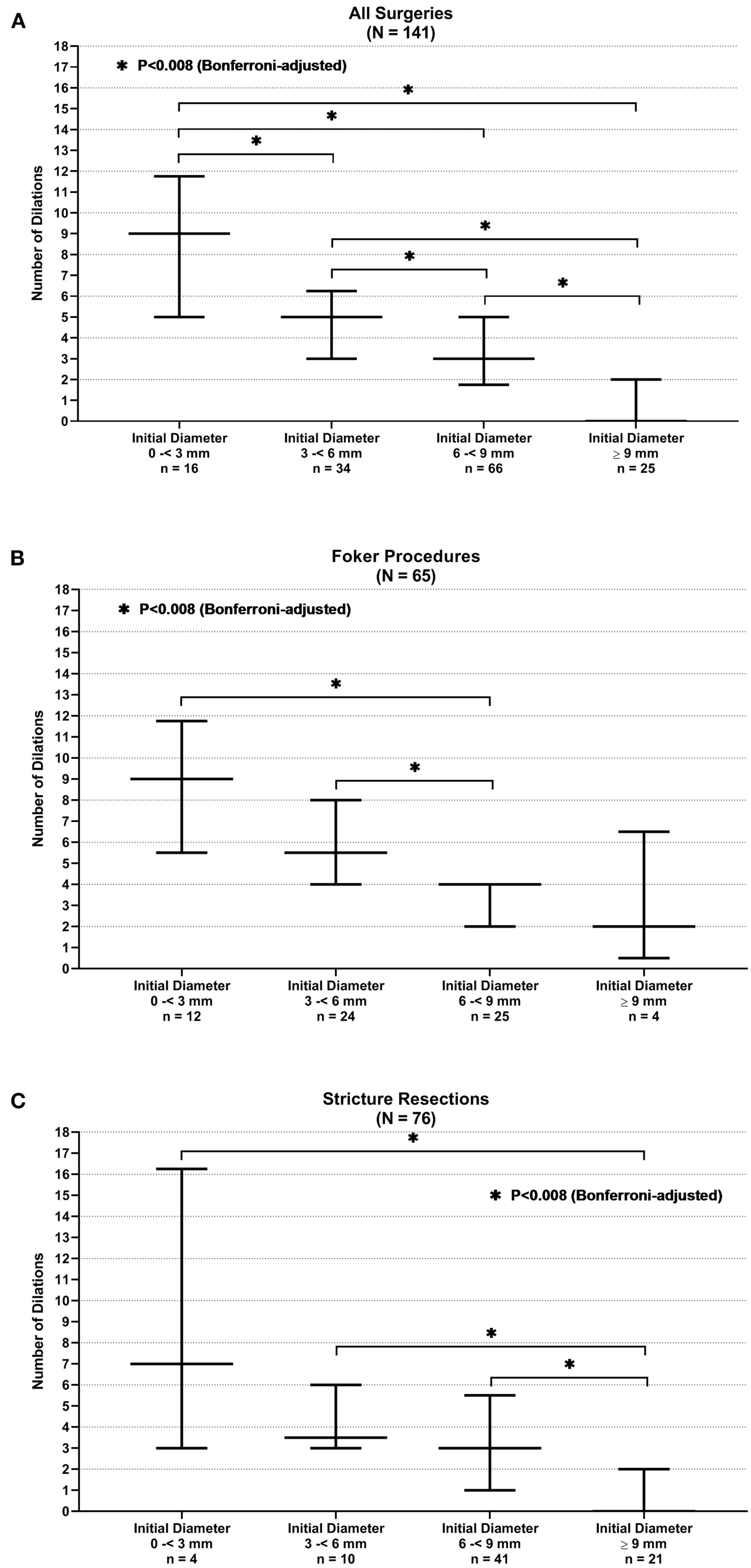

FIGURE 3 | Anastomotic initial endoscopic diameter and need for stricture resection. **(A)** All surgeries. **(B)** Foker procedure. **(C)** Stricture resection.

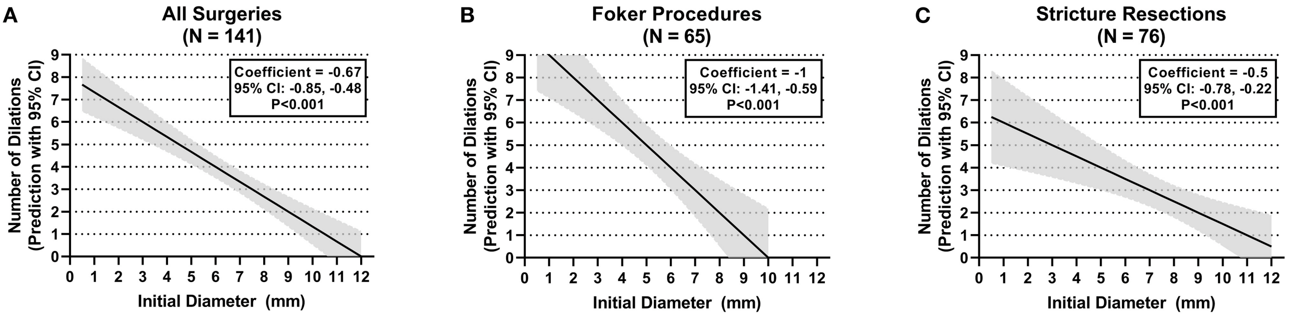

FIGURE 4 | Anastomotic initial endoscopic diameter and need for dilations. **(A)** All surgeries. **(B)** Foker procedure. **(C)** Stricture resection.

a predictor of future need for stricture resection and stricture dilations. In this study, the LGEA cohort of patients who has undergone a Foker procedure had the greatest need for stricture resection (22%) compared with patients in the stricture resection cohort (12%). In both cohorts of patients undergoing Foker procedure and in the stricture resection, there was a >20-fold increased likelihood of requiring a stricture resection if the initial diameter was ≤3 mm. This study also found an inverse relationship between the initial endoscopic anastomosis diameter and the number of dilations performed within 1-year postsurgical repair. Overall, the number of dilations significantly decreased as the initial diameter was wider.

The utility of risk stratification based on initial diameter may allow the provider to tailor a dilation schedule appropriate for each patient. In addition, it allows the provider to offer more information to patients and their families regarding the possible need for multiple dilations and the likelihood of a stricture resection in the future. This approach can be particularly useful for patients who are at high risk of developing an esophageal stricture. The authors acknowledge that this differs from the common approach of waiting for a patient to become symptomatic. Our study was not designed to evaluate the preferred approach to dilations in all EA patients; however, our data confirms that high-risk populations like those with LGEA or history of prior stricture resection are more likely to have anastomotic strictures that require multiple dilations. Therefore, a more proactive approach with early endoscopy may be considered in these populations. Clinically, esophageal stricture may cause vomiting, choking, dysphagia, and food impaction which may lead to oral aversion, which is one of the main causes of nutritional problems and is difficult to treat (13–15). It is a particular problem in children with EA; one study of 75 patients with EA found that 36% had a history of malnutrition and 54% were not taking age- or developmentally appropriate textures (14). The authors speculate that early effective detection and treatment of a stricture could help minimize feeding difficulties and oral aversion from developing.

Prior to this study, most attempts to predict outcomes of esophageal strictures utilized esophagram. Several studies have looked at esophageal measurements in different locations in order to create various stricture indexes to determine need for dilation in EA patients after surgery. These esophagrams were performed in the early postoperative period (5–10 days) (10, 16, 17). Only one of these found any statistical correlation between stricture indexes and any outcome (10); Landisch et al., in their 2017 study evaluating the efficacy of various stricture indexes in 45 EA patients, also evaluated this score and did not find it was significantly associated with need for dilation. The Landisch study did find esophagram measurements to be helpful when done farther out than the usual 5–10 days after surgery (18). These studies did not use the measurements to predict likelihood of stricture resection or assess median number of dilations based on the esophagram measurements. The Landisch study also suggests, as does our study, that the timing of the exam a month out from surgery may be what is the critical factor. Additionally, our results show that measurement of the anastomosis diameter alone without the need of a stricture index formula was useful to evaluate an anastomosis for increased risk of needing treatment.

Limitations of this study include the fact that it is a retrospective single-center experience with a large population of high-risk EA anastomoses. Our cohort was homogenous, including only pediatric EA patients, so our results may not be applicable to adults or to patients with strictures from other etiologies. We also acknowledge that determining the need for stricture resection is somewhat subjective with institutional bias. Prospective multicenter studies are needed to limit institutional bias. Furthermore, measurements of initial diameters are somewhat subjective, although the scopes that we use are of diameters similar to our groupings. In addition, we use fluoroscopy to confirm the diameter as an additional measure of accuracy, although this may not be available in all practice settings. We also feel having only two endoscopists who are making these estimations in a high-volume practice limits variability.

CONCLUSION

This study finds that the initial endoscopic measurement of an esophageal anastomosis diameter is predictive for need of future stricture resection as well as the number of dilations that may be required to treat the anastomotic stricture. Postoperative endoscopic evaluations could serve to stratify patients into high- and low-risk groups, which allows for more tailored treatment plans and may help to better manage patient family expectations for likely course and outcome of treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board at Boston children's hospital. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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frontiers in Pediatrics

ORIGINAL RESEARCH
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Use of Hypnosis in Paediatric Gastrointestinal Endoscopy: A Pilot Study

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Objectives: Experience of hypnosis in gastrointestinal (GI) endoscopy is scarce in children. Our aims were to assess the rate of successful GI endoscopy performed using hypnosis alone or in combination with midazolam, with or without additional equimolar mixture of oxygen and nitrous oxide (EMONO), and to identify predictive factors of successful endoscopy in children.

Methods: This prospective single-centre study included children older than 6 years requiring a diagnostic esophagogastroduodenoscopy (EGD) or rectosigmoidoscopy. Ericksonian hypnosis was performed alone or in combination with midazolam, with or without additional EMONO. Successful endoscopy was defined by a complete and well-tolerated procedure. Levels of satisfaction of the endoscopist, nurse, and patient were assessed.

Results: One hundred forty children [70 boys, median age: 12 years (Q1–Q3: 9–14)] were included over a 14-month period. They underwent EGD in 51.4% ($n = 72$) and rectosigmoidoscopy in 48.6% ($n = 68$) of cases. EMONO and midazolam were combined with hypnosis in 136 cases (97.1%). Successful endoscopy rate reached 82.9%. The procedure was interrupted due to poor tolerance and was rescheduled under general anaesthesia in 11 patients (7.9%). Predictive factors for successful endoscopy were older age (13 vs. 8 years, OR: 1.34, CI 95% [1.10–1.62], $p = 0.003$) and type of endoscopy (EGD vs. rectosigmoidoscopy, OR: 16.34 [2.14–124.68], $p = 0.007$). A good cooperation of the patient was reported by the endoscopist and the nurse in 88.4 and 86.9% of cases, respectively. Ninety-two per cent of patients mentioned that the procedure went well.

Conclusions: Our study suggests that hypnosis combined with EMONO and/or midazolam is of additional value to perform diagnostic EGD or rectosigmoidoscopy in children older than 6 years without systematic need for general anaesthesia.

Keywords: hypnosis, endoscopy, children, EMONO, midazolam

INTRODUCTION

Pain triggered by gastrointestinal (GI) endoscopy is, such as any pain, multidimensional and encompasses sensorial and emotional fields. Anxiety is an emotion close to painful experience, as it can increase the perception of pain. This situation commonly observed among children has been also seen in adult studies where scores of anxiety and pain often have a positive correlation (1, 2).

Hypnosis deals with a natural state of modified conscience involving focused attention and reduced peripheral awareness, allowing an enhanced ability to respond to suggestions (3). In clinical practice, hypnosis guided by a trained practitioner aims to change pain and anxiety perception of the patient using his/her mental resources, in order to improve comfort. Even if the practice of hypnosis in daily care is still rare, it has been considered as a valuable alternative in various clinical situations (4). Many studies have shown its efficacy in the management of pain but also anxiety among children (5, 6). In 2005, Calipel et al. demonstrated the efficacy of hypnosis on anxiety as premedication before surgery, comparing hypnosis and oral midazolam in a randomised controlled trial (RCT) involving 50 children from 2 to 11 years of age (5). Children who were under hypnosis were significantly less anxious than those who received midazolam and had significantly less behaviour disorders on days 1 and 7 after surgery. In 2009, another RCT showed the benefits of hypnosis combined with a local anaesthetic (EMLA®) compared with distraction combined with the same anaesthetic on venepuncture-induced pain in 45 children affected with cancer (6). Patients from the former group displayed less anticipatory anxiety and less behavioural distress during the intervention. A Cochrane meta-analysis published in 2018 by Birnie et al. reviewed the efficacy of distraction and hypnosis to reduce needle-related pain and distress among children and adolescents (7). Among the eight included RCT dealing with hypnosis, five studies including 176 participants showed a statistically significant effect of hypnosis on self-reported pain. Because of pain and anxiety, GI endoscopy under conscious sedation is usually not well-tolerated. While complications during GI endoscopies under general anaesthesia are generally scarce, especially in children, they are known to occur more frequently in the presence of patient risk factors, such as anxiety (8, 9). In adults, several studies pointed out the efficiency of hypnosis in the reduction of pain and anxiety during invasive procedures including GI endoscopy (10–12). The effectiveness of hypnosis compared with intravenous sedation in esophagogastroduodenoscopy (EGD) is still a matter of debate in adults (13, 14). To our knowledge, no paediatric study reported the use of hypnosis during GI endoscopy.

We conducted a prospective pilot study with the primary objective to assess the rate of successful GI endoscopy performed using hypnosis alone or in combination with midazolam, with or without equimolar mixture of oxygen and nitrous oxide (EMONO) in children. The secondary objectives were to identify predictive factors of successful GI endoscopy and to evaluate the level of satisfaction of children, nurses, and endoscopists with regard to the procedure.

METHODS

Patients

We conducted a prospective, monocentric pilot study over a 14-month period. All patients aged between 6 and 18 years for whom a GI endoscopy was scheduled at the Lille University Jeanne de Flandre Children's Hospital were considered for inclusion. For patients who underwent several GI endoscopies during the study period, only the first GI endoscopy procedure performed was selected for analysis. Exclusion criteria included age below 6 years, deafness without hearing aids, and/or cognitive disorders, corresponding to situations when hypnosis could not be fully understood. Cases of emergency procedure and cases when patients and/or their parent/guardian were not willing to participate were also excluded.

Endoscopic Procedure Under Hypnosis

Endoscopic procedures included diagnostic EGD and rectosigmoidoscopy. EGD associated with ileocolonoscopy and interventional EGD were systematically performed under general anaesthesia for patient's comfort and safety and therefore were not considered in the present study. GI endoscopy procedures were performed by seven experienced senior paediatric gastroenterologists, with a mean of 20 procedures per endoscopist during the study. Flexible video-endoscopes from PENTAX® or OLYMPUS® were used according to the patient's weight. The three nurses from the paediatric endoscopy unit were qualified to perform hypnosis (national certificate in hypnoanalgesia and distraction). Hypnosis was administered before the procedure by one nurse according to an Ericksonian approach. The Ericksonian approach relies on the child's imagination to allow him/her to escape and change the perception of the procedure. The Ericksonian approach uses verbal and non-verbal indirect suggestions, adapted on the child's reaction, to induce behavioural change (15). A hypnosis session started with the induction of the hypnotic condition by capturing the patient's attention and saturating his/her mind with sensory suggestions. The success of the hypnotic induction was assessed by the nurse who evaluated the state of deepening in which the patient kept the ability to answer to simple orders. Then, the patient underwent a dissociation of his/her real perception, before returning to ordinary sensoriality at the end of the procedure. The patient could choose to have GI endoscopy either with hypnosis alone (a) or with sublingual midazolam (b). Once installed on the examination table, he could choose to have additionally EMONO (c) or not (d). The dosage of midazolam depended on the patient's body weight, with a maximum of 10 mg (0.35 mg/kg for body weights <30 kg and 0.15 mg/kg for body weights >30 kg).

Successful endoscopy was defined as a complete procedure (i.e., not stopped before the end and when all planned biopsies were done), which was judged well tolerated by the patient. The procedure was assessed as complete or not by the endoscopist, and its tolerance was evaluated by the patient using one closed question ("do you think this procedure went well?").

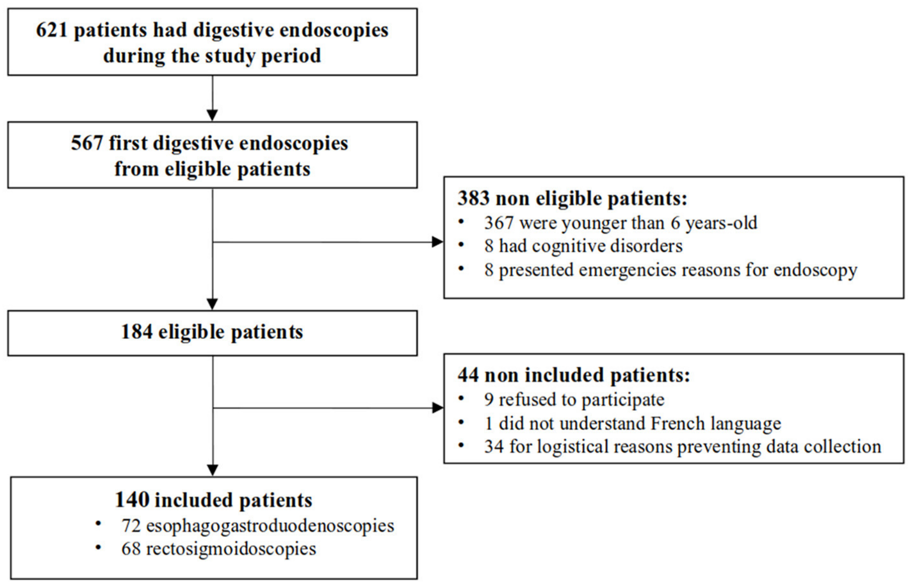

FIGURE 1 | Study flow-chart.

Data Collection

The following data were prospectively collected using a standardised questionnaire specifically designed for the study: age; gender; past history of GI endoscopy; indication for the present GI endoscopy; type of procedure (EGD or rectosigmoidoscopy); presence of at least one parent during the exam; time spent in the waiting room; time between arrival in the endoscopy room and beginning of hypnosis; level of patient's anxiety before the procedure ("not at all", "a little", "a lot", and "very much"); time spent in the endoscopy room; the use of midazolam and/or EMONO; duration of endoscopy and hypnosis; proportion of procedures requiring conversion to general anaesthesia; level of satisfaction of the patient, the nurse, and the endoscopist about the procedure ("good" or "bad"); patient's cooperation and pain caused by the endoscopy according to the patient using a Visual Analogue Scale; procedure performance; and proportion of biopsies performed when compared with the number of initially planned biopsies.

Statistical Analysis

Quantitative variables were described by mean values and standard deviations or median and interquartile range. Gaussian distribution of continuous variables was tested by the Shapiro–Wilk test. Qualitative variables were described by frequencies and percentages. Quantitative variables were compared by Student's t-test, and Wilcoxon non-parametric test was used in case of non-normality of the data. Categorical variables were compared by chi-square test or Fisher's exact test if $n < 5$. Factors associated with successful endoscopy in univariate analysis with a p-value < 0.1 were included in a multivariate model. SAS software version 9.4® (Cary, NC, USA) was used for the analyses. A p-value < 0.05 was considered significant.

Ethics

The research work was conducted in accordance with protocols, good clinical practice, and the relevant laws and regulations in France and did not need institutional review board (IRB) approval. Several days prior to the procedure, a preliminary information was given by phone to the family. At the day of the exam, an information letter and a written consent form were given to the patient, and his/her parents and/or guardian. In case of opposition, data were not collected or were immediately removed from the database. The study had an agreement from the Commission Nationale de l'Informatique et des Libertés (CNIL-French Data Protection Authority).

RESULTS

Study Population

One hundred eighty-four patients older than 6 years requiring a diagnostic EGD and rectosigmoidoscopy were considered for inclusion, which corresponded to 29.6% of the 621 patients who underwent GI endoscopy during the study period. Of these, 44 patients met exclusion criteria: nine refused to participate, one did not understand French, and data of 34 could not be collected. A total of 140 patients were included (**Figure 1**). One patient had both EGD and rectosigmoidoscopy during the same procedure. Compared with non-included patients, EGD was more frequently performed than rectosigmoidoscopy in included patients (51.4 vs. 22.7%, $p < 0.001$), mostly following an indication of abdominal pain (35.0 vs. 13.6%, $p = 0.012$) or gastroesophageal reflux/vomiting (25.7 vs. 6.8%, $p = 0.0059$). Conversely, rectosigmoidoscopy was less performed among included patients who were suspected of inflammatory bowel disease or had chronic diarrhoea (29.1 vs. 56.8%, $p < 0.001$) (**Table 1**).

TABLE 1 | Demographic characteristics and indications for gastrointestinal endoscopy in included and excluded patients.

	Eligible and included patients ($n = 140$)	Eligible and excluded patients ($n = 44$)	*p*-value
Male, *n* (%)	70 (50.0)	18 (40.9)	0.29
Median age (Q1–Q3)	12 (9.0–14.0)	12 (8.0–14.0)	0.36
Used sedation for past* GI endoscopy, *n* (%)	53 (37.9)	17 (38.6)	0.93
- General anaesthesia	32 (23.0)	12 (27.3)	0.57
- Hypnoanalgesia	21 (15.3)	5 (11.6)	0.55
- Sedation with EMONO and/or midazolam	30 (22.1)	8 (19.0)	0.68
Esophagogastroduodenoscopy, *n* (%)	72 (51.4)	10 (22.7)	**<0.001**
- Abdominal pain	49 (35.0)	6 (13.6)	**0.012**
- Gastroesophageal reflux/vomiting	36 (25.7)	3 (6.8)	**0.0059**
- Feeding difficulties	15 (10.7)	2 (4.5)	0.37
- Follow-up of known lesions	5 (3.6)	0 (0)	0.34
- Weight loss/failure to thrive	5 (3.6)	2 (4.5)	0.67
- Digestive haemorrhage	2 (1.4)	2 (4.5)	0.24
- Celiac disease	2 (1.4)	1 (2.3)	0.56
- Inflammatory bowel disease/chronic diarrhoea	1 (0.7)	0 (0)	1
- Other indication	0 (0)	1 (2.3)	0.24
Rectosigmoidoscopy, *n* (%)	69 (49.3)**	34 (77.3)	**0.002**
- Inflammatory bowel disease/chronic diarrhoea	38 (29.1)	25 (56.8)	**<0.001**
- Digestive haemorrhage	18 (12.9)	7 (15.9)	0.79
- Follow-up of known lesions	9 (6.4)	1 (2.3)	0.45
- Abdominal pain	5 (3.6)	2 (4.5)	0.67
- Other indication	5 (3.6)	0 (0)	0.34

GI, gastrointestinal; EMONO, equimolar mixture of oxygen and nitrous oxide.
**Previous GI endoscopy before the study period.*
***One patient had both esophagogastroduodenoscopy and rectosigmoidoscopy during the same procedure.*
The bold values correspond to significant p-values ($p < 0.05$).

Rate of Successful Endoscopy

Hypnosis was combined with sedation in 136 cases (97.1%) (**Table 2**). Mean time (±SD) between entering the endoscopy room and beginning of hypnosis was 15.6 (±8.9) min. GI endoscopy started after a mean time of 4.7 (±2.9) min after the hypnotic induction. Mean duration of GI endoscopy was 6.2 (±3.2) min, while the mean hypnosis duration was 12.7 (±5.4) min. Mean time between the end of the procedure and release from the endoscopy room was 8.0 (±4.0) min. Biopsies were planned by the endoscopist before the procedure in 86.9% of cases, and all planned biopsies were harvested. The mean (±SD) number of planned biopsies per patient was 4.1 (±2.6); and the mean number of biopsies harvested was 4.2 (±3.0). GI endoscopy was successful in 116 patients (82.9%) and failed in 24 patients (17.1%). The four procedures performed under hypnosis alone were all successful rectosigmoidoscopies, performed on two girls aged 6 years and two boys aged 8 and 12 years. The rate of successful GI endoscopy was 93.8% when hypnosis was combined with EMONO ($n = 60/64$) and 71.8% when hypnosis was combined with EMONO and midazolam ($n = 51/71$). Among the failed procedures, three were associated with a poor tolerance of the patient, and 13 were stopped because of a poor tolerance of the procedure according to the endoscopist, and/or all biopsies could not be obtained. The endoscopy procedure had to be rescheduled on general anaesthesia in 11 cases. Rates of successful GI endoscopy were similar between two nurses (91.1 and 87.7%) and were lower for the third nurse (72.9%), who practiced more often EGD (59.3%) than the two first nurses (53.3 and 33.3%). The range of success rate of the seven endoscopists comprised between 62.5 and 100%.

TABLE 2 | Sedation used in combination with hypnosis during gastrointestinal endoscopy in included patients.

	All GI endoscopies ($n = 140$)	EGD ($n = 72$)	Rectosigmoidoscopies ($n = 68$)
Hypnosis combined with sedation *n* (%)			
- EMONO	68 (48.6)	1 (1.4)	67 (98.5)
- Midazolam	1 (0.7)	0 (0.0)	1 (1.5)
- EMONO and midazolam	71 (50.7)	71 (50.7)	0 (0.0)

GI, gastrointestinal; EGD, esophagogastroduodenoscopy; EMONO, equimolar mixture of oxygen and nitrous oxide.

Level of Satisfaction With Endoscopy Under Hypnosis

Patients showed a good cooperation according to the endoscopist and the nurse in 88.4 and 86.9% of cases, respectively. Ninety-two per cent of patients mentioned that the procedure went well. When considering the possibility of repeating the procedure under hypnosis, scores were consistent between the endoscopist, the nurse, and the child (81.9, 83.1, and 81.2% of positive answers, respectively), with 80.7% ($n = 113$) of doctors and nurses and 81.4% ($n = 112$) of patients who would do it again. Among individuals who would repeat the intervention, 96.5% ($n = 109/113$) of doctors and nurses and 88.8% ($n = 103/112$) of patients experienced a successful endoscopy.

Before the procedure, 68.3% of patients described anxiety, while nurses considered 76.2% of patients as anxious. Assessment of anxiety intensity was significantly different between patients and nurses ($p = 0.003$): 38.1% of patients perceived anxiety as mild (vs. 27% of nurses), 15.9% as moderate (vs. 20.6% of nurses), and 14.3% as severe (vs. 28.6% of nurses). Patients declared feeling pain during the exam in 70.1% of the cases, with median evaluated pain at 2.5 (min–max: 0.0–5.0). The evaluated pain was lower in the successful group than in the failure group (2.0 (0.0–4.0) vs. 5.0 (3.0–7.5), $p < 0.001$, respectively). Median pain was evaluated at 3.0 (0.0–5.5) for EGD and 2.0 (0.0–4.0) for rectosigmoidoscopy.

TABLE 3 | Predictive factors of successful gastrointestinal endoscopy.

	Success group (n = 116)	Failure group (n = 24)	p-value	Adjusted OR	95% CI	p-value
Male, n (%)	54 (46.6)	16 (66.7)	0.07	–	–	–
Median age (Q1–Q3)	13.0 (10.0–14.5)	8.0 (7.0–11.5)	**<0.001**	1.34	[1.10–1.62]	**0.003**
History of digestive endoscopy, n (%)	46 (39.7)	7 (29.2)	0.33	–	–	–
Presence of anxiety before the exam, n (%)	76 (69.1)	19 (79.2)	0.32	–	–	–
Intensity of anxiety before the exam, n (%)	–	–	0.09			
Absence	34 (30.9)	5 (20.8)	–			
Mild	50 (45.5)	12 (50.0)	–			
Moderate	12 (10.9)	0 (0.0)	–			
Severe	14 (12.7)	7 (29.2)	–			
Presence of parents during the procedure, n (%)	73 (64.6)	10 (43.5)	0.06	–	–	–
Esophagogastroduodenoscopy, n (%)	52 (44.8)	20 (83.3)	**<0.001**	16.34	[2.14–124.68]	**0.007**
Required biopsies, n (%)	99 (86.1)	20 (90.9)	0.74	–	–	–
Time spent in the waiting room (mean in min ± SD)	36.0 ± 24.8	49.6 ± 43.0	0.27	–	–	–
Time between the entrance in the endoscopy room and the beginning of hypnosis (mean in min ± SD)	14.8 ± 9.1	19.4 ± 7.4	**0.03**	1.06	[0.96–1.17]	0.27

OR, odds ratio; 95% CI, 95% confidence interval.
The bold values correspond to significant p-values (p < 0.05).

Predictive Factors of Successful Gastrointestinal Endoscopy

Children in the successful group were older than those in the failure group (median age of 13 vs. 8 years, $p < 0.001$) in the univariate analysis (**Table 3**). There were more cases of failure with EGD compared with rectosigmoidoscopy (83.3 vs. 16.7%, $p < 0.001$). Median time between entrance in the endoscopy room and beginning of the hypnosis was significantly lower in the successful group than in the failure group (14.8 vs. 19.4 min, $p = 0.03$).

In multivariate analysis, success of the endoscopy was associated with age of the children (13 vs. 8 years, OR: 1.34, CI 95% [1.10–1.62], $p = 0.003$) and type of procedure (rectosigmoidoscopy vs. EGD, OR: 16.34 [2.14–124.68], $p = 0.007$). An additional year of age was associated with 1.33 times more likelihood to have a successful procedure. After adjustment of age and time between entrance in the endoscopy room and beginning of the hypnosis, there were 16 times more cases of failure in EGD than in rectosigmoidoscopy.

Factors associated with successful EGD in univariate analysis were older age (12 vs. 9 years, $p = 0.001$) and presence of parents during the procedure (60.8 vs. 31.6%, $p = 0.029$), whereas male gender was significantly associated with cases of failure (40.4 vs. 70.0%, $p = 0.024$). In multivariate analysis, only patient's age and presence of parents were significantly associated with the success of EGD. There were no differences in success or failure of hypnosis if parents where present ($n = 83$) or not ($n = 53$). When considering only successful endoscopies, no difference was found ($n = 73$ and $n = 43$).

DISCUSSION

This is the first prospective study reporting the use of hypnosis during GI paediatric endoscopy in a large number of patients. Overall, we observed a high success rate of GI endoscopy under hypnosis combined with sedation induced by EMONO and/or midazolam. Four rectosigmoidoscopies were performed with hypnosis alone and were all successful. Older age and rectosigmoidoscopy were significant predictive factors associated with success of endoscopy.

Previous studies reported the use of hypnosis without sedation during GI endoscopy in adult patients. Cadranel et al. used hypnotic relaxation to perform colonoscopy in 24 patients with a mean age of 43 years (16). Hypnosis resulted in moderate or deep sedation in half of them. Pain was lower when hypnosis was successful. In addition, completeness of colonoscopy was observed in all patients in the successful group as compared with only half of them in the failure group. Dominguez-Ortega et al. observed an efficacy of hypnosis used alone in EGD ($n = 6$) and colonoscopy ($n = 22$), with a good tolerance reported by the patient in 85% of cases (17). Elkins et al. studied the effect of hypnosis in the management of pain and anxiety during colonoscopy performed for colorectal cancer screening. Patients having a hypnotic induction had lower anxiety before the procedure, reduced recovery time after the procedure, lower vasovagal events, and a high level of satisfaction of the endoscopic procedure compared with the patients without hypnosis. Successful hypnosis was associated with less intense pain as compared with failed hypnosis (18). In a preliminary report on patients who underwent colonoscopy under hypnosis ($n = 38$) or midazolam ($n = 29$), Bersani et al. showed less pain (Visual Analogue Scale 2.97 vs. 5.48, $p < 0.05$) and higher satisfaction (63 vs. 24%, $p < 0.05$) in the hypnosis group compared with the midazolam group (19). Other authors pointed out the efficiency of hypnosis as part of a psychological preparation to GI endoscopies, in order to reduce pre-operative anxiety (20, 21).

In the present study, older age was statistically associated with successful endoscopy. This predictive factor could be expected since older children better understand and apprehend the course of the procedure. The median age in the successful group was 13 years (vs. 8 years). According to Wood and Bioy, age is a major criterion to consider in hypnosis since children are more likely to be receptive to hypnosis between 7 and 14 years of age (22). For Olness and Kohen, the ability to be hypnotised is limited before the age of 3 years, reaches a peak between 7 and 14 years, and decreases during adolescence, followed by stabilisation and a final decrease at maturity (23). Healthcare situations may be stressful for younger children, yet fear increases the perception of pain. In multivariate analysis, successful endoscopy was strongly influenced by the type of GI endoscopy since there were more cases of failure in EGD compared with rectosigmoidoscopy. This difference is very likely associated with a lower tolerance and higher level of stress with regard to EGD by patients in comparison with rectosigmoidoscopy, independently of hypnosis efficacy (24). Our results revealed more cases of successful GI endoscopies when patients used hypnosis combined with EMONO than patients using hypnosis combined with EMONO and midazolam. The higher success rate in the first group can be explained by a higher number of rectosigmoidoscopies (98.3%) when all procedures from the second group were EGD, but also more parental presence (66.7 vs. 60.8%). Median time between entrance in the endoscopy room and beginning of the hypnosis was significantly shorter in the success group. Older age and more frequent parental presence may have influenced this difference. We assumed that older patients may have required less time to understand the procedure and have been more easily reassured. The presence of parents during EGD was associated with successful endoscopy. In addition to a preparation session when clear information is given to parents and their child, parental presence is known to participate in the relief from child pre-operative stress (25). In a study including 42 adults who underwent EGD, alone or accompanied, it was shown that patients with a guide tended to have lower anxiety than those without, with a higher benefit when the patients had a higher level of anxiety before the procedure (26). In an RCT on 130 children who underwent painful procedures, significant decreases in scores on pain experience and stress were observed in the parental presence group compared with the group of children using a kaleidoscope toy or the control group (without parents) (27). One could expect a lower efficiency of hypnosis during GI endoscopy requiring multiple digestive biopsies, or in very anxious children. However, in our study, the child's pre-existent anxiety, history of previous endoscopy, or requirement of biopsies did not influence the rate of successful endoscopy.

With a monocentric recruitment, this study offered the advantage of displaying a homogeneous patient care. However, the study lacked statistical power, particularly regarding the assessment of predictive factors of successful endoscopy due to the small number of patients in the failure group. For this reason, the roles of the endoscopist and the nurse who performed hypnosis have not been evaluated as a prognostic factor of successful endoscopy. However, the range of success rate of the seven endoscopists did not vary significantly. The low failure rate may be explained by the evaluation of success with one closed question, preventing a more precise graduated answer. The study design with a planned protocol could also have implied the caregivers to explain the procedures to the patient and his/her family more carefully than usual. Plus, when considering the median age, our study population could have been particularly sensitive to hypnosis success, as detailed above (22, 23). The definition of success was arguable as we randomly chose to consider the endoscopist's and the patient's point of view, even if the judgment criteria were defined to be as objective as possible. The evaluation of both anxiety and satisfaction could have been standardised using validated and blinded questionnaires. We did not assess the long-term effects of hypnosis since we did not expect any long-term adverse event after discharge from the hospital, although this is a limitation of our study. To our knowledge, no patients reported long-term events after the study. We regret that some patients could not be included because of logistical reasons, such as the insufficient number of trained caregivers to perform hypnosis. We did not assess patient's hypnotisability or the depth of hypnotic state, which could have been interesting to compare between different age groups. Finally, the study was designed to be observational, allowing assumptions about the benefit of hypnosis during paediatric GI endoscopy only and hindering the establishment of causality. We did not choose to compare GI endoscopy with and without hypnosis, but we compared different modalities of sedation combined with hypnosis. This question could be clarified in further studies using a higher number of randomised patients, allowing comparisons with a control group. However, since the success rate using combination of hypnosis and sedation is very high in our pilot study, we do believe this technique is of interest for clinical practice.

Currently, the shortage of anaesthesiologists urges the development of alternatives to general anaesthesia for effective sedation in children. The choice of sedative drugs is large (e.g., propofol, ketamine, and midazolam), but none of them possesses all the ideal properties: quick efficacy, predictable dose-dependent effect, large therapeutic window, anxiolytic effect with anterograde amnesia during the exam, quick half-life, and minimal side effects (28). Moreover, the use of sedative drugs by doctors other than anaesthetists is not allowed in many countries. Sedation represents a continuum going from mild to deep sedation; therefore, there is always a risk of involuntarily move from a mild to deep level of sedation with loss of airway protection reflexes, respiratory depression, and haemodynamic instability. Sedation procedure must offer an effective and safe alternative to general anaesthesia. Hence, hypnosis combined with conscious sedation, such as sub-lingual midazolam and EMONO, is an interesting sedative choice for GI endoscopy.

Several conditions are required to apply hypnosis in paediatric GI endoscopy in clinical practice. Members from the medical team have to be trained and habilitated to practice hypnosis. The endoscopy room needs to be adapted for hypnosis, including the reduction of external stimuli (light and noise) to create a quite atmosphere. The targeted population receiving hypnosis has to be selected: diagnostic EGD or rectosigmoidoscopy and age older than 6 years. When children arrived in the endoscopy room, a clear information has to be delivered to the children and their parents/guardians, to decide an individualised choice of hypnosis alone or associated with conscious sedation. The GI endoscopy procedure can be performed only when the distraction of the children is obtained. Child's satisfaction must be evaluated after the procedure.

This prospective pilot study suggests that hypnosis combined with midazolam and/or EMONO is an effective technique and may be of additional value to increase the success and tolerance of diagnostic GI endoscopy in children older than 6 years. The use of hypnosis represents a complementary tool for patient's sedation with the ambition to transform a care experience into a moment of pleasant escape for the child. By changing communication with the child and renewing the caregivers' routine organisation, hypnosis would thus be integrated into an improved conception of paediatric care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SC, CR, VD, and DL conceived and designed the study. LT, SC, CR, and DL did the analysis and interpretation of the data. LT, SC, CR, and DL drafted of the article. SC, MA, AN, DG, DT, FG, and DL brought critical revision of the article for important intellectual content. All authors approved the final version of the article.

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ORIGINAL RESEARCH
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Pediatric Gastrointestinal Endoscopy: Diagnostic Yield and Appropriateness of Referral Based on Clinical Presentation: A Pilot Study

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Objectives: There is a lack of evidence-based consensus for the utility of gastrointestinal endoscopy (GIE) in an array of frequently occurring symptoms in children. We aimed to assess the diagnostic yield of endoscopy in an effort to aid clinical decision making.

Methods: Retrospective analysis included patients ≤18 years who underwent GIE during one calendar year at Shaare Zedek Medical Center. We excluded children referred for predefined obvious indications for GIE, planned follow-up procedures, and therapeutic endoscopy. Clinician-assigned indication for endoscopy as well as endoscopic and histologic findings were recorded. Diagnostic yield of GIE was determined according to referral indication.

Results: There were 794 endoscopies performed of which 329 were included in the analysis (mean age 9.3 ± 5.0 years, 51% female). No significant complications of GIE were recorded. Six major referral indications were identified among which abdominal pain was the most frequent 88/329 (26%) of whom 32/88 (36%) had a significant diagnostic finding. Among the other major indications, diagnostic findings were found in 36/85 (43%) children with primary indication of chronic diarrhea, 14/33 (42%) failure to thrive, 15/32 (46%) short stature, 30/56 (54%) iron deficiency, and 20/48 (42%) weight loss.

Conclusions: Pediatric GIE is a safe procedure with diverse clinical indications. The diagnostic yield of endoscopy is variable, depending on the referral indication. These data can assist formulating judicious referral practices.

Keywords: indications, resource allocation, diagnostic yield, pediatric, gastrointestinal endoscopy

HIGHLIGHTS

- Gastrointestinal endoscopy (GIE) is a safe and useful diagnostic intervention in children.
- There exist multiple clinical scenarios for which its utility remains uncertain.
- The majority of recommendations in the ESPGHAN/ESGE guidelines of pediatric GIE are weak with low quality of evidence.

- Diagnostic yield ranged significantly based on the referral indication.
- Low yield for abdominal pain (AP) with diarrhea and AP with constipation if blood results are normal.
- High yield for AP with iron deficiency, chronic diarrhea with weight loss, and isolated iron deficiency.
- There is a higher diagnostic yield with objective indications than subjective symptoms.

INTRODUCTION

Gastrointestinal endoscopy (GIE), including esophagogastroduodenoscopy (EGD) and colonoscopy, has become an integral component of diagnosis and therapeutics in pediatric gastroenterology. Although there is some overlap in referral indications between adults and children, significant differences exist. Screening colonoscopies, for example, provide the critical mass of endoscopic investigations in adults, whereas gastroscopy for suspected celiac is proportionally more frequent in children (1).

Unlike in adults (2), until recently, there was a dearth of evidence-based guidelines of appropriate indications for endoscopic evaluations in children. Although there are clinical scenarios that are considered an absolute indication for GIE, such as significant upper gastrointestinal bleeding, the correct placement of GIE for a multitude of clinical scenarios has not been formalized. As a consequence of the lack of guidelines, endoscopies may be performed inappropriately with resultant patient inconvenience and cost burden (3).

In this study, we aimed to assess the diagnostic yield of pediatric GIE in various clinical scenarios based on symptoms, signs, and laboratory findings. Determination of the diagnostic yield of endoscopy by indication of referral could facilitate more judicious decision making as to which patients would benefit from an endoscopic procedure.

METHODS

Patient Population

We conducted a retrospective review of all pediatric GIEs performed during calendar year 2015 at Shaare Zedek Medical Center in Jerusalem. Recorded data included demographics, referral source, and clinical features, including presenting symptoms and anthropomorphic data, laboratory results, endoscopic findings, and histology. The indication for referral to GIE was determined from either the referral letter completed by the referring pediatric gastroenterologist and/or from the previous clinic visit summary.

Under our aim of determining the diagnostic yield of endoscopy in clinical scenarios of uncertainty, we excluded endoscopies that were undertaken for what we defined as obvious indications, including significantly elevated celiac serology [≥3x upper limit of normal (ULN)], significant UGI bleed, and lower GI bleed in the absence of clinical suspicion of constipation. Similarly, scheduled follow-up procedures and therapeutic endoscopies, such as foreign body impaction, stricture dilatations, or esophageal varices, were excluded from analysis. This study was reviewed and approved by the Shaare Zedek Medical Center Helsinki ethics committee.

Endoscopic Procedures

The endoscopic procedures were performed as per routine protocol under general anesthesia. *Helicobacter pylori* was assessed by hematoxylin & eosin and Giemsa staining.

Endoscopic or histologic findings were considered significant if they had diagnostic or prognostic value, defined as a reasonable explanation for presenting symptoms, and/or a finding that effects management change. Minor, non-specific endoscopic findings, such as subtle erythema, minor increase or decrease of vascularity, or mild pallor were considered normal if there were no corresponding histologic changes of significance. Similarly, minor, non-specific histologic findings, such as mild chronic gastritis with no activity, were considered normal if seemingly unrelated to the presenting indication (4–6). Borderline results were defined as a histological abnormality of questionable significance, for example, mild, non-specific duodenitis or mild basal hyperplasia of esophageal mucosa with no associated inflammation. Incidental findings unrelated to the referral indication, for example, *H. pylori* in a patient referred with diarrhea, were noted but not considered a positive find.

RESULTS

A total of 794 GIE procedures were performed on 683 individuals among which 329 met criteria for inclusion (**Figure 1**). Mean age of included children was 9.3 ± 5.0 years (range 0–18), 51% female. Of the 329 procedures, 273 (78%) underwent EGD only, five (3%) underwent colonoscopy only, and 51 (19%)

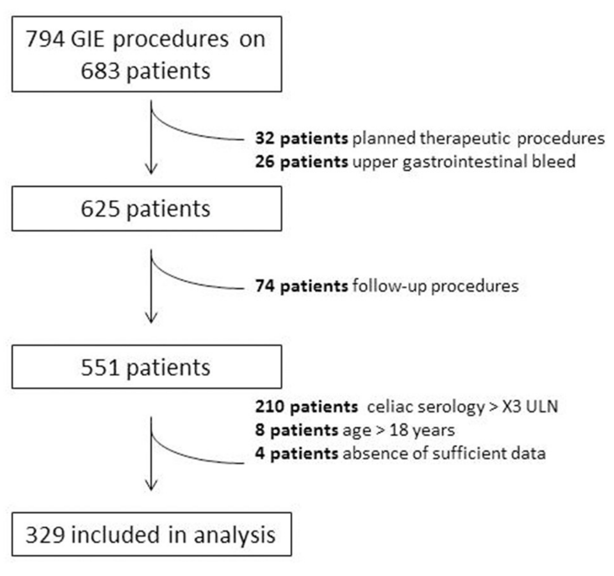

FIGURE 1 | Selection of patients included in study.

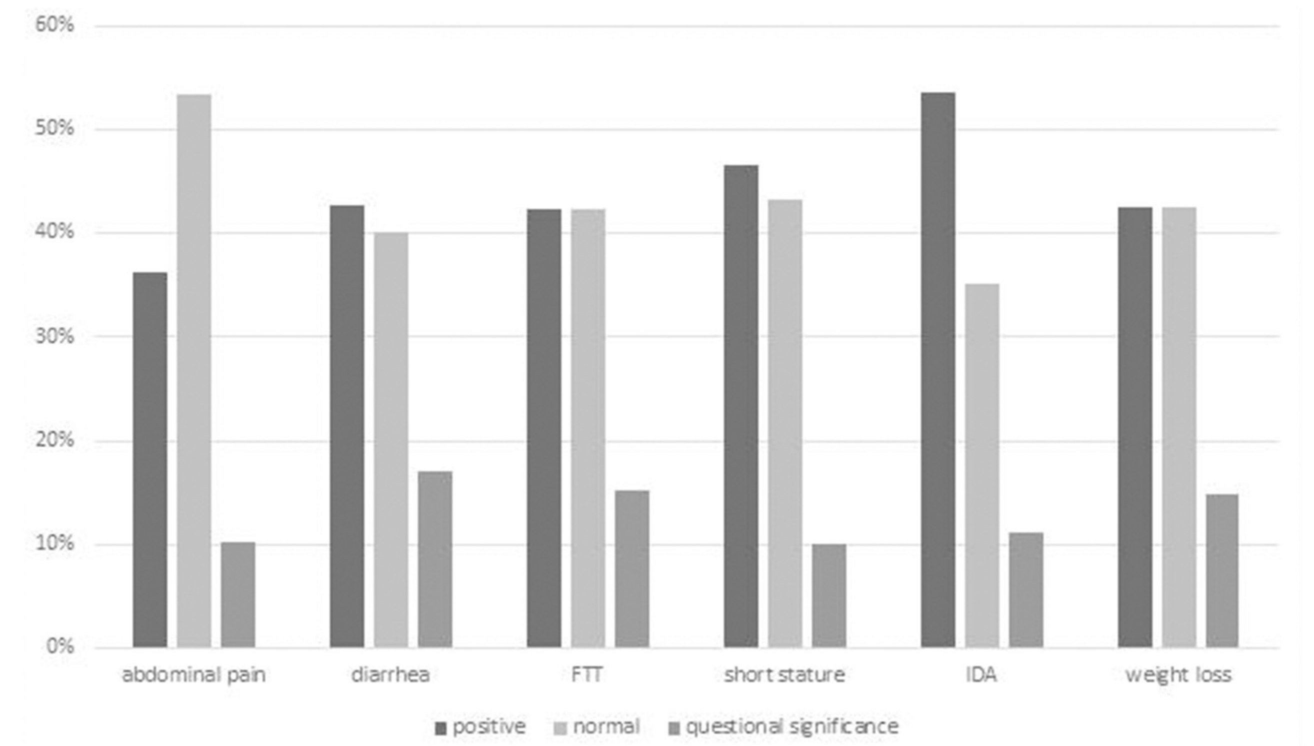

FIGURE 2 | Overall diagnostic yield of GIE by indication. Positive finding = definite diagnostic finding relating to indication; Questionable significance = finding of uncertain relationship to indication or minor finding of uncertain significance. FTT, failure to thrive.

underwent both EGD and colonoscopy. No major procedure-related complications of GIE, such as postendoscopy bleeding, bowel perforation, or unplanned postendoscopy admissions, were recorded. We identified six major indications for GIE: abdominal pain, diarrhea, failure to thrive (FTT), short stature, iron deficiency, and weight loss. Patients with referral indications other than these are described separately. In the majority of these indications, the diagnostic yield was above 40% (**Supplementary Table 1**; **Figure 2**).

Abdominal Pain

Eighty-eight children (26% of the cohort) underwent GIE with abdominal pain as a major indication (**Figure 3**). Overall, 32/88 (36%) children had a diagnostic finding relating to abdominal pain. Incomplete descriptions in patient notes precluded the ability to analyze epigastric pain independently. Children in whom abdominal pain was a sole indication had a similar rate of findings as those with joint indications. Among those joint indications in which the positive diagnostic yield was <25% were constipation, loss of appetite, and nausea. Patients with abdominal pain and iron deficiency and/or weakly positive celiac serology had diagnostic findings in more than 50% (**Supplementary Table 1**).

Chronic Diarrhea

Eighty-five children (26% of the cohort) presented with chronic diarrhea as a major indication. Overall 36 (43%) had a diagnostic finding relating to chronic diarrhea. Eleven children (3%) underwent GIE in which chronic diarrhea was the sole indication (**Supplementary Table 1**; **Figure 4**), five (45%) of whom had diagnostic biopsies related to diarrhea. Children with chronic diarrhea and iron deficiency anemia had a positive finding identified in 3/6 (50%). Diagnostic findings related to diarrhea were obtained in 2/5 (40%) children who presented with chronic diarrhea and FTT.

Iron Deficiency Anemia

Fifty-six children (17% of the cohort) underwent endoscopy with iron deficiency as a major indication, of whom 30 (54%) had a positive diagnostic finding related to the indication. Among those patients referred with iron deficiency anemia and weakly positive celiac serology, celiac disease was confirmed in 4/6 (67%) (**Supplementary Table 1**).

Failure to Thrive

Thirty-three endoscopies (10% of the cohort) were performed with an indication of FTT, in eight (25%) of whom FTT was the only indication. Overall, positive diagnostic findings relating to FTT were identified in 14 (42%) of these patients. FTT with a joint indication of iron deficiency anemia had diagnostic findings in 6/12 (50%) (**Supplementary Table 1**).

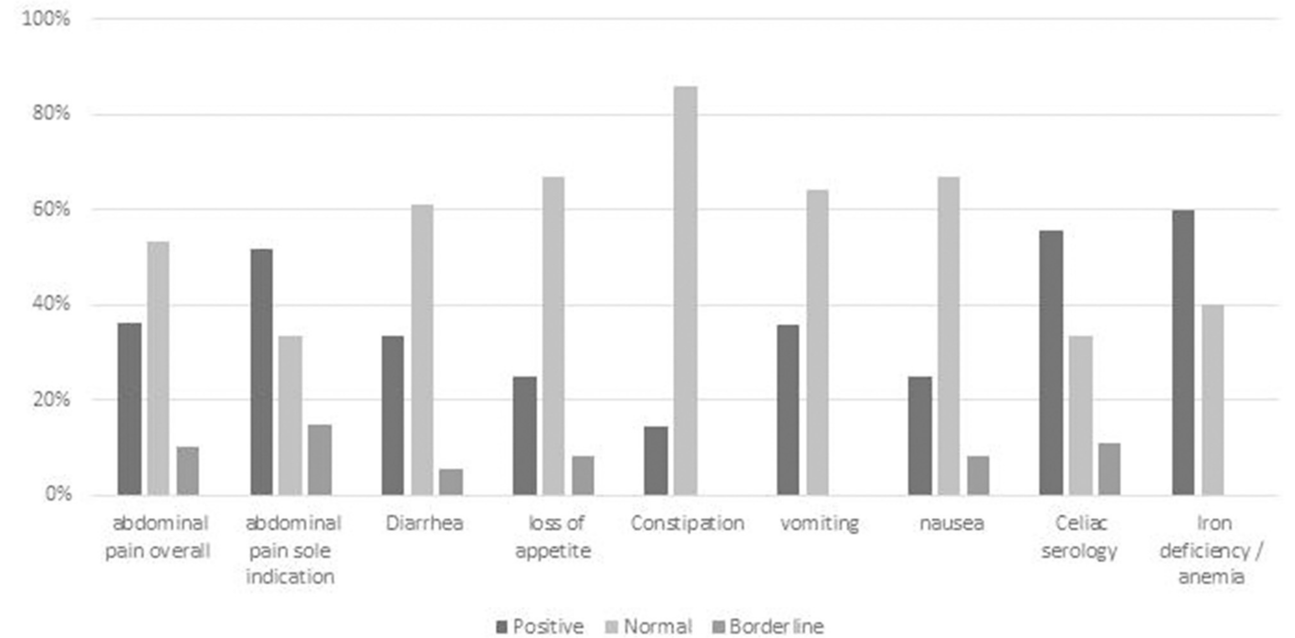

FIGURE 3 | Diagnostic yield of GIE in subgroup analysis of abdominal pain with different joint referral indications. Positive = definite diagnostic finding relating to indication; Borderline = finding of uncertain relationship to indication or minor finding of uncertain significance; Negative = no finding or incidental finding unrelated to indication. AP, abdominal pain; celiac serology < x3 ULN.

Short Stature

Thirty-two children (10% of the cohort) underwent endoscopy for a primary indication of short stature. Positive findings were recorded for nine (29%) of these patients, all of whom had a second indication besides short stature. Among the 11 children who presented with short stature and weakly positive celiac serology, five (45%) were diagnosed with celiac based on histology (**Supplementary Table 1**).

Weight Loss

Forty-eight children (15% of the cohort) were referred due to unexplained weight loss as a major indication, among whom 20 (42%) had diagnostic findings. Six (19%) of these children were diagnosed with IBD, all of whom had a secondary indication besides weight loss. In those children with both weight loss and iron deficiency anemia, the diagnostic yield increased to 5/9 (56%) (**Supplementary Table 1**).

Weakly Positive Celiac Serology

Celiac serology $\geq$3x ULN was excluded from analysis as per the study protocol. Among the 329 endoscopies included in the analysis, 35 (11%) patients had borderline celiac serology of <3x ULN. Of these, two (6%) children had no other indication with the others presenting with joint indications of abdominal pain, short stature, iron deficiency, diarrhea, weight loss, and/or FTT. Two (6%) of these children had IgA deficiency with borderline IgG-based serology.

Twenty-two (63%) of these children had histologic features consistent with celiac, and four (11%) had borderline histology. Celiac was more likely in children with additional indications, such as iron deficiency (67%) and abdominal pain (56%), than in children with FTT (21%) or weight loss (4%) (**Supplementary Table 1**).

Miscellaneous

Other than the major indications described previously, there were a few other indications that had a very high rate of positive findings. Family history of celiac disease, combined with weakly positive celiac serology, yielded positive histology in eight out of nine (89%) children. Similarly, there were five children referred due to fatigue and weakly positive celiac serology among whom celiac was diagnosed in three (60%) of these children.

All children diagnosed with celiac disease over 3 years of age had either borderline or weakly elevated serology. All patients diagnosed with IBD had at least one abnormal blood result, such as anemia, hypoalbuminemia, and/or raised inflammatory markers.

Overall, the diagnostic yield of GIE ranged significantly based on the referral indication, from 14% (abdominal pain with constipation) to 67% (chronic diarrhea with weight loss). Various presentations or combinations of symptoms had a particularly low yield of positive findings, including abdominal pain with constipation 1/7 (14%), abdominal pain with diarrhea 6/18 (33%), and short stature 2/8 (25%) in the absence of clinical or biochemical suggestion of celiac or IBD.

The difference between the diagnostic yield of subjective symptoms such as loss of appetite 6/36 (17%), constipation 9/29 (31%), and nausea 3/12 (25%) was consistently lower than the

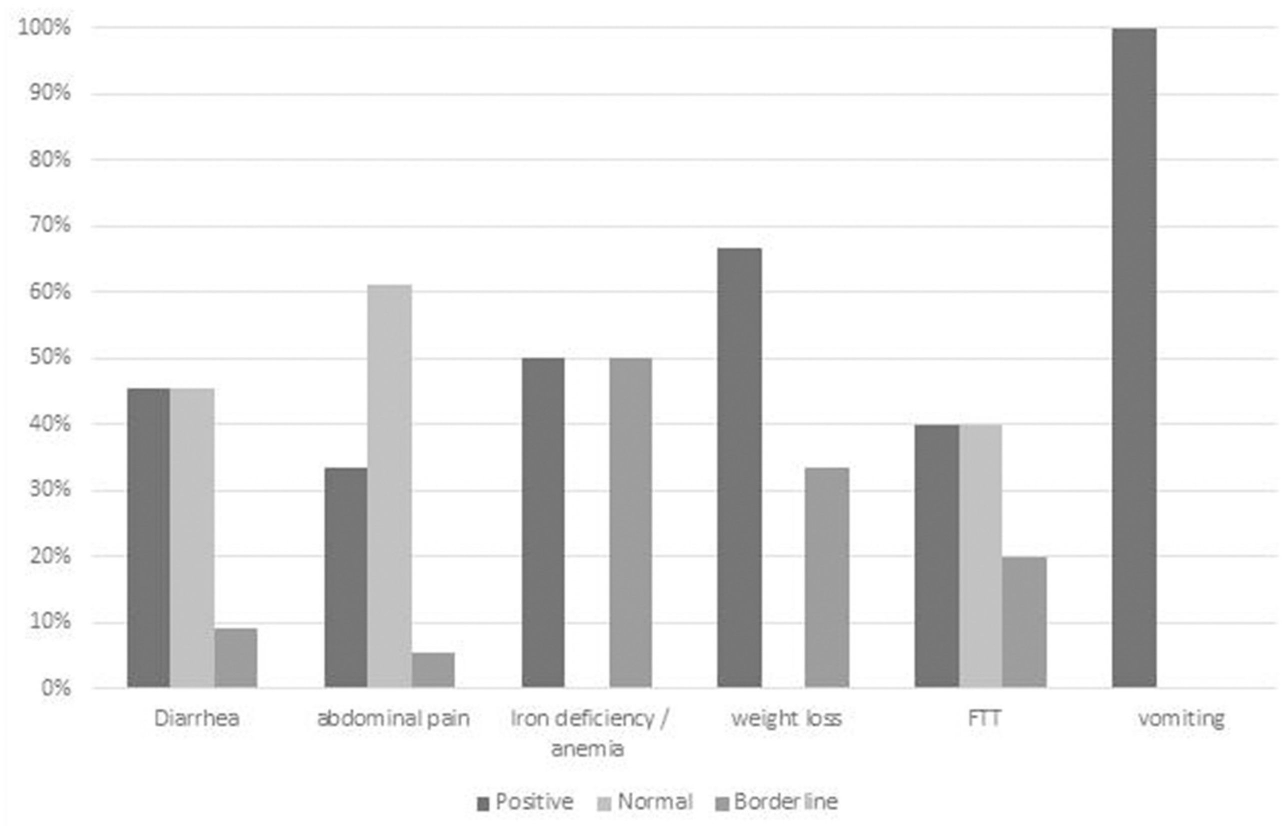

FIGURE 4 | Diagnostic yield of GIE in subgroup analysis of chronic diarrhea with different joint referral indications. Positive = definite diagnostic finding relating to indication; Borderline = finding of uncertain relationship to indication or minor finding of uncertain significance; Negative = no finding or incidental finding unrelated to indication. IDA, iron deficiency anemia; FTT, failure to thrive.

diagnostic yield of more objective clinical indications, such as iron deficiency anemia 30/56 (54%) and slightly increased celiac serology 22/35 (63%).

DISCUSSION

The utility of GIE has expanded tremendously in pediatric gastroenterology, including a 1,200% increase at one large center over the 20-year period till 2005 (7) and a 400% increase over the last decade at the authors' center (unpublished data). With the associated burgeoning costs, it is important to utilize this service efficiently and minimize unnecessary investigations in those children with a low pretest probability of finding any significant pathology.

In our study, diagnostic yield ranged significantly based on the referral indication with a low diagnostic yield for joint indications of abdominal pain and diarrhea, constipation, loss of appetite, and nausea in the absence of significant abnormal blood results and a high diagnostic yield in children with abdominal pain and iron deficiency, chronic diarrhea with weight loss or vomiting, and also in isolated iron deficiency.

The indications for GIE have changed over time, being initially reserved for more critical circumstances. GI bleeding made up 34% of all procedures in 1985 compared with only 5% in 2005 with an increase in procedures performed for abdominal pain over the same time period from 23 to 43% (7).

Despite its widespread use, there remains a lack of consensus as to the appropriate indications for GIE in children. The overwhelming majority of the recommendations in the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the European Society of Gastrointestinal Endoscopy (ESGE) guidelines of pediatric GIE are weak with low quality of evidence (8).

To address this need, we analyzed all GIE procedures from a relatively large-volume pediatric service to analyze the diagnostic yield of GIE, specifically in those cases in which consensus is lacking. With the aim of identifying diagnostic yield in those circumstances of greater doubt, we excluded planned follow-up procedures, therapeutic procedures, and procedures predefined as "necessary" by consensus.

Diagnostic yield of GIE in relation to presenting symptoms has been reviewed in several previous studies (3, 9–13); however, there is significant variability between these data. Some studies analyze all GIE procedures, and others only diagnostic procedures, and another only those performed for abdominal pain. Furthermore, the definition of a positive finding was not uniform with some studies including all findings, others histologic findings, and another including only those findings that led to a change of diagnosis and/or management. The resultant diagnostic yield ranged from 19 to 76% overall. When specifically assessing those cases referred for abdominal pain, the diagnostic yield ranged from 38 to 69%. In comparison, our study tended to a lower diagnostic yield than in most previous studies, which was not surprising considering our targeted analysis excluded those patients in whom consensus would suggest the need for the procedure.

Some findings are of uncertain significance to the referral indication, and others are clearly incidental. An example of this is *H. pylori*, in which, with carriage rates upward of 40% in young adults in Israel (14), this is frequently an incidental finding. There is uncertainty about the relationship between *H. pylori* and both abdominal pain and iron deficiency in the absence of significant endoscopic gastritis or ulcerations (15–21). Despite conflicting data, we assumed *H. pylori* to be clinically significant in our study, when the procedure was performed for abdominal pain or iron deficiency.

This study's main limitation is its retrospective nature in which the need to represent complex combinations of patient findings into simple, defined referral indications remains a challenge. As such, due to multiple permutations and combinations of clinical features, despite the large number of children included in our study, only small numbers were represented in some clinical scenarios. Additionally, the number of sole colonoscopies was relatively low, and this seemingly reflects pediatric endoscopy practice. These limitations may have been overcome somewhat with a larger sample size; however, expanding the number of included procedures beyond what was included was not possible in this study. As such, this publication should be seen to pave the way for larger and more powerful studies, preferably of a prospective nature, to further address the study question. Furthermore, laboratory data was not universally available for all patients, precluding comprehensive statistical analysis and limiting conclusions to more general qualitative outcomes as described. Regardless, our study is one of the largest studies to address this question and the largest to include only those patients in whom GIE would not be considered an absolute requirement.

This study makes an important contribution in identifying indications for pediatric endoscopy that have a relatively higher diagnostic yield and can assist the clinician in deciding on the need for diagnostic GIE in these common scenarios. The ultimate responsibility for deciding on recommending GIE to a patient rests with the clinician based on his or her experienced assessment of the patient's symptoms, signs, and laboratory results. Our data, combined with previously published data, assists the clinician to refer patients more judiciously.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

TF: acquisition, analysis and interpretation of data, and drafting manuscript. ES, EO, IS, RL, YR, AB, and DT: data acquisition and critical review of manuscript. OL: conception and design of the study, analysis and interpretation of data, drafting manuscript, and final approval of version to be published. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

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REVIEW
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Pediatric Endoscopy During COVID-19 Times

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The global COVID-19 pandemic has led to healthcare resources being diverted or stretched, especially during periods of lock-down in affected countries. Disruptions to normal services have resulted in reduced or delayed provision of endoscopy in many countries, with consequent impacts on diagnosis or management of digestive diseases and upon endoscopy training. This review article aims to highlight key aspects of the impact of the pandemic upon endoscopy services, with a focus upon endoscopy in children.

Keywords: endoscopy, children, pediatrics, COVID-19, healthcare

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INTRODUCTION

Severe acute respiratory coronavirus (SARS-CoV)-2 is a member of the *Coronaviridae* family: this family of viruses includes a number of virulent strains known to infect animals and humans (1). The disease caused by SARS-CoV-2, known as coronavirus disease (COVID)-19, was first noted in 2019. Subsequently, the World Health Organization (WHO) declared COVID-19 to be a pandemic on March 11, 2020 (2). Since then, the COVID-19 pandemic has spread worldwide with more than 250 million laboratory-confirmed cases and more than 5 million deaths as of November 20th, 2021, (https://www.worldometers.info/coronavirus/) leading to widespread social and economic disruption.

Soon after the WHO declaration in March 2020, numerous health authorities across different countries (for e.g., the US Surgeon General, the American College of Surgeons, the Centers for Disease Control and Prevention, and Chief Medical Officers across Canada) advised medical practitioners to suspend all elective medical procedures (3). This decision affected surgeons, gastroenterologists and other disciplines (4). Consequently, endoscopy centers have undergone significant changes based on international and local guidelines and have taken significant and unprecedented steps to avoid transmission of the virus (4).

While some early reports suggested that there was a low risk of COVID-19 transmission consequent to GI endoscopy (5), other reports indicated a high prevalence of SARS-CoV-2 infection in patients scheduled for digestive endoscopy (6). These contradictory reports resulted in confusion and uncertainty in decision making.

Although the initial force of the pandemic has passed in most countries, there remain ongoing waves of infection with particular impact in some parts of the world. Further, this impact will have ongoing repercussions for some time. This review focuses on the impact of the COVID-19 pandemic upon endoscopy services, focusing on pediatric services where available, highlighting the immediate effects in 2020 and some of the ongoing consequences thereafter.

METHODS

A literature search was performed using MEDLINE, Pubmed, and the Cochrane Library with the last search date of November 1st 2021. Search terms included COVID-19, endoscopy, children, pediatric, guidelines "SARS-CoV-2," "gastrointestinal endoscopy," and "digestive system endoscopy."

Severe Acute Respiratory Coronavirus (SARS-CoV)-2 and COVID-19

SARS-CoV-2 can spread from person to person by contact, airborne and droplet routes (7). It behaves as an opportunistic airborne pathogen following a cough or during procedures that generate aerosols (3). van Doremalen et al. (8) showed ongoing detection of the virus in aerosols for up to 3 h. Aerosols can also be transmitted for several meters (9). Furthermore, the virus can persist on surfaces, such as on items in the rooms of patients with active COVID-19 (9).

Children of any age can be infected by SARS-CoV-2, but is more commonly recognized in older children and adolescents. Overall, pediatric cases of COVID-19 are thought to represent <5% of total cases (10). However, the true rate of infection in children is likely much higher than this. Testing in many studies was undertaken only in symptomatic individuals or those who were hospitalized (11). This is relevant given that many children infected with COVID-19 are asymptomatic or have mild symptoms, such as fever, cough, gastrointestinal symptoms, pharyngitis, or changes in sense of smell or taste (11). In addition, recent data suggests that children are less likely to become infected after contact with someone who is infected with SARS-CoV-2 (11).

Recent reports demonstrate that children and adolescents infected with the virus have similar viral loads to adults (12, 13): consequently, they are just as likely to transmit the virus to others (14). In addition, the viral load may be unrelated to the presence or absence of symptoms in that individual (15, 16). For example, Sola et al. (17) studied the pattern of positive SARS-CoV-2 test results in 33,041 asymptomatic children presenting for surgical or medical care at 28 children's hospitals across the United States of America (USA). Two hundred and fifty of these children (ranging in age between 0 and 18 years) had positive SARS-CoV-2 tests.

The overall pooled prevalence was 0.65% (95% CI, 0.47–0.83%), with rates varying from 0 to 2.2% between centers.

Transmission of SARS-CoV-2 During GI Endoscopy

The characteristics of the SARS-CoV-2 virus mean that an endoscopic procedure is a potential mechanism for spreading the infection. Person-to-person spread, respiratory droplets, generation of aerosols, and direct contact with contaminated surroundings or body fluids are all relevant to endoscopy (18).

Keil et al. (19) studied spread of the virus using an experimental model of endoscopic procedures in a specialized laboratory. This model evaluated the formation and movement of potentially infectious fluid particles from the patient's body to the environment via the endoscope. They found liquid coming through the working channel of the endoscope with biopsy forceps or other instruments generates droplets with a diameter in the range of 0.1–1.1 mm and an initial velocity of up to 0.9 m/s. They developed a protective cover that completely eliminated droplet spread (19).

In addition to the concern about spread by respiratory secretions, there is also an increasing concern about the potential for fecal-oral spread. The high frequency of gastrointestinal symptoms in individuals with COVID-19, the localization of angiotensin converting enzyme 2 in the intestinal mucosa and the identification of active viral particles in stool for prolonged periods after infection highlight these concerns (20, 21).

Although there are significant concerns about the risk of spread of the virus from an infected patient to endoscopy staff, the overall risk if appropriate precautions are followed appear to be low (22). In addition to the patient-related processes mentioned earlier, other suggested steps within the endoscopy unit include the use of personal protective equipment, limitations on the number of staff in the endoscopy suite and procedural modifications.

Papanikolaou et al. (23) conducted a multicenter study to assess the risk of infection with an endoscopic procedure. In the setting of low risk or negative COVID-19 testing in 1,135 individuals, 254 were tested after their procedure and eight were shown to be positive. Amongst 163 endoscopic personnel assessed in this report, five tested positive during the study period.

Guidelines for the Undertaking of Endoscopy in the Setting of COVID-19

Guidelines have been issued by several adult societies (24–26) and one pediatric society (3). These guidelines concentrate on four main themes: (a) How to perform endoscopic procedures during the COVID-19 pandemic, (b) Which endoscopic procedures should always be done and which should be deferred? (**Tables 1**, **2**), (c) How to protect endoscopy unit staff during the pandemic? and (d) What are the gaps in current knowledge and what is still required in this rapidly evolving field?

Initially, the AGA recommended that endoscopy units may recommence doing elective endoscopic procedures when the number of new cases of COVID-19 in the local area has reduced consistently for at least a fortnight (American

TABLE 1 | Patients considered high risk for endoscopic procedures [adapted from Sinonquel et al. (27)].

1. Patients with symptoms suggestive of an upper respiratory infection or with an elevated temperature of $\geq$37.5°C.
2. Patients with a history of close contact with more or more individuals with established or suspected COVID-19 within the last fortnight.
3. Patients with a personal history of travel to area(s) with pandemic COVID-19 within the last fortnight. Including any new or emerging "hot spots."
4. Patients reporting significant general fatigue and/or shortness of breath.
5. Patients complaining of dysosmia and/or dysgeusia (loss of smell or taste) without any clear underlying cause.
6. Patients complaining of GI symptoms (including diarrhea) lasting for at least 4 days without a clear identifiable cause.

TABLE 2 | Conditions that may need urgent endoscopy regardless of COVID status.

- Bleeding (or suspected bleeding) from the upper/lower gastrointestinal tract
- Cholangitis requiring endoscopic retrograde cholangiopancreatography
- Symptomatic bile duct/pancreatic disease
- Endoscopic release of a gastrointestinal stricture
- GI cancer requiring early treatment
- Other conditions requiring urgent treatment based on the decision by the facility

Gastroenterological Association, Digestive Health Physicians Association. AGA/DHPA Joint Guidance for Resumption of Elective Endoscopy. Available at: https://gastro.org/news/aga-dhpa-release-guidance-forresuming-elective-endoscopy/). The time of resumption of endoscopy services must also consider other local or national advice, local resources and the ability to provide a safe environment for patients and staff.

The AGA guide specified that scheduled endoscopies should still be prioritized by level of urgency, depending upon individual patient considerations and physician professional judgement. They also stated that, wherever possible, all patients should be tested for active COVID-19 infection with PCR-based testing within 48 h prior to their endoscopy. Subsequently, the AGA Institute recommended not undertaking pretesting in "high" prevalence or "low" prevalence (<0.5%) areas, due to the possibility of false negative results in the former and false-positive results in the latter areas (28).

The position paper presented by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommended that all endoscopic procedures in children should be performed in a negative pressure room with all personnel following strict airborne, contact and droplet precautions regardless of the individual risk category of the patient (3). These precautions (i.e., enhanced PPE) include using a standard filtering facepiece respirator (such as N95, N99, FFP2/3, or PAPR), two pairs of gloves, full facial protection (either a visor or a face shield), a hairnet, full body water-resistant disposable gown or coveralls and appropriate shoe covers.

Practical Considerations Prior to Undertaking an Endoscopic Procedure

The exact processes to be considered prior to endoscopy may vary according to current local requirements or restrictions. Factors such as the current number of community cases and the vaccination status of the individual are relevant. In addition, the clinical indication for the endoscopic procedure needs to be assessed.

In general terms, however, pre-admission screening conducted by telephone or video consultation is highly recommended (27). Before arrival, patients should be asked the following questions: (1) recent or current fever, (2) recent travel history (especially travel to any country or region with a high incidence of COVID-19 transmission within the last 2 weeks), (3) history of contact with anyone who has respiratory or general symptoms (in the last 14 days) and (4) any clustering. If one or more of these risk factors is present, the patient should be considered to be a suspected case and COVID-19 RT-PCR testing (e.g., nasopharyngeal swab) should be conducted prior to undertaking the endoscopic procedure.

Before entering the waiting room, patients should have measurement of their temperature and the above questions should be asked again. Local social distancing rules should be strictly applied in the waiting area: this may include the use of face masks and appropriate spacing of chairs (27). Children should be accompanied by a maximum of one parent.

In addition, before any clinical examination the attending physician should again ask the patient about any systemic or respiratory symptoms that could be suggestive of active COVID-19 (27). If a patient has a positive or inconclusive RT-PCR test, the procedure should be considered high risk and should only be conducted if the clinical situation demands (27). Furthermore, if a patient has current symptoms or is otherwise at high risk for current infection (**Table 1**), but has such an urgent indication for endoscopy that there is inadequate time to have a nasopharyngeal swab, then their procedure should also be considered high risk (6).

Any endoluminal procedures (such as diagnostic or therapeutic endoscopy or even placement of feeding devices) should be considered potentially high-risk. Before commencing any procedure involving the GI tract it is important to fully assess the necessity and urgency of the procedure. Assessment of the presence of alarm symptoms such as involuntary weight loss, dysphagia, bleeding or obstructive jaundice is highly important (**Table 2**) (24, 27).

Implications of Pre-procedural COVID-19 Polymerase Chain Reaction Testing on Routine Endoscopic Practice

Forde et al. (29) performed 396 PCR tests in patients prior to endoscopy in April and May 2020 in one North American centre. Only one of these patients had a positive PCR result, providing a positive test rate of 0.25% (95% confidence interval, 0.01–1.4%). None of the patients who denied any suggestive symptoms on initial screening and had a negative PCR test failed their immediate pre-procedure questionnaire or body temperature check on the day of procedure. Furthermore, none of the endoscopy staff involved in the management of these patients were diagnosed with COVID-19 or developed symptoms suggestive of infection. The authors concluded that screening questionnaires are an effective tool for the identification of patients at greater risk of infection who should have deferral of their procedure.

Bowyer et al. (30) retrospectively reviewed pre-procedural screening evaluations in a group of 1,000 patients who were scheduled to have an elective outpatient endoscopic procedure between May 22 and June 28, 2020. Key data included demographics, symptoms as reported in the American Society for Gastrointestinal Endoscopy (ASGE) COVID-19 risk preprocedural screening questionnaire, and the results of PCR testing. Eight of the 1,000 patients had positive COVID-19 tests: three of them had reported at least one symptom on the risk screening questionnaire. In addition, 119 patients reported symptoms on the risk screening questionnaire but had negative COVID-19 tests. This assessment of the ASGE COVID-19 risk screening questionnaire provided positive and negative predictive values of 2.46 and 99.43%, respectively. The authors concluded that symptom-based screening alone was not sufficient as a primary preprocedural assessment tool during the COVID-19 pandemic.

Khorrami Minaei et al. (31) performed a retrospective review to assess the usefulness of clinical screening and pre-procedure PCR testing for the identification of high risk patients for SARS-CoV-2 infection. They included a consecutive cohort of 361 patients undergoing endoscopy at a tertiary teaching hospital between 22nd April and 22nd June 2020. Clinical screening, following a defined protocol, detected 13 patients with a high risk of infection (3.6%, 95% CI 2.62–4.58) while the pre-procedure PCR test was positive in five patients (1.40% 95% CI 0.20–2.60). Three patients developed COVID-19 and one died from the disease. Agreement between both strategies was poor, with a Kappa value of 0.093 (95% CI 0.001–0.185). Clinical screening only identified one of the five patients with a positive PCR test. The authors concluded that clinical screening prior to endoscopy has poor agreement with pre-procedure PCR testing.

Say et al. (32) suggested that patient risk stratification before endoscopy should be performed based on symptoms and sick contacts if PCR testing for infection was not available. The authors recommended that urgent procedures should be prioritized. Examples included the removal of foreign bodies, evaluation of gastrointestinal bleeding, and procedures in hospitalized patients. The authors further recommended only performing "essential" procedures in outpatients: these were defined as procedures that would lead to significant patient harm if they were delayed for >2–3 months. Overall, the process to finalize the scheduling and timing of an endoscopic should include discussions and shared decision-making involving the endoscopist, the patient, and the patient's family.

Endoscopic Procedures Involving Patients With Inflammatory Bowel Disease During the COVID-19 Pandemic

Endoscopy is mandatory for patients with a high suspicion of IBD. In patients with a clinical suspicion of Crohn's disease who have a normal endoscopy, visualization of the small intestine is also required. Iacucci et al. (33) addressed the issue of endoscopy in patients with IBD. The authors suggested that in addition to excluding SARS-CoV-2, exclusion of other gastrointestinal infections is also important. They suggested using detailed history and the results of biomarkers to differentiate between IBD and IBS whenever possible.

Iacucci et al. (33) suggested postponing endoscopic assessments in patients who have only mild abnormalities on blood tests and fecal calprotectin (33). In the setting of acute severe exacerbation of known ulcerative colitis they suggested that flexible sigmoidoscopy (at least) should be undertaken if the patient's last colonoscopy was more than 3 months earlier. This assessment would be considered essential to confirm the clinical findings, to define the current extent and severity of disease and to exclude concurrent GI infections (such as cytomegalovirus).

In a similar fashion, Turner et al. (34) also recommended non-urgent endoscopy in children with IBD should be postponed during the pandemic.

Worldwide Impact of COVID-19 Upon Adult and Pediatric Endoscopic Practice

Several authors have assessed the impact of the pandemic upon endoscopy practice. Ruan et al. (35) performed an international survey of pediatric endoscopists across 27 countries. Most of the 145 respondents reported that elective procedures were postponed with a reduction in activity to <10% of usual activity. Although almost all the units were undertaking emergency or urgent endoscopy procedures, only half of the units employed specific guidelines to determine urgency. Furthermore, the units of the respondents differed widely in the use of screening or testing guidelines.

These findings were similar to those reported in adult centers. Forbes et al. (36) conducted a web-based survey of the impact upon endoscopic activity in North American centers in March and April 2020. Two-thirds of the 73 respondents reported a 90% reduction in endoscopy volume. These findings were extended internationally in a web-based survey of endoscopy activity across 252 adult gastroenterology units in 55 countries (37). This study, conducted in April and May 2020, showed a mean reduction of 83% in endoscopy volume across all areas of the world except Australasia, where activity was maintained at ∼40% of normal activity.

Recent studies have demonstrated this impact in specific countries. Issaka et al. (38) retrospectively examined delays in endoscopic procedures in one centre in USA. In the cohort of 480 patients, colonoscopy was most frequently delayed (49%), especially in the setting of colorectal cancer screening. At the time the report was written, less than half of the delayed procedures had been completed, with the diagnosis of 12 cancers eventually made. The median time of delay in those who had undergone their planned procedure was 88 days.

A study conducted in one geographical area of Korea illustrated further impact on endoscopic procedures (39). This retrospective study was conducted in Daegu, a region of Korea with a high case burden at that time. Three hundred and thirty-six emergency procedures conducted over a five and half week period in February and March 2020 were evaluated. The number of cases was less than half of the procedures conducted in the same unit during the same periods in both 2018 and 2019. The patients who were endoscoped in 2020 appeared to be sicker (with a lower hemoglobin), were twice as likely to have endoscopic abnormalities seen and almost five times as likely to need an endoscopic intervention.

These findings appeared to indicate that the triage process at this location enabled the identification of more severe patients and that less severe patients were deferred. The authors did not present any data on adverse outcomes on patients were not triaged to undergo a procedure. They did, however, report that there were no cases of transmission from patients to hospital or endoscopy staff.

Worldwide Impact of COVID-19 Upon Adult and Pediatric Endoscopic Practice

Consequent to the dramatic reduction in endoscopy volume and alterations in patient selection, significant impact upon endoscopy training has also been noted (40, 41). Recently, Shin et al. (42) evaluated the impact upon training for GI fellows in Korea, using a web-based questionnaire. More than half of the 94 respondents noted a reduction in endoscopy sessions and volume, with 78.9% reporting concern about their education and training.

The impact on endoscopy for pediatric gastroenterology fellow training in North America was assessed in a short survey in April 2020 (43). Fellows ceased involvement in endoscopy procedures in 26 of 51 programs that gave replies to the survey. The survey did not assess the impact upon endoscopy procedures over a longer time period.

Nita et al. (44) surveyed 144 young members of ESPGHAN in mid-2020. The COVID-19 pandemic almost universally resulted in adverse impacts upon the endoscopy practice of the respondents. In particular, 82 of the respondents mentioned restrictions to semi-urgent or emergency endoscopy procedures.

One consequence of the pandemic is a move from face-to-face to virtual interactions when feasible. This has also occurred in the setting of trainee interviews (45). An assessment of satisfaction with this mode of interviewing showed generally high acceptance and satisfaction.

The changes in endoscopy practice have also resulted in the development of innovative technology. These include new shielding devices (46) and even the use of robotic endoscopic processes (47). More recently, Furukawa et al. (48) described their development of a surgical mask designed to prevent spread of droplets from a patient undergoing an upper endoscopic procedure. The authors demonstrated a marked reduction in droplets using specialized imaging technique. Other novel devices include the Endoprotector (49), the C-Cube (50), the ORIGAMI face shield (51) and an endoscopic shield (52). These innovations have not been evaluated specifically in children.

Ongoing Repercussions of COVID-19-Related Changes in Endoscopic Activity

Even though the first waves of the pandemic have passed, the repercussions persist. Ho et al. (53) attempted to predict the recovery of disrupted endoscopy activity in England using national data from prior to the pandemic to the end of October 2020. The analysis indicated that there would be a backlog of almost 500,000 endoscopic procedures by January 2021. The authors further predicted that elimination of this backlog would take until mid-2022 even with an increase in capacity to 130% of normal. Further and ongoing interruptions would only exacerbate this impact and delay catch-up substantially.

CONCLUSIONS

The COVID-19 pandemic has had a global adverse effect on humanity, with significant morbidity and mortality. While healthcare services have been greatly impacted overall, due to diversion of resources to care for those diagnosed with COVID-19, there have also been great impacts on endoscopy procedures. The predicted flow-on effects of a reduction in endoscopic activity have included consequences such as longer diagnostic delay and reduced training opportunities.

Much of the data available reflects regional and time-related differences in infection rates and consequent variations in practice. As the effects of the waves of infection wax and wane, so to will the direct impacts. These features of the pandemic do impact on the way that endoscopy services are conducted in various locations and countries. None-the-less, depending on the course of the COVID-19 pandemic over the coming months, there will likely be further impacts on endoscopy services.

AUTHOR CONTRIBUTIONS

RS and AD contributed to all aspects of the preparation of this manuscript and have reviewed and approved the final version of the manuscript. Both authors contributed to the article and approved the submitted version.

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Therapeutic Upper Gastrointestinal Endoscopy in Pediatric Gastroenterology

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This paper seeks to give a broad overview of pediatric upper gastrointestinal (GI) pathologies that we are now able to treat endoscopically, acquired or congenital, and we hope this delivers the reader an impression of what is increasingly available to pediatric endoscopists and their patients.

Keywords: endoscopy, therapeutic, pediatric, emergency, bleeding, varices, foreign body (FB), reflux

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INTRODUCTION

The last 50 years has witnessed an explosion in what is therapeutically feasible *via* an endoscope in the gastrointestinal (GI) tract. This paper seeks to give a broad brushstroke of pediatric upper GI pathologies that we are now able to treat endoscopically, acquired or congenital and we hope this delivers the reader a taste of what is increasingly available to pediatric endoscopists and their patients.

EMERGENCIES IN UPPER GI ENDOSCOPY

Upper GI Bleeding (UGIB)

In the case of UGIB, endoscopy is often the intervention of choice as it is both diagnostic and therapeutic (1). However, procedures might require advanced endoscopy skills for efficient hemostasis and should therefore only be undertaken by experienced endoscopists, who have the ability to perform therapeutic procedures. This was true prior to the advent of topical hemostatic substances—but more of that later. Emergency endoscopy should not be realized in a hemodynamically unstable child and preferably performed after complete resuscitation within 12 h of admission in the case of variceal bleeding and within 24 h for non-variceal bleeding. If endoscopy is performed in the first 24 h after onset of symptoms, the chance to detect a bleeding lesion is over 80% but decreases significantly to <40% if performed after 48 h (1).

In adults, well-validated and robust scoring systems, like Rockall, Blatchford, and Forrest, have revolutionized the endoscopy intervention in UGIB (2). Based on parameters such as urea level, age, presence of comorbidities, and presence of "shock," these scoring systems identify not only patients at high risk (of repeat bleeding, need for blood transfusion, surgical intervention, and mortality), who require immediate endoscopic intervention, but also those patients of low risk, helping to avoid unnecessary endoscopies and interventions. These scoring systems are unfortunately not applicable in the pediatric population, as its hematological, biochemical, and physiological parameters differ from those of adults, with different values between age groups. Thomson et al. developed a scoring system to predict the need of endoscopic hemostatic intervention. It includes a total score of 24, involving history, clinical assessment, laboratory findings, and management and resuscitation, with a cutoff for intervention at 8 (**Table 1**). This "Sheffield scoring system" had a positive predictive value (PPV) of 91.18%, a negative predictive value (NPV) of 88.57%, and a sensitivity and specificity of 88.7 and 91.18%, respectively (2). Such scoring systems are extremely useful in identifying which child should receive potentially life-saving endoscopic hemostatic treatment.

Variceal Bleeding

Esophageal Varices (EVs)

In advanced liver disease or portal vein thrombosis leading to portal hypertension, EVs are a common finding in children. Fortunately, EV rupture and associated mortality are rare in children, compared with the adult population, but may result in significant bleeding and represent a life-threatening condition which requires emergent endoscopic evaluation (3). The aim of endoscopic intervention is not only the cessation of EV bleeding but also the reduction of the variceal wall tension (by obliterating the varix), to prevent further bleeding episodes (4). However, treatment of variceal bleeding remains a challenging intervention even for experienced pediatric endoscopists, with potentially high complication rates, as described in the King's College Hospital report, with a complication rate of 37%, using banding, sclerosants (76%), or both in their study population (5). Complications include esophageal ulcers, esophageal strictures, and erosive gastritis. To date, there have been various techniques for EV treatment, which are discussed below.

Banding. This is the first choice for EV bleeding, as meta-analyses have shown it to be superior to sclerotherapy in terms of higher eradication rates and lower rates of rebleeding and complications (6). Banding consists of the placement of rubber rings on the variceal column by sucking the varix into the plastic cylinder, attached to the tip of the endoscope (**Figure 1A**). In active bleeding, the focus should be on the point of bleeding, and inaccurate bands applied do not cause adverse events—in comparison to sclerotherapy (4). Originally, banding devices allowed the application of only one band at a time, which required reloading with each subsequent band ligation. Now, however, multiple band ligators may be applied at one intubation, which means that four to seven bands can be sequentially deployed without the need for repetitive intubating or the use of an overtube. These are manufactured for use with the adult-sized scopes and added with an extra 2–3 mm to the diameter, limiting its use in children younger than 12 months or under 8 kg.

The ligated tissue with the rubber band may fall off between 1 and 10 days after the procedure (4). It is therefore crucial to inform the family about the increased risk of bleeding recurrence during this time span. Repeat endoscopy before discharge is considered advisable in cases of acute bleeding.

Sclerosants. The use of variceal injection (**Figure 1B**) is less popular in the pediatric population and is only usually indicated in younger children, where banding is difficult due to the diameter of the scope exceeding the esophageal diameter—specifically the cricopharyngeal narrowing. Efficacy and complication rates vary among pediatric studies. Eradication varies between 11 and 87% in different studies (3, 7). Complications related to sclerotherapy are esophageal ulcers, strictures, and erosive gastritis (8).

Various sclerosing agents are available and can be classified as follows:

- Synthetic (sodium tetradecyl sulfate 1 and 3%, polidocanol 0.5–3%)
- Fatty acid derivatives (ethanolamine oleate 5%, sodium morrhuate 5%)
- Alcohol (ethanol 99.5%, phenol 3%)
- Sugars (hypertonic 50% dextrose solution).

Individual discussion of the pros and cons of these agents is beyond the scope of this article.

Gastric Varices

Injection of Histoacryl "glue" is the technique of choice, although complications such as fever, infection, gastric ulcer, damage to/blockage of the endoscope, perforation, and peritonitis can occur (9). There is a non-negligible risk of embolization of collateral vessels or other organs, in particular if an insufficient amount of cyanoacrylate has been injected (9). As in adults, embolization is a potential risk, with a higher risk for systemic embolization in case of the presence of a right-to-left intracardiac communication such as an atrial or ventricular septal defect (10).

N-Butyl-2-cyanoacrylate (*n*-BCA, NBCA) is an efficient injection substance in acute esophageal and gastric variceal bleeding and for obliteration of fundal varices (**Figure 1C**). In children, the use of the glue injection technique has been utilized in infants in whom the diameter of the esophagus may preclude introduction of the banding devices, and in pilot studies, it seems effective and safe in the short term, with a rebleeding rate of 3/8 young children under 2 years old within 12 weeks (11). The main complication was rebleeding resulting from extrusion; the prognosis of the patients depended on the severity of the underlying liver disease (12). Other side effects include glue extrusion and potential damage to the biopsy channel of the endoscope minimized in skilled hands. This

TABLE 1 | Sheffield Scoring System.

History taking
Significant pre-existing condition: 1
Presence of melaena: 1
History of large amount of hematemesis: 1
Clinical assessment
HR > 20 (from mean HR for age): 1
Prolonged CRT: 4
Laboratory findings
Hb drop > 20 g/L : 3
Management and resuscitation
Need for fluid bolus: 3
Need for blood transfusion (Hb < 80 g/L): 6
Need for other blood product: 4
Total score: 24
Cut-off: 8 (> 8 considered as threshold for intervention)

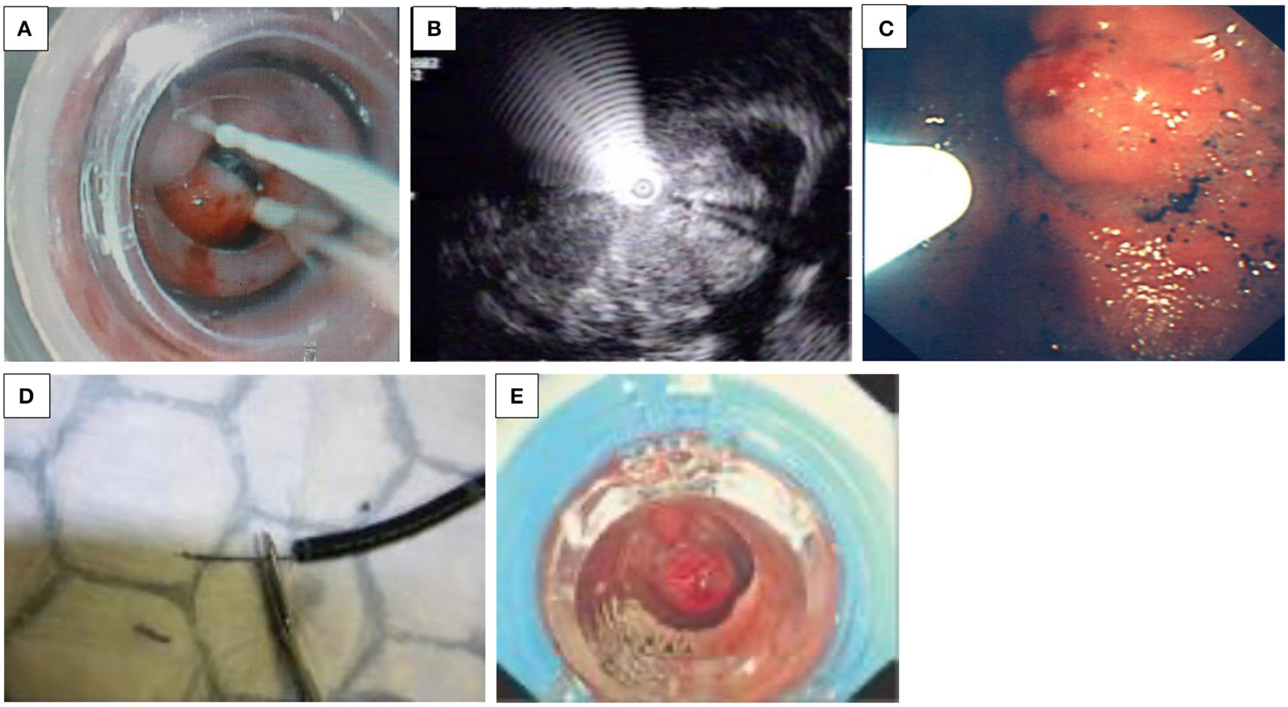

FIGURE 1 | (A–E) Endoscopic treatment of variceal bleeding. **(A)** Banding of esophageal varices. **(B)** Echo-endoscopic vision of needle injection of an esophageal varix. **(C)** Injection of glue into a fundal varix. **(D)** An inadvertent introduction of glue into the biopsy channel is prevented by cutting the catheter tip off. **(E)** Banding of jejunal varix.

certainly dictates that the operator employs great care when performing this procedure. As **Figure 1D** demonstrates, the ideal technique following glue delivery is to cut the catheter tip off with any extraneous glue attached before withdrawing through the biopsy channel, while maintaining suction to prevent inadvertent introduction of the glue into the biopsy channel. Thrombin may be used, and patients usually receive one to four sessions of thrombin, with a mean total dose of approximately 10 ml for variceal eradication (13).

Intestinal Varices

Recurrent UGIB due to intestinal varices is rare. Apart from portal hypertension, intestinal varices can develop after intestinal surgery, by accidental venous occlusion, by microthrombi, or by accidental ligature during surgery, leading to the development of collateral vessels. While they account for up to 5% of all variceal bleeding in adults with portal hypertension, to date, only a few case reports exist in the pediatric population. Belsha and Thomson reported an 8-year-old with jejunal varices with short-bowel syndrome after multiple surgeries for gastroschisis and duodenal and colonic atresia, which was successfully treated by banding (**Figure 1E**) (2).

An alternative is radiological coil stenting as surgical intervention would include the resection of the reanastomosis, which might be challenging due to adhesions secondary to repeated surgical interventions.

Non-variceal Gastric and Small-Bowel GI Bleeding

UGIB related to lesions in the stomach include, among other pathologies, diffuse hemorrhagic gastritis, Dieulafoy's lesions, other angiodysplasias, and peptic ulcer disease (PUD). The incidence of PUD in children is much lower than in the adult population, varying between 2 and 8% and between 0.5 and 4.4 of 100,000 individuals in case of UGIB (14). There are various treatment options for GI bleeding, including injection of sclerosing or hemostatic agents, thermocoagulation techniques, and different clip devices. Epinephrine (1:10,000–1:100,000) can be used in acute situations in order to identify the source, but it must be remembered that vasoconstriction and tamponade effects only last for 10–15 min, and it is therefore not to be used without more definitive subsequent therapy. Thermocoagulation techniques include monopolar and bipolar coagulation, argon plasma coagulation (APC), and laser photocoagulation. As these are well-described in textbooks, we will hence concentrate on more recent therapeutic developments (8).

Over-the-scope Clips (OTSC®)

OTSC® are now used in non-variceal bleeding, anastomotic dehiscence, perforation, and fistulae closure (e.g., IBD and post-gastrostomy removal). It is often proposed as the final option in endoscopic treatment before surgery (15). The OTSC® system is composed of four components, including a grasper/clip device, a twin grasper, an "anchor" forceps, and a stiff tissue "brush." The OTSC® is attached on the tip of the endoscope, similar

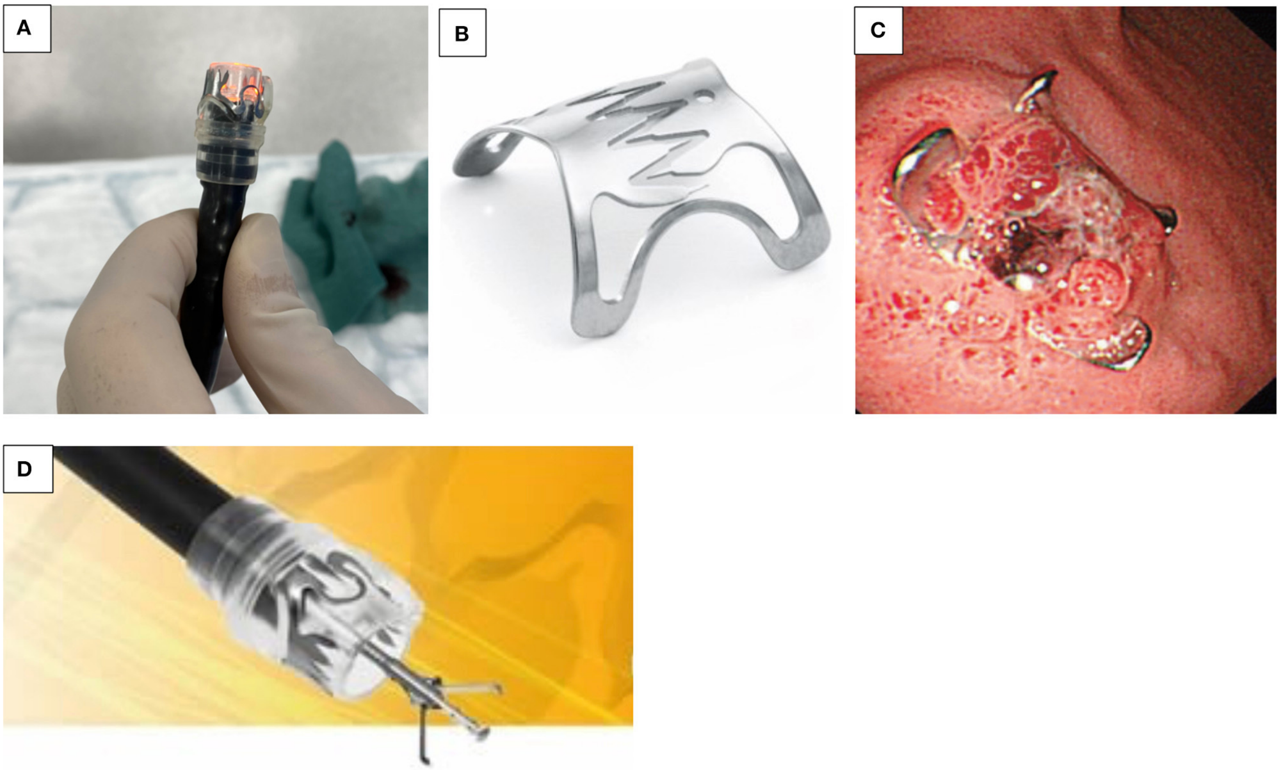

FIGURE 2 | (A–D) Over the scope clip (OTSC®). **(A)** OTSC® attached to the tip of the endoscope. **(B)** Grasping device of the OTSC®. **(C)** OTSC® with its effective anchor mechanism. **(D)** Mucosal healing after OTSC® application.

to variceal banding devices (**Figure 2A**). When compared to "through-the-scope" hemostatic clips, the primary benefit of its use in UGIB appears to be related to a combination of stronger tensile grasping strength of the jaws of the clip, a more effective anchor mechanism, and an improved size of tissue bite (**Figures 2B,C**). Additionally, the inter-clip space allows a continuous blood flow to the grasped tissue, preventing tissue necrosis during the tissue healing process (**Figure 2D**). In case of improper application, the novel alloy of the clip, Nitinol®, can be easily detached by the passage of electric current, with the aid of a specifically designed endoscopic cutting device. There are different sizes available, the smallest with a diameter of 8.5–9.8 mm, resulting in an intubation diameter of 14.6 mm, which is an issue in younger children. Kobara et al. recently reviewed a total of 1,517 OTSC® cases with an average clinical success rate of 78%. In the case of anastomotic pathology, efficacy for prevention of rebleeding was 85%, and for fistulae, effective closure was 52% (15). A case series of seven pediatric patients has been reported (16).

Topical Hemostatic Endoscopic Approaches for GI Bleeding

Endoscopy for UGIB remains a challenging intervention, even for experienced endoscopists, as the incidence in children is relatively rare. A recent nationwide survey in the United Kingdom revealed that in the 16 tertiary Centers of Pediatric Gastroenterology, only 19% claimed that all their consultants were proficient in all endoscopic hemostatic techniques. Indeed 19% admitted that those interventions were beyond the technical capability of *any* of their staff. Only just over a half of the centers had an out-of-hours call service, of which 69% was covered by pediatric surgeons, who were also often unfamiliar with most of the techniques required (17). In this regard, a technique which is easily accessible even for less-experienced endoscopists is extremely valuable. Topical approaches lend themselves to lowering the threshold of endoscopic competency as they are so easy to apply—this may allow a wider and earlier hemostatic option.

A hemostatic spray (Hemospray®) is now licensed for non-variceal UGIB in the adult population in United States, Canada and Europe and has a CE mark (European approval) for its use in children (**Figures 3A–D**).

It is a highly absorptive, inert mineral powder, which functions as a mechanical tamponade by coagulation with the active GI bleed through the increase of clotting factors and the activation of coagulation cascade, resulting in immediate clotting (**Figure 3B**) (18). Besides its easy handling, one of its advantages is expeditious coverage of large surfaces (**Figures 3C,D**). However, the endoscope channel should be vigorously flushed with air prior catheter insertion as contact with any moisture might block the Hemospray® catheter, making it unusable (17).

A recent meta-analysis of 11 prospective adult studies reported acute hemostasis of 93% in UGIB with 14.4% risk

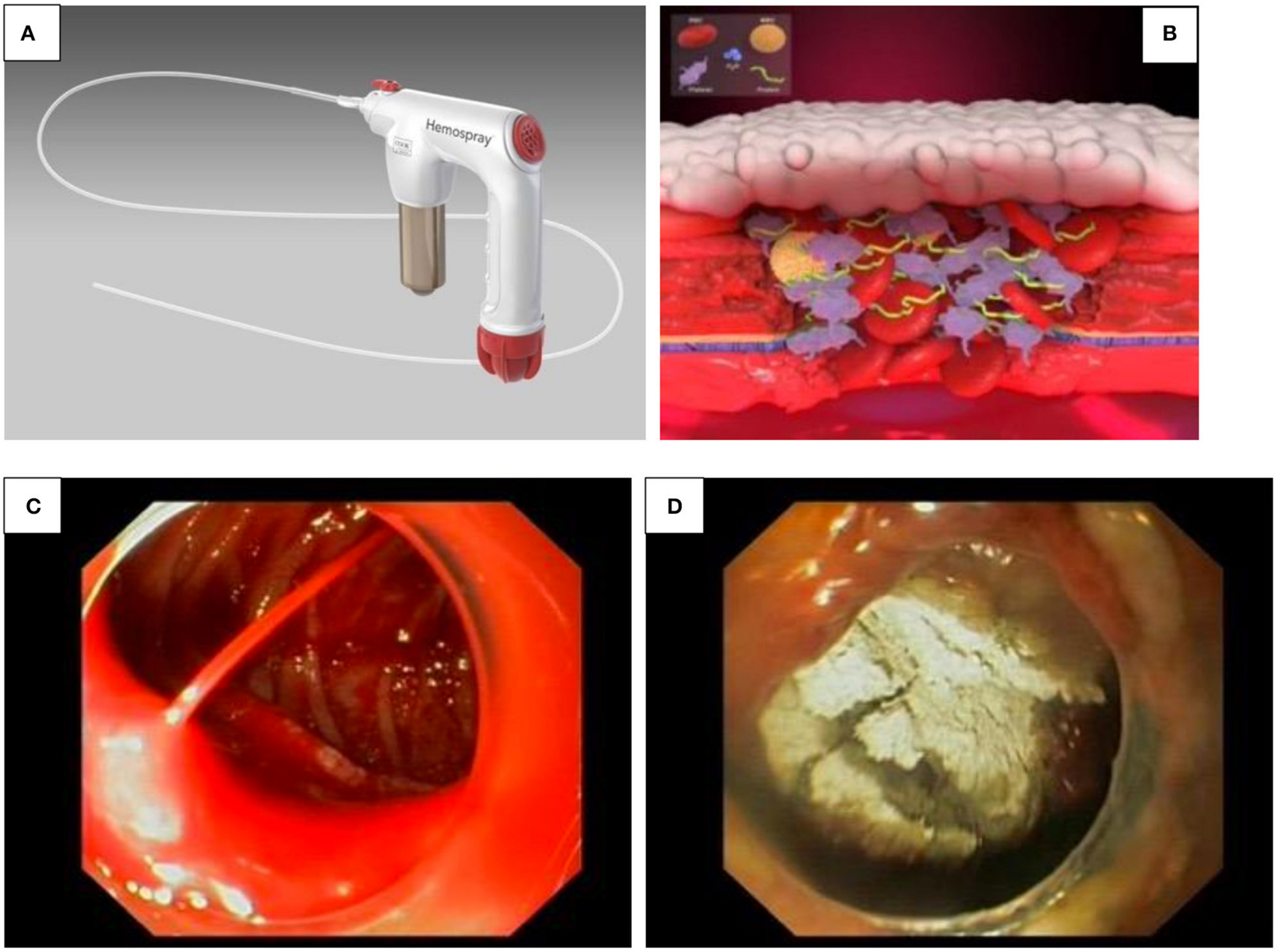

FIGURE 3 | (A–D) Hemospray®. **(A)** Hemospray® device. **(B)** Activation of the coagulation cascade by Hemospray® results in immediate clotting. **(C,D)** Significant GI bleeding before **(A)** and after Hemospray® procedure **(B)**.

of rebleeding episodes. Hemostasis was nearly as successful in variceal bleeding with a rate of 92.7% and a rebleeding rate of only 3.1% (19). Another meta-analysis reviewed the efficacy of Hemospray® in non-variceal UGIB and found a technical success in 97% of the cases treated with Hemospray®. In particular, in more recent studies (2011–2019), this compared favorably to 87% for other hemostatic measures (18). Thomson et al. prospectively enrolled 17 patients treated with Hemospray® for UGIB and compared them to a second group, where conventional endo-hemostatic treatment had been applied. Both groups had achieved initial hemostasis in 100%, with 18% rebleeding in the Hemospray® group, compared to 24% in the conventional group. The failure rate was also similar, with 6% for the former group vs. 7% for the latter (17).

Two new products, PuraStat (20) and EndoClot Plus (powder form), help reduce delayed bleeding following procedures such as GI endoscopic submucosal resection in the colon. EndoClot Plus (powder form) has also been used for treatment of bleeding ulcers (21).

Foreign Body (FB) Ingestion

The management of FB ingestion can be a challenging situation for the pediatric gastroenterologist who has to determine the indication and timing for endoscopy, based on sometimes imprecise history, symptoms, and radiology.

This is usually in the under 5-year-old age group. FBs can be categorized in subgroups, such as blunt (e.g., different types of coins and toys), pointed/sharp (safety pins, nails, toothpicks, and hairpins), toxic (button batteries, magnets, drug packets, and caustics), and food impaction. Timing of endoscopy should be based on the clinical status, type and size of the FB, and if possible, the time of ingestion, last oral intake, and the location of the FB in GI tract.

Expert panels from Italy, ESPGHAN and NASPGHAN, suggested categories, with emergent (<2 h), urgent (<24 h), and elective (>24 h) (22–24). Depending on the FB and the age and size of the child, devices such as retrieval Roth nets, forceps (rat-tooth and alligator) polypectomy snares, tripod forceps, latex cones, and overtubes are used. To date, there are no pediatric studies comparing different retrieval devices (22). If the patient exhibits any signs of respiratory compromise, crepitus, neck swelling, or perforation, surgical consultation is mandatory (22–24).

Blunt Objects

Coins have been reported to be the most ingested object over a 10-year period in the United States, with over 250,000 ingestions with 20 deaths reported in younger children (<4 years old) likely related to airway blockage with a small coin (23). Depending on the size of the coin and the size of the patient, 30–60% may spontaneously pass through the esophagus into the stomach. Prior to endoscopy, biplane radiographs should be performed with careful inspection of the edges of the coin, to exclude a double-halo sign, which is suggestive of button battery (BB) ingestion, requiring immediate removal. Coins stuck in the esophagus should be removed within 24 h, in order to prevent esophageal injury or erosions into neighboring structures. However, if the child is unable to manage secretions or develops respiratory distress, then emergent retrieval is indicated (22–24). The coin or FB can be grasped with alligator-jaw forceps or rat-tooth forceps and retrieved back into the mouth; sometimes, however, it might be easier to gently push the FB into the stomach and grasp it there. If the coin/FB is located in the distal esophagus and endoscopy is not available, subcutaneous injection of glucagon might be used to relax the lower esophageal sphincter (LES) with spontaneous passage of the coin into the stomach. However, study results have been equivocal (24).

Once in the stomach, emergent endoscopy is generally not indicated for blunt objects except for those considered unlikely to pass the pylorus, e.g., between >2 and 3 cm for children younger than 1 year and between >3 and 5 cm for children older than 1 year (22–24).

Pointed/Sharp Objects

The incidence of pointed or sharp FB ingestion has been reported to be between 11 and 13% in European and Asian centers (**Figures 4A–E**) (23). If the FB is located in the upper/mid esophagus, symptomatic ingestion tends to present with pain and dysphagia; however, up to half of the children can remain asymptomatic for weeks. Ingestion of toothpicks and bones are associated with a higher risk of perforation and are the most common FB requiring surgical removal (22). The main reported complications are perforation, migration into neighboring organs (liver, heart, lung, and bladder), abscess, and peritonitis, with the most common site of perforation being the ileocecal region (23). Prior to endoscopy, radiographic evaluation is crucial as it has a positive predictive value of 100% for metallic objects, but only 43% in glass and 26% in fish bones (**Figures 4A,B**) (23). If located in the esophagus, retrieval forceps, Roth nets, or polypectomy snares are useful retrieval accessories. However, if the sharp tip of the object is facing upwards, it might be safer to gently push the object into the stomach and retrieve it with the sharp part pointing downwards. Beyond the esophagus, an FB protector hood is a useful tool. It is attached to the tip of the endoscope and can be turned inside out by rubbing against the gastric mucosa (**Figure 4E**). The FB is then grasped with forceps or a polypectomy snare and then withdrawn into the protector hood and can then be safely removed. If the FB is located beyond the ligament of Treitz, either enteroscopic removal (if available) or surgery can be an option. If the patient is asymptomatic, observational monitoring might be considered but would need close follow-up with daily abdominal X-ray to assure continuous passage. It has been reported that the average transit time for FB in children is 3.6 days, whereas perforation occurred at a mean time after 10.4 days. Therefore, in case of non-progression after 3 days, surgery should be taken into consideration (22, 23).

Toxic Objects and Liquids

Magnets

While single magnets do not require endoscopic removal, the ingestion of two or more magnets presents an increased risk for the creation of an entero-enteric fistula between magnets located in adjacent bowel loops, leading to perforation, peritonitis, and necrosis, and these should therefore be removed. There has been an alarming report of The National Electronic Injury Surveillance System database in the United States, showing >16,000 estimated magnet ingestions in children between 2002 and 2011, which signifies an 8.5-fold increase of the incidence of magnet ingestion in children (23). It is therefore imperative to determine the number of magnets in the GI tract by obtaining at least two radiographic views of the chest or abdomen. Endoscopic retrieval nets are the best option for small round magnets. If conservative management is opted with an asymptomatic patient, daily abdominal X-rays should be performed, and in the case of non-progression, surgical intervention is the treatment of choice if enteroscopy is unavailable.

Button Batteries

BB ingestion accounts for between 7 and 25% of FBs ingested by children, most of them younger than 6 years, with a peak at 1 year of age. The incidence of BB ingestion has increased worldwide over recent years, and larger and more powerful batteries lead to a significant risk of severe morbidity and mortality, especially when impacted in the esophagus juxtaposed to large vessels—which has increased sevenfold in the last 20 years (25). When the BB comes in contact with the mucosa of the esophagus, the tissue serves as a conductor between the two battery poles, leading to H^+ formation at the cathode, which results in the increase of pH with tissue liquefaction and necrosis. Damage might go beyond the esophageal wall, leading to fistulization into adjacent structures such as the trachea, aorta, and subclavian artery with sometimes life-threatening complications (22–25). Unfortunately, severe damage can already occur within 2 h after the first tissue contact. This is the reason why BB ingestion with impaction in the esophagus is *THE* emergency for a pediatric endoscopist *per se* and should not be delayed. Larger and newer BBs pose a greater risk for the creation of severe lesions, and even old batteries have the capacity to create a sufficient voltage to cause damage (25).

Biplane radiographs including the entire neck, chest, and the abdomen should be performed, and the image should be closely inspected with recognition of the "double-halo sign," as well as the step-off side, visible on the lateral film, indicating the cathode of the BB, which is the part causing most of the

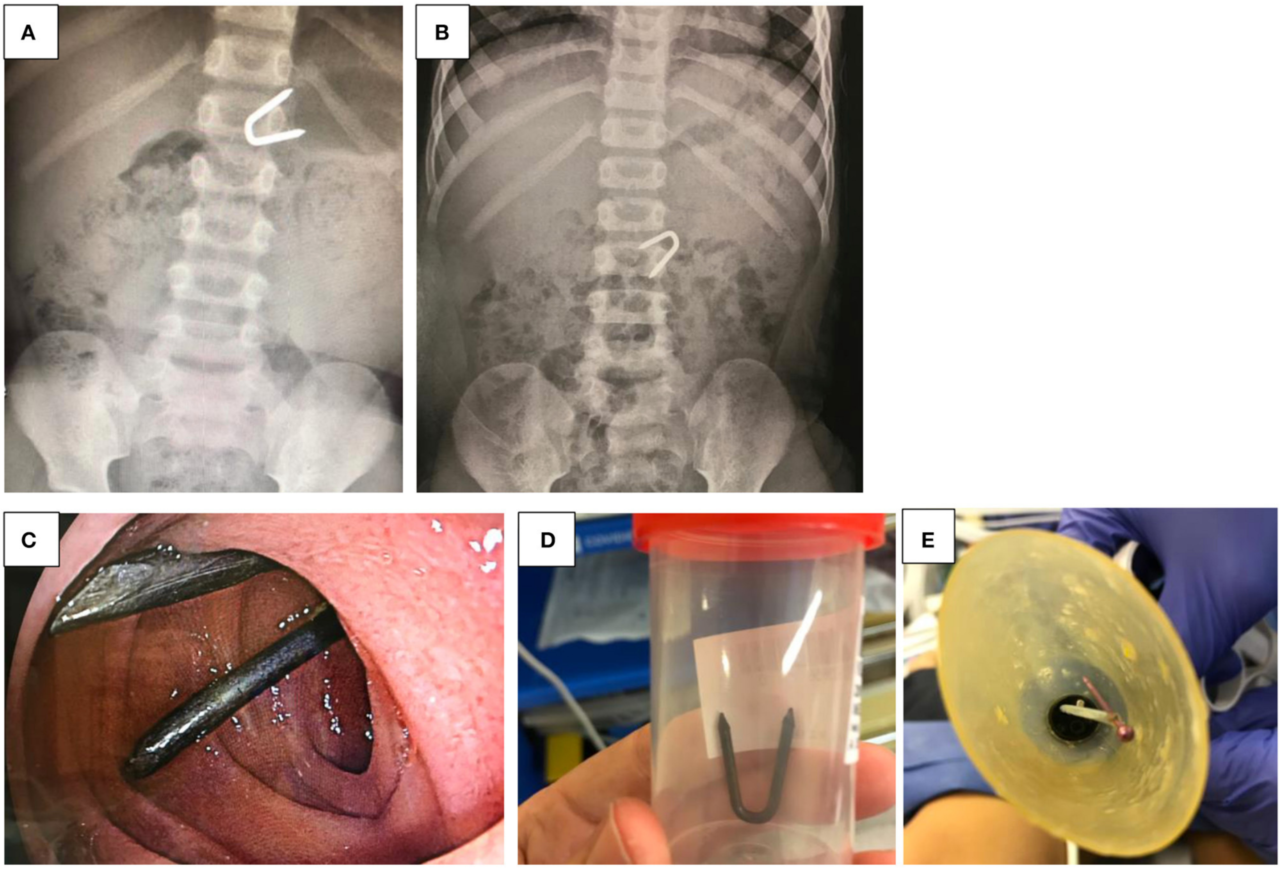

FIGURE 4 | (A–E) Ingestion of a pointed foreign body. **(A,B)**. Abdominal x-ray of a pointed foreign body ingested by a 5-year old child. **(C)** Foreign body in the mid-duodenum. **(D)** FB after successful extraction with a retrieval forceps. **(E)** Foreign body (pin to fasten clothing) which has been grasped *via* a polypectomy snare and withdrawn into a protector hood.

damage. A CT scan with contrast is usually indicated, especially in the case of delayed diagnosis with doubt about already-existing complications. This may need to be repeated the next day as aortic aneurysm may be delayed in its appearance.

Endoscopy should be performed, if possible, in the presence of a pediatric cardiothoracic surgeon, especially in the case of delayed diagnosis and a battery held up at the level of the aortic arch with esophageal ulceration at endoscopy. In the case of proximal localization, tandem work with the ENT team might be indicated. During endoscopy, meticulous inspection of the esophageal mucosa for localization, extension, and depth of the lesion is mandatory. If possible, the direction of the cathode (side without the "+" and without the imprint) should be determined, as it is generally the most affected site. The BB can be extracted either with a rat-tooth or alligator forceps or by using a retrieval net. If on X-ray the BB is already located in the stomach, endoscopic removal is only advised if it remains there after 7–14 days, as most of the BBs will pass the stomach during this period, rarely causing complications (25). If however the BB exceeds 20 mm, then spontaneous gastric passage is less likely, and therefore, these should be removed if still in place after >48 h (22).

In the case of severe lesions, repeat endoscopy should be performed at 24–48 h post-removal. Esophageal lesions can occur very quickly, but the development of complications may be delayed. If the anterior wall of the esophagus is affected, vascular and tracheal injuries are of great concern, whereas lesions in the posterior wall might lead to spondylodiscitis. Perforation generally appears within a 48 h time frame. Fistulization can even occur 4 weeks after removal, and other complications such as spondylodiscitis or laryngeal nerve damage can even take several weeks to months to occur (25). Horner's syndrome has also been reported as a complication of BB ingestion (26).

Caustic Ingestion

Fortunately, with the advent of child-unfriendly packaging of domestic products (such as detergents, softening, and dissolving agents), accidental ingestion of caustic products has significantly decreased in children (22). However, if agents are stored in non-original containers, ingestion of higher volume is possible, also called "accidental-deliberate ingestion," leading to potentially life-threatening conditions (24). The role of endoscopy is initially of pure diagnostic nature; following the Zargar classification (**Table 2**), esophageal lesions are classified as absent/mild till

TABLE 2 | Zargar classification.

Grade	Endoscopic finding
0	Normal
I	Edema, hyperemia of the mucosa
IIa	Friability, hemorrhage, erosion blisters, exudates or whitish membranes, superficial ulcers
IIb	Grade IIa and deep discrete or circumferential ulcers
IIIa	Small scattered areas of necrosis, areas of brownish-black or gray discoloration
IIIb	Extensive necrosis

severe, and the subsequent treatment will be adapted following the Zargar grade, in order to prevent future complications, such as esophageal strictures.

Other

Food Impaction

Compared to data in the adult population, where food bolus is the most common type of impaction, data in children are sparse (22–24). However, in most of the few studies existing, food bolus impaction in children tend to be secondary to underlying conditions, such as esophageal or reflux esophagitis, anastomotic strictures, achalasia, or other motility disorders.

If clearance is not spontaneous and the child cannot manage to secrete the impacted food, endoscopy should be performed in up to 24 h but may require urgent intervention if signs of near-complete obstruction occur (drooling and neck pain). Approaches like piecemeal or repetitive suction might be required. The latter can be performed by using the transparent cap of an EV banding device, which has been proven efficient in suctioning larger pieces of meat impaction (23). In some situations, a gentle push of the food bolus in the stomach might be an option but should only be performed if there is definite direct visualization of the esophageal lumen, as esophageal strictures or FB impaction might be present. Perforation can occur in up to 2% of the cases (24). After successful retrieval, esophageal biopsies are mandatory for the diagnosis of a potential underlying pathology. Hence, dilation may be delayed, contingent on the pathology leading to the impaction (22–24).

Gastric Bezoar

A bezoar is defined as a mass of accumulated substance found trapped in the GI tract, mostly in the stomach. The overall incidence of bezoars in children is unknown, and to date, only few studies exist, most of them case reports or case series. There are several types of bezoars with phytobezoars (composed of plant and vegetable components) being the commonest type (27). In comparison, trichobezoars are composed of hair, undigested fat, and mucus. The hair may come from the patient, other humans, animals, carpet fibers, or blankets. Hair fibers tend to get trapped in gastric folds, resisting peristalsis, as they are slippery.

One variant of trichobezoars is the "Rapunzel syndrome." This is a trichobezoar extending from the stomach into the small intestine, sometimes even involving its entire length. The twisted hairs can become hard like a wire. There are reports in which these can cause compression of the mesenteric wall of the intestine, occluding the blood supply and resulting in pressure necrosis and perforations (**Figures 5A–C**) (28, 29).

The current management of gastric bezoars include dissolution (either by Coca-Cola beverages, cellulose, or papain), endoscopy, or surgery (laparoscopic and open) (27). With the help of an endoscope, the bezoar can be separated into smaller pieces using a polypectomy snare, biopsy forceps, directed water jets, injection of enzymes (papain and cellulose for phytobezoars), or mechanical lithotripsy (bazotome, a needle knife device, or bezotriptor, a lithotriptor), a device commonly used for the treatment of large bile duct stones (**Figure 5D**) (27, 30). Once the bezoar is broken into smaller pieces, these can then be either removed endoscopically or allowed to pass through the pylorus.

In a recent case series of 30 pediatric patients with gastric bezoars (one trichobezoar and the rest phytobezoars), the majority was removed by endoscopy, using a retrieving net (Roth net), generally requiring multiple passes (6–20). Four patients (13%) required surgery. Of note was a high prevalence of underlying GI disorders and dysautonomia in 20% of the children, suggesting that both are risk factors for gastric bezoars in children.

Even if the above-mentioned reports suggest a successful treatment of bezoars *via* endoscopy, endoscopic devices should be used cautiously. It is also important to know what is the constituent substance of the bezoar (31).

ELECTIVE THERAPEUTIC UPPER GI ENDOSCOPY

Endoscopic Treatment of Pediatric Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux (GER) is a common phenomenon especially in young infants and resolves in the vast majority in the first 2 years of life (32). However, if GER leads to troublesome symptoms that affect daily functioning and/or complications, it is defined as GERD (33).

If GER becomes GERD, management aims to achieve symptom relief while preventing complications. Patients who fail to achieve control with conservative methods may have persistent severe esophagitis or become dependent in the long term on anti-reflux treatments. In such cases, an anti-reflux procedure may be indicated (34). The principle of surgery in GERD is to reconstruct an anti-reflux barrier, although exactly how efficacy is achieved is not fully understood. Among several technical variants, the Nissen fundoplication is the treatment of choice to date. Its initial open approach has been replaced by laparoscopy since the early 1990s, but superior efficacy and safety have yet to be demonstrated in the pediatric population (35). In adult studies, complications are less commonly reported, success rate is good, and the laparoscopic procedure cosmesis is clearly superior (36, 37). Therefore, it could be argued therefore that there remains little or no place for open anti-reflux procedures in pediatrics.

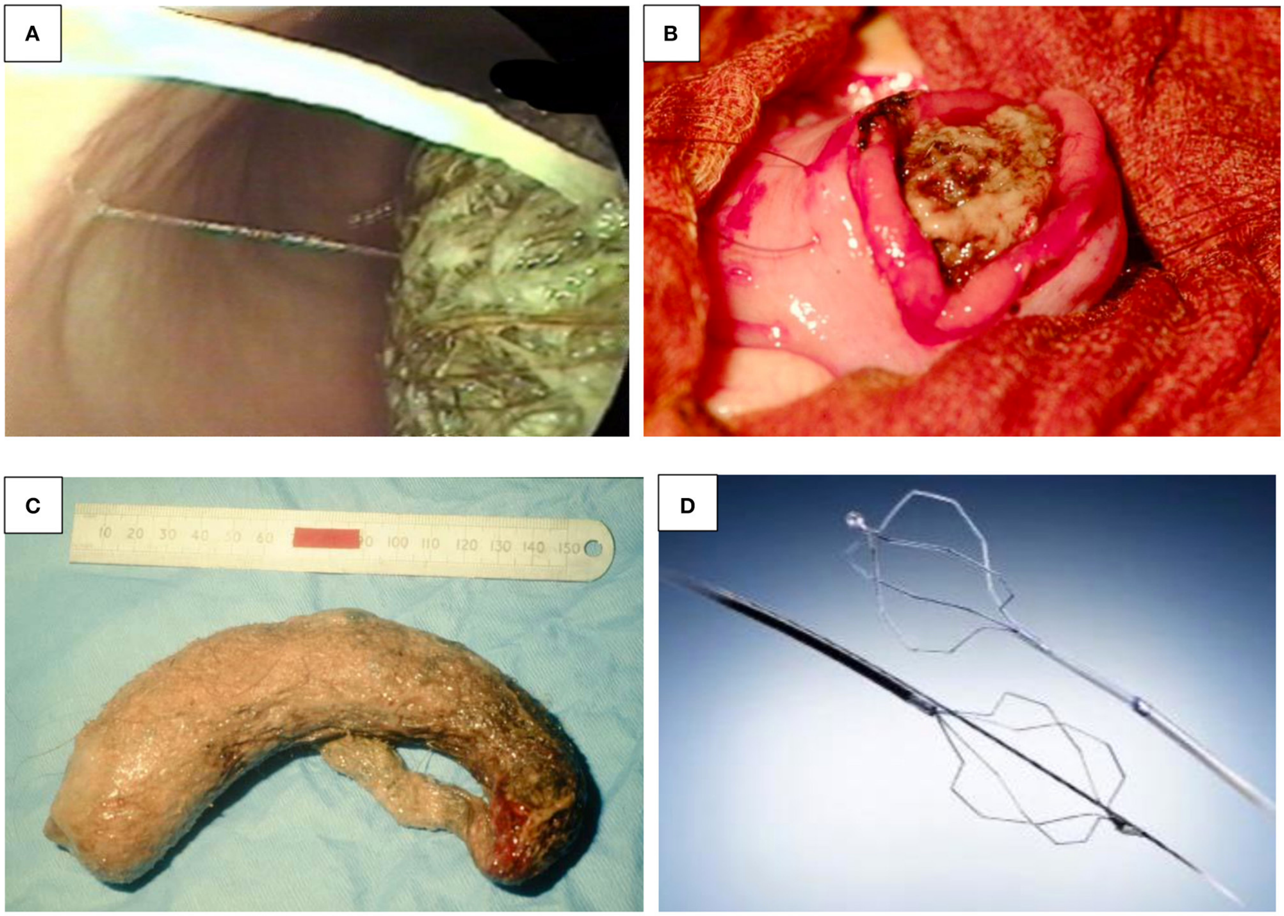

FIGURE 5 | (A–D) Bezoars. **(A)** Bezoar seen at endoscopy. **(B)** Surgical removal of the bezoar from the same patient. Endoscopic removal wasn't possible. **(C)** A large bezoar removed. **(D)** Bezotriptor/Lithotriptor device.

A number of endoscopic techniques have been devised and used for treatment of pediatric GERD. These are described below.

Endoscopic Suturing Devices

Various endoscopic techniques have been developed in recent years, aiming to improve the function of the gastroesophageal junction (GEJ) to prevent GERD. We will briefly illustrate the different endo-suturing techniques, as most of them are now not used and most operators have translated their efforts on to Stretta® (see below).

The EndoCinch Device

EndoCinch is one of the historical endoscopic sewing systems, attached to the endoscope for the use of endoluminal gastroplication. Three pairs of stitches were placed below the GEJ, creating three internal plications of the stomach (38–40). According to the operator's preference, those plications may be applied in any manner, circumferentially or longitudinally (**Figures 6A–C**) (41). This is now historical.

Trans-oral Incisionless Fundoplication (TIF)

The TIF procedure using EsophyX mimics anti-reflux surgery in constructing an anterior partial fundoplication with tailored delivery of multiple fasteners during a single-device insertion (**Figures 6D,E**). The TIF procedure was designed to restore the anti-reflux competency of the GEJ through reducing small hiatal hernias, increasing LES resting pressure, narrowing the cardia, and recreating the acute angle of His.

In a meta-analysis, including seven trials with a total of 1,128 patients, TIF had the highest probability of increasing patient's health-related quality of life. However, it was not proven to be as efficient as the laparoscopic Nissen fundoplication in increasing LES, and based on the evaluation of benefits against risks, the authors did not recommend TIF as an alternative to PPI or fundoplication in the long term (42). This technology is now no longer available.

In summary, these trans-oral techniques are evolving and require further objective comparison with established laparoscopic fundoplication approaches in longitudinal prospective studies stratified for morbidity, in particular

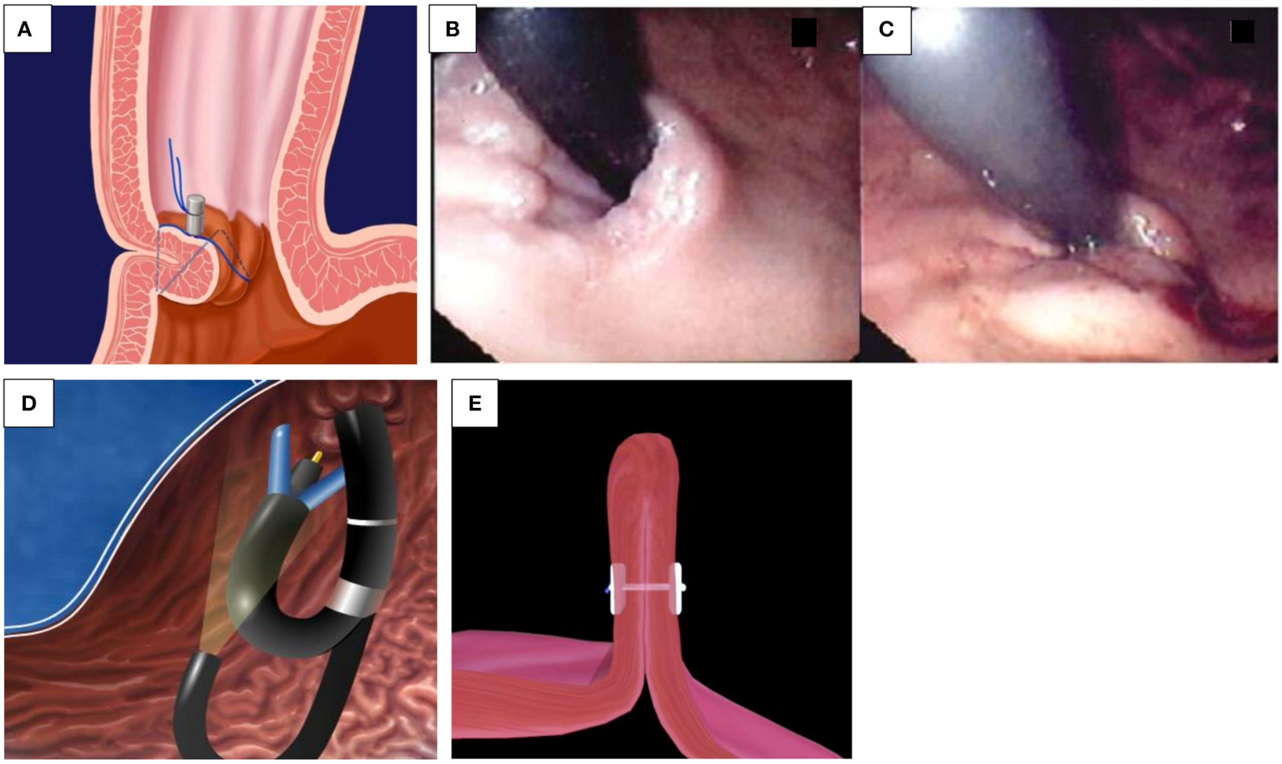

FIGURE 6 | (A–E) Endocinch® and full thickness Plicator® (Ndo-Surgical). **(A)** Endoscopic gastroplication with a zig-zag stich when applied with an Endocinch® sewing maching. **(B,C)** View (J maneuver) of a lax GO junction in a child with major reflux before **(A)** and after **(B)** application of stitch with the EndoCinch®. **(D)** Application of a full Thickness Plicator® (Ndo-Surgical). **(E)** After application of the full Thickness Plicator® (Ndo-Surgical).

neurological compromise. Only then will the Stretta procedure be recognized as a viable alternative with its provisional advantages to date of being applicable to mainstream pediatric reflux management.

Delivery of Radiofrequency Energy (the Stretta® System)

The Stretta® procedure is a technique of tissue remodeling of the LES by delivering radiofrequency energy to the LES, muscle, and gastric cardia, hence improving the motility of the LES and its barrier function. The system has two parts: one a Stretta® catheter and the other a Stretta® control module. The Stretta® catheter is a flexible, handheld, single-patient-use device that delivers radiofrequency energy generated by the control module (**Figure 7**). It is inserted over a flexible guidewire into the patient's mouth and advanced to the GEJ. A balloon is inflated, and needle electrodes are deployed into the tissue. Radiofrequency energy is delivered through the electrodes to create thermal lesions in the muscle of the LES and gastric cardia. As these lesions heal, the tissue contracts, resulting in a reduction of reflux episodes with improvement in symptoms. The Stretta® control module delivers this radiofrequency, while at the same time providing feedback to the physician regarding treatment temperatures, tissue impedance values, elapsed time, catheter position measurement, and irrigation rate.

This treatment has been used in adults since 1999. Complications are rare and almost exclusively occurred with the first iteration of the device and not with the more recent device—but among those previously reported were ulcerative esophagitis with gastroparesis, esophageal perforation, and a case of aspiration following the procedure (43–45).

A recent meta-analysis including 28 studies involving 2,468 patients showed that Stretta® significantly improved health-related quality of life and reduced heartburn. The mean follow-up was 25.4 (14–36.7) months, and reported adverse events were small in number, including small erosions in nine patients (0.36%), mucosal lacerations in seven (0.28%), gastroparesis in three (0.12%), and bleeding ulcer, mediastinal inflammation, pleural effusion, pneumonia each in one patient (0.04%) (46).

In pediatrics, the use of STRETTA® was first reported in an uncontrolled study of a group of six teenagers (mean age 18.0 ± 3.4 years). These patients had a previous failed surgery (initial operation was 12 ± 4 years). Acute gastric distension was reported in one patient post-surgery and five of six were asymptomatic at 3 months' follow-up (43).

Liu reported the use of STRETTA® in eight children (11–16 years) with a variable follow-up period of 5–15 months (47). It

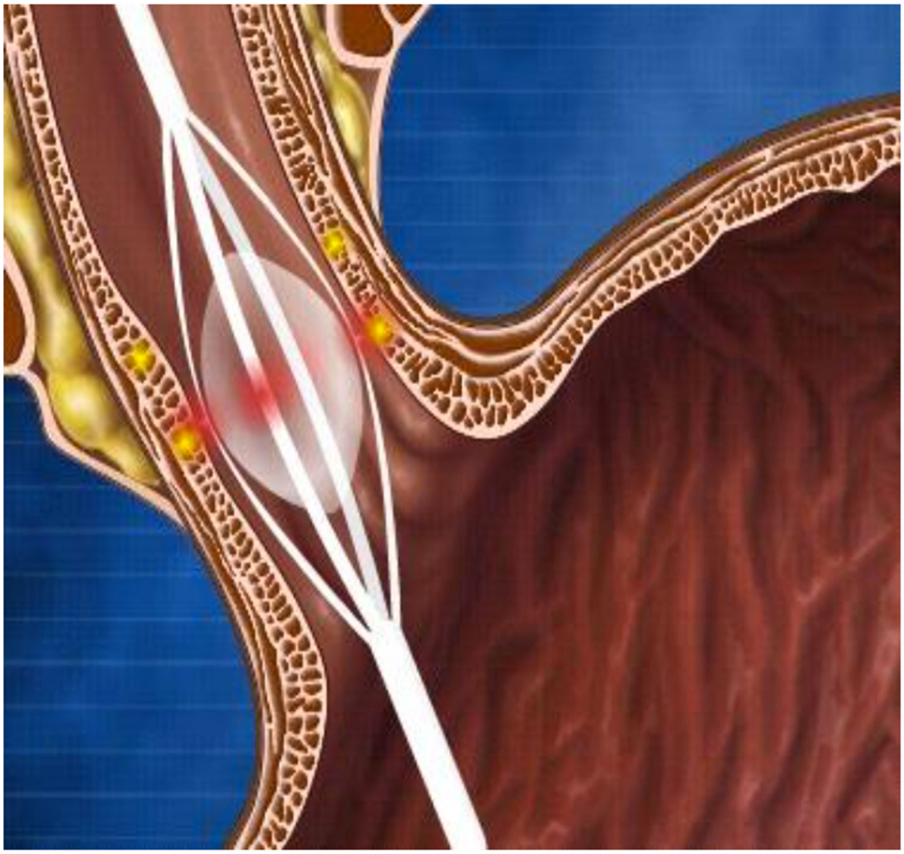

FIGURE 7 | The Stretta® procedure.

was reported that six of eight children improved (75%), and the cohort included three neurologically impaired children who also had concomitant percutaneous gastrostomy (PEG) placement. One of these groups had a post-procedure aspiration, which was successfully treated. Of the two failures, one remained dependent on PPI and the other had a successful Nissen fundoplication. Since this report in 2005, there have been no further publications of its use in children.

Although a recent meta-analysis shows the benefit of Stretta® treatment for GERD (48), pediatric gastroenterologists may be guarded in using this form of treatment as clearly using thermal energy treatment in a 70-year-old is different from using it in a child who may have unknown consequences in the long term. An ongoing study in adolescents is occurring in our center.

Advances in Endo-Dilatation for Treatment of Esophageal Stenosis and Strictures

Various etiologies can cause esophageal strictures and stenosis in children, with caustic, anastomotic, congenital, GERD, and eosinophilic esophagitis being the most common (22, 49–54). To date, there are various endoscopic treatment options, of which endoluminal balloon dilatation is probably the most useful and safe. Management focuses on long-term efficacy and safety, but the ideal timing of endoscopic dilatation remains a topic of debate. Recently, the initial recommendation of systematic subsequent dilatation every 3 weeks has been abandoned, and on-demand dilatation when symptoms occur is now the recommendation for benign strictures (22).

Esophageal Dilatation

The purpose of esophageal dilation is to alleviate symptoms and to permit free intake of enteral nutrition while reducing complications such as pulmonary aspiration. For dilation, two types of devices are available. One is the push bougie (Savary-Gilliard or Eder-Puestow) and the other the balloon dilator.

Push dilators are made of rubber and may be weighted (tungsten/mercury filled) or wire guided (polyvinyl, metal, or Celestin type). The weighted dilators may be used blindly and vary in size from 7 to 20 mm (**Figure 8A**). It is generally agreed that unguided passage of weighted bougies should be used only in treatment of simple strictures and no more than two sizes for each dilatation session (55). Bougie-type dilators exert both radial and longitudinal forces due to the shearing effect, and balloon dilators exert a radial force. Due to this significant difference, it is recommended that radial balloon dilators are the tool of choice in children, with a lower rate of complications and equal efficacy, although prospective comparative studies are ongoing.

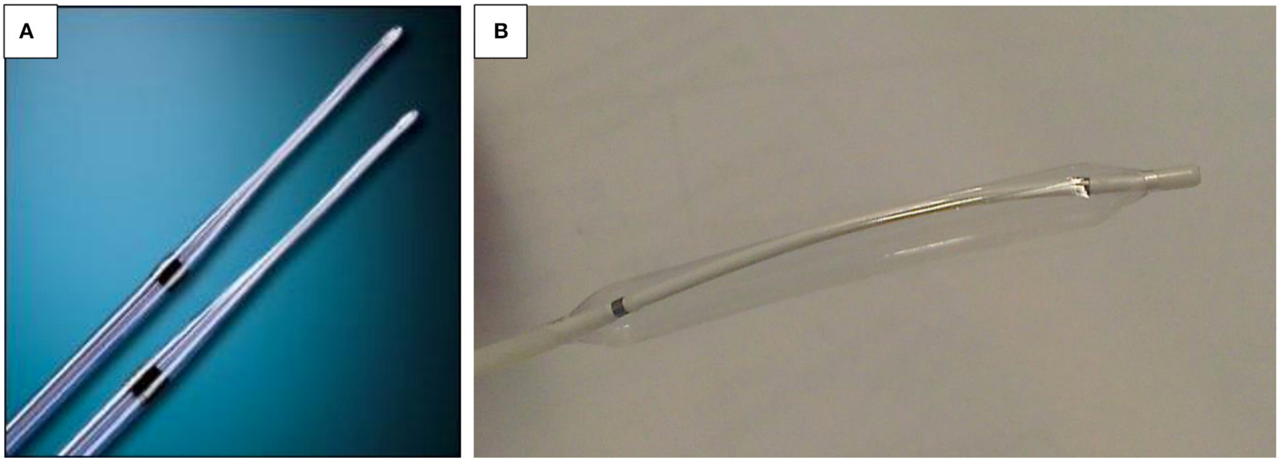

FIGURE 8 | (A,B) Dilatation device. **(A)** Bougie dilator (Savary-Gilliard). **(B)** Balloon dilator.

The balloon dilators may also be wire guided, or they may be passed through the endoscope. These vary from 4 to 20 mm (**Figure 8B**). It is suggested that a guidewire should be placed under direct vision. The authors, in common with most endo-therapeutic practitioners, prefer balloon dilation under direct vision with the balloon centered at the tightest point of the stricture.

The threshold for screening should be low, and fluoroscopy during the procedure is recommended in most cases and especially when using non-wire-guided dilators, during dilation of complex esophageal strictures, or in patients with a tortuous esophagus (22).

To reduce the risk of perforation, it has been suggested that no more than three dilators of progressively increasing diameter should be passed in a single session (56). The "rule of three" also suggests that no more than a three-fold increase in luminal diameter is attempted each time.

Esophageal perforation is a worrying complication of dilation therapy, with a global risk for perforation between 1.5 and 2.6%, according to different observations. The "rule of 3," to prevent perforation, has been adopted from the ASGE recommendations and implies that the dilation of a stricture should not be greater than three times the diameter of the stricture. However, Clark et al. have recently challenged this recommendation for children with stenosis of esophageal anastomosis: by reviewing charts from 284 children who underwent in total 1,384 balloon dilatations, they observed that dilatation of $\leq$5 mm did not unduly increase the risk of perforation, with a cumulative rate of perforation for dilatations $\leq$5 mm of 0.74%, whereas the risk increased to 4.85% in dilations $\geq$6 mm (49).

Readily available pediatric surgical support is vital while performing this procedure in children. Adult studies show that the risk of perforation is four times higher if the endoscopist has performed <500 therapeutic endoscopies (57).

Perforation should be suspected in any child developing continued chest pain, breathlessness, fever, or tachycardia. A chest X-ray is a useful first-line investigation. This is particularly true if the stricture is man-made, i.e., anastomotic, as perforation is more likely in such a situation.

Adjuvant Treatments With Dilatation

Dilatation of esophageal strictures creates a repetitive local mechanical trauma which may result in the stimulation of fibrogenesis and additional collagen disposure and therefore formation of fibrosis and scar tissue, resulting in stricture recurrence (51, 53). Several adjuncts to esophageal dilatation are nowadays in use to prevent stricture recurrence, which are detailed below.

Intralesional Steroid Injection

The intralesional injection of triamcinolone acetate has been studied in adults and in children without convincing results. However, Ngo et al. recently observed a significant increase in stricture diameter in 158 patients with anastomotic strictures post-esophageal atresia, with triamcinolone acetate and balloon dilatation compared to those treated with dilatation alone. However, benefit was limited to the first three dilatations (53). Therefore, intralesional injection of triamcinolone acetate might be an option for refractory esophageal stricture but should be limited to three procedures.

Use of Mitomycin C (MMC) Following Dilation

Recurrent stricturing due to any cause should suggest the use of an anti-fibrotic topical treatment post-dilation. Circumferential or deep caustic burns have a poor outcome, with an increased risk of perforation and/or stricture formation, even with early steroid treatment.

Thomson et al. reported the first use of MMC in a child with caustic stricture necessitating recurrent dilations (58). An 18-month-old girl at that time developed two strictures after accidental ingestion of caustic soda and was treated with dilation many times before topical application post-dilation of MMC, preventing the need for further dilation. At 20 years' follow-up, she is asymptomatic.

Since the publication of this first report, MMC has been used worldwide in different pathologies, e.g., caustic, post-surgical stenosis, and epidermolysis bullosa strictures (59). A French multicenter study showed a 67% success rate in their 39 patients with a significant decrease in number of dilatations prior (102) and post MMC application (17) (51). Wishahy et al. observed a significant improvement in dysphagia score in their 17 children treated with MMC (54). In general, patients received an MMC dose between 0.1 and 1 mg/ml. It is not known if the early use of MMC is more beneficial.

Electrocautery Incisional Therapy (EIT)

Another option for the management of refractory esophageal strictures is endoscopic EIT, which has been reported in adults and has recently been successfully employed in children by Manfredi et al. (52). A total of 133 EIT have been performed for 58 anastomotic strictures in 57 pediatric patients, subdivided into refractory (36) vs. non-refractory strictures (22). Treatment success, defined as no requirement for stricture resection, appropriate diameter for age, and less than seven dilatations in 24 months, was achieved in 61% in the refractory group and in 100% in the non-refractory group (52). Performed by an experienced endoscopist, EIT might be an interesting option, especially in asymmetric strictures, where balloon dilatation with exertion of equal force in all direction might tear less dense tissues easily. Manfredi et al. used a needle knife to incise strictures at their most obviously dense part, followed by a second incision and balloon dilatation to cause tearing at the incision site, hence fortifying the incision and dividing the fibrotic tissue. However, perforation occurred in 2.3% without the need for surgical intervention but was higher than that in most of the cohorts with simple balloon dilatation. Therefore, performance only by an experienced endoscopist and in conjunction with a surgeon is recommended.

Fully Covered, Self-Expandable Metal Stent (FCSEMS)

FCSEMSs have been used for refractory esophageal stenosis in children and in adults (**Figures 9A–D**). In three pediatric studies, including in total 25 patients, complete clinical response (no recurrence of dysphagia or need for subsequent dilatations) after stent removal was achieved in 50–85%. However, the most frequent adverse event was stent migration, which occurred in up to 29% (22).

FCSEMS also represents an attractive therapeutic option for the management of anastomotic leaks after esophageal or gastric surgery (**Figures 9C,D**). Sometimes, especially after multiple complex surgical procedures, conservative treatment (using broad-spectrum antibiotics, drainage, and parenteral nutrition) might be indicated, and FCSEMS has emerged as a promising minimally invasive option in adults to promote leak closure. In a recent case series of 10 children with post-surgical anastomotic leaks, perforation closed in 9 of 10 patients but 4 of 9 developed subsequent stenosis after stent removal (60).

Endoscopic Treatment of Barrett's Esophagus

Barrett's esophagus is a complication secondary to chronic acid exposure/reflux esophagitis resulting in columnar metaplasia of cells in the distal esophagus extending ≥1 cm proximal to the GEJ. Barrett's esophagus is a worrying condition as it is considered to be a major predisposing factor for development of adenocarcinoma conferring a 0.5% to 7% lifetime risk of developing malignancy, or approximately 0.66% per year in the adult population after development of dysplasia (61–63). Compared to prevalence in adults, that in children and adolescents is very low, ranging from 0.055 to 0.13% (63). It is an uncommon condition in children, but there is evidence of genetic predisposition in one pediatric study (64).

Identification of the GEJ is important, and biopsies are taken following the Seattle protocol (62). Over the years, several techniques have been developed, through which successful ablation is proposed: use of Nd-YAG laser (65, 66), KTP (potassium titanyl phosphate) laser (67–69), multipolar electrocoagulation (70, 71), APC (72–74), and photodynamic therapy (67, 75, 76). These techniques have been little used in pediatric practice except anecdotally, and the details of each are beyond the scope of this chapter.

Peroral Endoscopic Myotomy (POEM)

Achalasia is a rare progressive motility disorder, characterized by esophageal aperistalsis and impaired LES relaxation, leading to increased dysphagia of solids and liquids and regurgitation of indigested contents (77–82). Its presentation is particular in adult life, and diagnosis in childhood is quite rare. Achalasia is not curable, and treatments focus on the reduction of LES pressure. Current management includes laparoscopic Heller myotomy (LHM), POEM, pneumatic dilatation, and the injection of botulinum toxin. Since its first description in 2010 by Inoue et al., POEM has become an effective and safe procedure worldwide with the advantage of significant lower operation time and a shorter length of stay, and hence, it has replaced LHM as first-line treatment in adults (77, 82).

After endoscopic identification of the GEJ, a submucosal bleb is created by the injection of saline-indigo or methylene blue solution in the mid-esophagus. Then a 1.5–2 cm longitudinal incision is made, using either a dual, triangular-tip, or hook knife (**Figure 10A**). A submucosal tunnel is then extended to the gastric cardia, using minimal electrocautery, methylene injection, or blunt dissection.

Myotomy is performed starting at 2–3 cm distal to the mid-esophageal incision with either full thickness or circular dissection onto the proximal cardia approximately 2 cm below the GEJ (**Figure 10B**). An endoscopic clip is placed to close the entry site at the end of the procedure.

Clinical success rates in adults vary between 82 and 100% with particularly good results in patients with prior failed therapy: a recent meta-analysis indicates a 98% success rate in patients who had failed LHM (77). POEM has now been reported in children. A recent multicenter study, including 117 pediatric patients, showed clinical success in 90.6%, with only seven

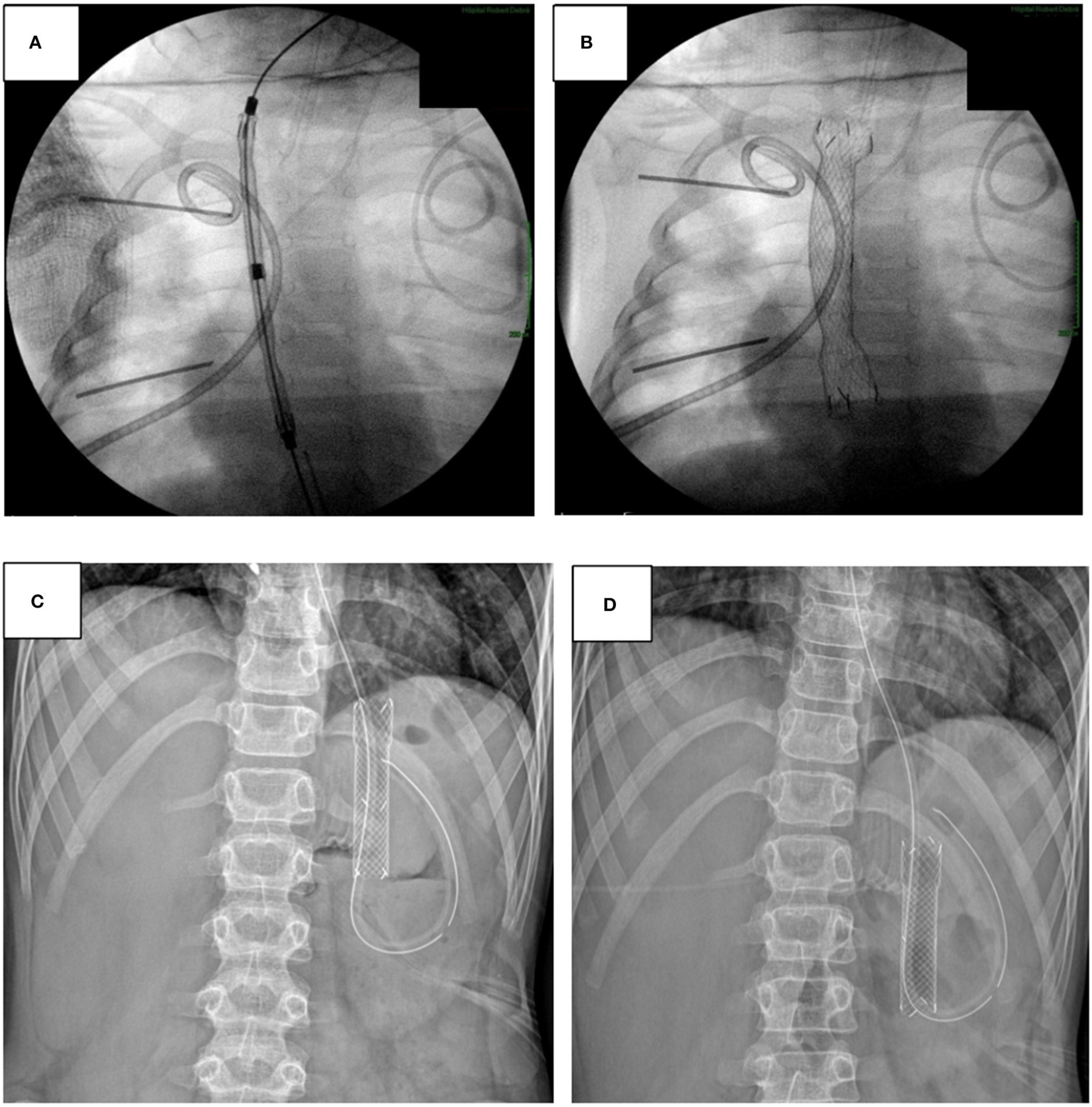

FIGURE 9 | (A–D) Fully covered, self-expandable metal stent (FCSEMS) with the courtesy of Prof. Jérôme Viala, Robert-Debré University Hospital, Paris, France. **(A)** Insertion of a FCSEMS the esophagus *via* a guide-wire. **(B)** FCSEMS after expansion. **(C)** FCSEMS placement in a 12 year old child after Toupet perforation. **(D)** Displacement of the stent in the stomach, requiring insertion of a longer stent with afterwards satisfying hermeticism and closure of the perforation.

adverse events (6%), including mucosotomies, subcutaneous emphysema, and one esophagopleural fistula (79). A recent meta-analysis, including 12 studies with 146 pediatric patients, revealed a significant reduction of clinical symptoms and LES pressure, with at least 93% of the patients experiencing improvement post-POEM (78).

Owing to well-established training programs for this highly technical procedure, the perioperative complication rate is very low in the adult population. However, GER secondary to POEM is observed, ranging between 15 and 19% in the pediatric and adult populations, respectively (79).

Endoscopic Pyloromyotomy for Congenital Pyloric Stenosis

Ramstedt's pyloromyotomy (open and laparoscopic) has been the gold-standard operation for treatment of congenital

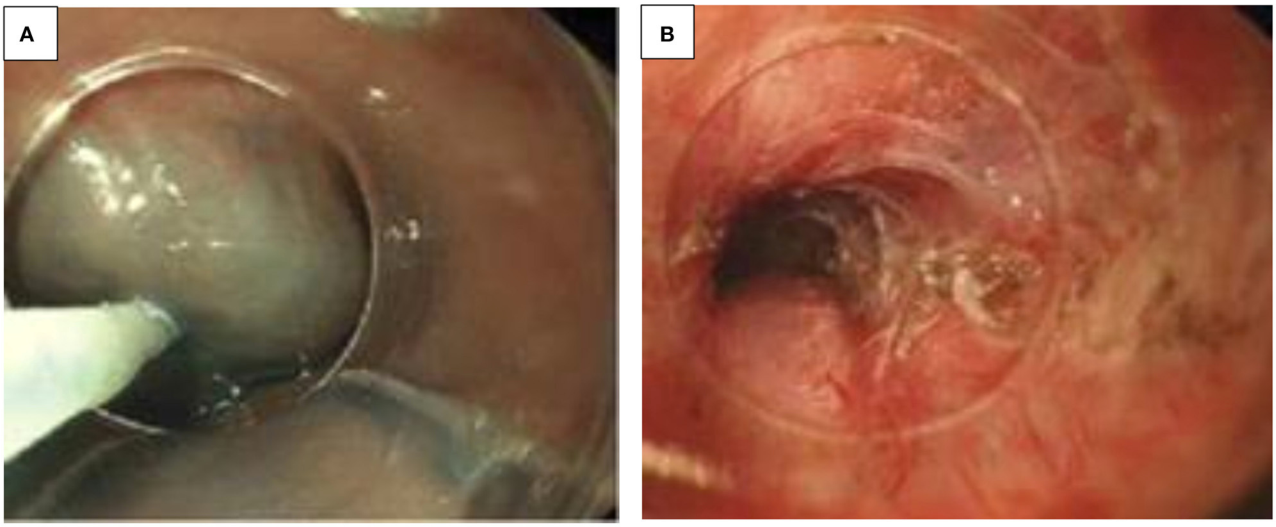

FIGURE 10 | (A,B) Peroral Endoscopic myotomy (POEM). **(A)** POEM procedure: Incision of the submucosal bleb to create a submucosal tunnel. **(B)** Myotomie during POEM procedure.

hypertrophic pyloric stenosis (CHPS) for more than 80 years. Ibarguen-Secchia from Texas has reported the use of endoscopic pyloromyotomy in a series of 10 children (83). This was performed with a view to achieving a quicker operation and postoperative recovery time. Of the 10 children, nine had the procedure as a day case and one needed electrolyte correction before being treated the next day. All children were fed after only 11 h following the procedure compared to the median time of 38 h for laparoscopic pyloromyotomy and 64 h for an open abdominal procedure. Vomiting continued to a lesser degree in two but eventually resolved in all over 6–18 months' follow-up. Zhang et al. treated nine infants with CHPS, using an endoscopic electrosurgical needle knife. All patients started feeding 2–10 h after the intervention. There was a resolution of vomiting after 1 week in eight of nine patients. One child required a second endoscopic pyloromyotomy related to recurrent vomiting (84).

Despite these promising case series, indicating that endoscopic pyloromyotomy is a safe, effective, and minimally invasive procedure, there are no further recent case series about endoscopic pyloromyotomy, which is probably related to a very safe and effective surgical procedure. To date, laparoscopic pyloromyotomy remains the treatment of choice in most pediatric centers, but pre-pyloric congenital webs and peptic/caustic pyloric stenosis have been treated endoscopically in children.

Percutaneous Endoscopic Feeding Tubes: Gastrojejunostomy

Percutaneously placed feeding tubes can be used in various techniques, ranging from PEG, single-stage PEG (SSPEG), percutaneous gastrojejunal (PEGJ), and direct laparoscopic-assisted percutaneous jejunal (LAPEJ) tubes. Standard and SSPEG insertion is not covered in this paper as it is such a widespread technique and is covered in detail in textbooks (8).

In children with severe GERD and/or gastroparesis, post-pyloric feeding might be indicated. With the PEG tube, it is also now possible to place a PEGJ tube. A thinner jejunostomy tube is placed through the PEG tube lumen. The jejunostomy tube then traverses the pylorus and extends down beyond the ligament of Treitz. Gastrojejunal button devices are also available in two different lengths and sizes, for children under and over 10 kg, and can be placed as an initial procedure. Unfortunately, gastrojejunal tubes are fraught with problems and tend to get blocked or displaced easily, requiring recurrent radiological and/or endoscopic replacement and necessitating either radiological exposure or general anesthesia. However, complication rates vary widely, and complications such as displacement or obstruction depend not only on the endoscopist but also on the training and experience of the care team who handles the enteral nutrition devices. Direct surgical procedures (in general modified Roux-en-Y jejunostomies) have the disadvantage of being more invasive and related to a higher rate of complications (85). In general, working hand in hand with the pediatric surgeon is essential, in particular in children with reflux disease and/or requiring enteral feeding access, as these children usually have complex comorbidities which could potentially require surgical assistance.

A minimally invasive technique combining endoscopic and laparoscopic approaches has recently been reported, which allows the direct insertion of a jejunostomy using simultaneous endoscopic and laparoscopic visualization to maximize safety and potentially improve outcome (85). The LAPEJ involves the following steps: insertion of the endoscope by the endoscopist into the proximal jejunum while the surgeon uses a laparoscopic camera and one or two additional instruments to identify the duodenojejunal flexure and clamp the distal jejunum to prevent

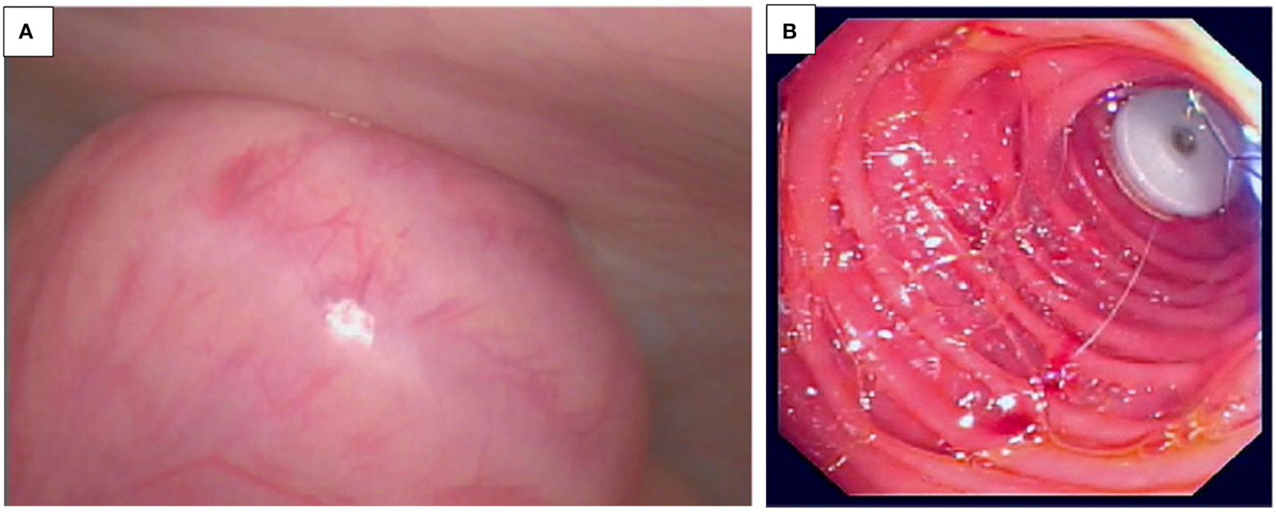

FIGURE 11 | (A,B) Laparoscopic-assisted percutaneous endoscopic jejunostomy (LAPEJ). **(A)** Laparoscopic view of the proximal jejunum pulled to the abdominal wall by PEG tube insertion. **(B)** Endoscopic view of the Corflo in the jejunum.

excessive insufflation of small bowel obscuring the laparoscopic view (**Figure 11A**). A trocar is then inserted to introduce a wire across the abdominal wall into the jejunum, which is visualized, grasped, and retrieved by the endoscopist followed by a standard "pull" technique to bring a PEG tube out through the jejunum, across the peritoneal cavity, and out of the skin. Placement is confirmed endoscopically and laparoscopically (**Figure 11B**). In a case series of 16 patients, the LAPEJ procedure has been proven a safe, effective, and minimally invasive technique to achieve medium- to long-term direct jejunal access for feeding and could be completed in a short operative time (85).

Endoscopic Mucosal Resection (EMR)

EMR was originally described by Deyhle et al. and has been developed by Japanese endoscopists for the resection of sessile and flat lesions of the upper GI tract in adults and children (8, 85, 86). EMR is now an established standard procedure for sessile polyp removal in adults with the advantage of avoidance of thermal damage and reduced procedure times (87, 88). It permits the resection of flat and sessile lesions by longitudinal section through the submucosal layer (89). The European Society of Gastrointestinal Endoscopy (ESGE) recommends EMR with a cold snare in diminutive polyps ($\leq$5 mm) and sessile polyps up to 9 mm (88). In a retrospective analysis, Zhan et al. compared two case series of patients treated with either high-frequency electrocoagulation (HFEC) or EMR. Operation and intraoperative and postoperative bleeding were similar in both groups, without any perforation. Only hospital stay was longer in the EMR group compared to the HFEC group (90). EMR facilitates complete histological analysis of the resected lesion and makes it possible to determine precisely the completeness of excision in both the horizontal and vertical resection planes. This makes it advantageous compared to primary tissue ablative techniques such as APC (91) and electrocoagulation (92). Numerous EMR techniques have now been described using transparent caps fitted to the proximal aspect of the endoscope and using an insulation-tipped cutting knife (86).

Botulinum Toxin Injection

Esophagus

Botulinum has been used for treatment of achalasia of the esophagus, but the symptom relief when achieved is only short-lived. Functional esophagogastric junction obstruction with intact peristalsis (in the absence of achalasia) has been described in adults (93).

Pylorus

Botox has been used in the pylorus to help delayed gastric emptying. In a 32-patient randomized-controlled trial (RCT) in Philadelphia, intra-pyloric injection of botulinum toxin improved gastric emptying in adult patients with gastroparesis, although this benefit was not superior to placebo at 1 month (94). A systematic review on intra-pyloric botulinum toxin injection for gastroparesis confirms the findings of the RCT (95). The authors have successfully used botulinum toxin injection in children in the esophagus and the pylorus.

Sphincter of Oddi

Following an initial report of successful use of botulinum toxin in the bile duct of a canine model to decrease biliary pressures (96), it has been used for relaxation of the sphincter of Oddi in selected patients with acalculous biliary pain (97). The pain relief was followed by sphincterotomy in the responders and cholecystectomy in the non-responders.

Pancreatic Pseudocyst Drainage

Pancreatic pseudocysts are secondary to pancreatic damage and may be multi-etiological: traumatic; post-pancreatitis of

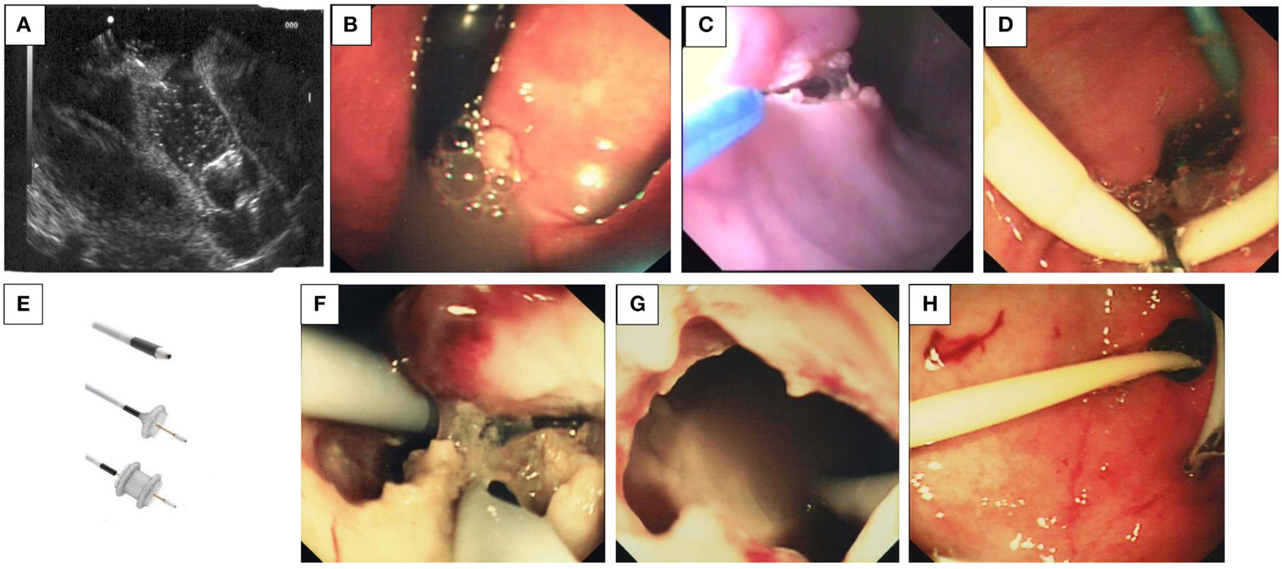

FIGURE 12 | (A–H) Drainage of pancreatic pseudocysts. **(A)** Trans-gastric linear endo-ultrasound needle puncture of a pancreatic pseudocyst. The linear needle can be seen as a straight white line in the upper part of the picture. **(B)** The indentation into the gastric wall can be seen easily identifying the position of the pseudocyst. **(C)** Creation of a cauterized entry from the stomach into the cyst by using and endoknife and sphincterotome: After endo-ultrasound has identified the cyst and a site which is free from gastric vessels, an endoknife followed by a sphincterotome (tapertome is best) is used to create a cauterized entry point from the stomach in to the cyst. Adrenaline can be injected prior to the incision to further diminish the possibility of hemorrhage during incision. **(D)** Grasping forceps are used to manipulate the stents [pig-tailed (blue) or straight (white)] through the gastro-cystostomy that was created. **(E)** Self-expanding metal stents. **(F)** The stents are endoscopically observed in the pseudocyst, and membranes between loculations can be punctured as necessary. **(G)** The endoscope is withdrawn from the pseudocyst. **(H)** The endoscope is withdrawn from the stomach and the gastro-cystostomy is left in place.

idiopathic origin; following chemotherapy; or any other cause of acute pancreatitis. They should be differentiated from malignant cysts, but this is unusual in childhood and is a distinction necessary predominantly in adult practice.

Presentation may be with a persistently raised amylase, with chronic pain, as an abdominal mass, or with consistent nausea/vomiting. Treatment to date has been either conservative or surgical, with the use of anti-secretory agents such as octreotide or its longer-acting analogs (e.g., lanreotide) or *via* ERCP.

More recently, trans-gastric cystostomies have been performed by endoscopy (98). These are either guided by endo-ultrasound (EUS), which may be a safer option by avoiding gastric vessels (**Figure 12A**), or blind with prior epinephrine injection into the bulge in the gastric wall from the luminal surface and then incision into the injected area. Indeed, EUS has become the accepted guidance approach for drainage of pancreatic fluid collections in the past decade. EUS has been shown to be safe and effective, and it has been the first-line therapy for uncomplicated pseudocysts. Where walled-off pancreatic necrosis was originally thought to be a contraindication for endoscopic treatment, multiple case series have now shown that these fluid collections also can be treated endoscopically with low morbidity and mortality (99). Usually, the cyst can be indirectly identified abutting the lesser or greater curvature and is quite obvious as a mass effect into the gastric lumen (**Figure 12B**).

The initial incision may be made with an endo-knife (**Figure 12C**), and once this is made, a sphincterotome may be inserted and employed to safely expand this incision. However, this has the disadvantage of then obscuring the endoscopy view with an outpouring of a great deal of fluid. A better approach is to use a cystotome which requires a 3.2 mm working channel in the endoscope but which prevents loss of access to the cyst—this is because the endo-knife is within the cystotome and the incision and then introduction of a guidewire can be seamless—the stents can then be passed down the 3.2 mm working channel and into the cyst with the proximal portion in the stomach. Subsequently, either straight ERCP plastic stents or pig-tailed stents can be inserted into the pseudocyst and left *in situ* (**Figure 12D**). Recently, the temporary placement of self-expanding metal stents has been reported (AXIOS, **Figure 12E**) (100, 101). Fluid will then follow the path of least resistance, and the presumed communication with the pancreatic duct will close, preventing further accumulation of pancreatic fluid in the cyst. An endoscope may be inserted into the cyst, but this is not strictly necessary (**Figures 12F,G**). It is hoped that the gastric wall and the cyst will become adhesive and fibrotic, creating a channel such that the stents become unnecessary as when the cyst naturally deflates, the stents are extruded and the fistula closes (**Figure 12H**). This is the normal course of events. Patient symptom relief is acute and usually long-lasting. Complications are not common as long as gastric vessels are avoided initially. A combined approach involving drainage through the papilla and transmural endoscopic drainage can be useful in the larger and more loculated cysts. The efficacy and safety of this procedure in the pediatric population have been described by utilizing ultrasound-guided drainage (102).

Endoscopic Treatment of Obesity

The endoscopic treatments for obesity include space-occupying devices (balloons), endoscopic techniques that reduce gastric capacity (suturing methods for plication and partition), endoscopic treatments modifying gastric motor function (injections and implants), and use of malabsorptive methods (gastrojejunostomy and bypass).

To date, the only reported treatment for obesity in teenagers or children by endoscopy has used bariatric balloons, which achieved a success of about 10% weight reduction but which, 6 months after removal, invariably ended up with weight gain again. Certainly, endoscopic treatments are likely to offer a non-invasive, reversible "next-step" treatment option, when compared to surgery (103).

Duodenal Web Division

Congenital duodenal membranes, also known as duodenal webs, are a rare condition with an estimated incidence of 1/10,000–40,000 birth and are often associated with genetic, cardiovascular, or GI abnormalities and are particularly prevalent in syndromes such as Down's or 22q deletion (104). In the case of complete obstruction or atresia, it is usually diagnosed antenatally or soon after birth, but if obstruction is incomplete, diagnosis might be made later in life. Traditionally, treatment was surgical (either laparoscopic or open), but several endoscopic techniques have emerged in the last decade, including endoluminal balloon dilatation, the use of division by sphincterotome, and laser ablation. A combination of endoscopic balloon dilatation and electrocautery endo-knife (MicroKnife, Boston Scientific Microinvasive, Natick, MA, USA)/sphincterotome (Cook MiniTome, Bloomington, IN, USA) has recently been described in 15 children, but this has graduated to balloon dilation only as the use of the endo-knife can be associated with inadvertent perforation of the pancreaticobiliary radicle, which is anatomically opposed to the membrane (104). It is crucial to always check for a secondary, more distal membrane, as this has been observed in up to 20% of cases (104). A single intervention has been sufficient in 60% of the cases, but some of the patients might need a second or third procedure (8). Cases requiring supplementary procedures have been related to the presence of the annular pancreas; hence, Thomson et al. have suggested performing an MRCP prior to the endoscopic procedure—this may highlight the relative position of the ampulla of Vater to the web and suggest whether balloon dilation or balloon and dissection by an endo-knife will be the approach of choice (104).

THE FUTURE

Availability of newer computer chips, better computer processing power with use of 4K and 8K imaging, and improved screen refresh rate are likely to assist the endoscopist in viewing a high-resolution smoothly transitioning dynamic image. Artificial intelligence (computer-assisted diagnosis) with "endoscopists eye tracking" is a technology to further enhance the endoscopist's diagnostic and therapeutic precision. This is also likely to shorten the procedure time with more safety. Unpredictable longer therapeutic procedures can potentially be made safer with the use of CO_2 insufflation over air insufflation. CO_2 insufflation is well-tolerated in children and used already in several pediatric GI centers, but a consideration for use in therapeutic pediatric endoscopy with more studies needed to understand its potential benefits has prompted a recent multinational prospective study into its safety and risk mitigation. Robotic-assisted endoscopy is a novel new diagnostic tool for patients who may not tolerate conventional endoscopy, and it may be that therapeutic procedures are possible with this technology in the future. The appropriate application of natural orifice endoluminal surgery (NOTES) in children is yet to be established but maintains a promising future, with incisionless approaches being the eventual aim.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

DS wrote the first draft of the manuscript. NA and MT revised critically the intellectual content. All authors contributed to manuscript revision, read, and approved the submitted version.

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