RESEARCH ARTICLE

Endoscopic Point of Care Ultrasound: Foundations, Present Applications, Future Potentials

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ABSTRACT

Introduction: The present review details the evolution of endoscopic ultrasound, the acquisition of subepithelial imaging of the gastrointestinal tract during endoscopy, in pediatrics. Similar to its use in adults, the majority of its present applications involve obtaining fluid and or tissue for diagnosis. Simultaneously, the indications for point of care ultrasound, in which physicians caring for a patient personally obtains images which can be incorporated immediately into diagnosis and management, are also expanding. A history of endoscopic ultrasound from its inception to its current utilization is presented. The data reflecting its successful current employment as the procedure of choice to analyze and drain pancreatic cysts, to diagnose biliary tract and pancreatic diseases, to direct subepithelial biopsies, and to evaluate gastrointestinal tumors as well as less common gastrointestinal pathologies, is summarized with an emphasis on pediatric studies. In addition, the recent expansion of point of care ultrasound and endoscopic ultrasound to yield images to analyze subepithelial pathology including fibrosis in eosinophilic esophagitis and in inflammatory bowel disease is highlighted. A brief summary of the challenges, range of instruments, costs, and safety provides the reader with the background to fully appreciate this emerging technique. Finally, there is an overview of exciting new developments that will further extend its indications. Conclusions: With anticipated improvements including better resolution of endoscopic ultrasound probes, the routine incorporation of point of care elastography and contrast enhanced ultrasound, and the potential of artificial intelligence to provide more reproducible and uniform analysis of endosonographic images, new indications are anticipated to enable endoscopic point of care ultrasound, E-POCUS, to further improve patient care in the near future

Introduction

Ultrasonography is based on the transmission of very high frequency sound waves by a transducer. The waves are sent into the body and reflected back to the transducer with different acoustic properties that are able to generate the ultrasound image. Endoscopic ultrasound (EUS) is the application of ultrasonographic images to assist the endoscopist in diagnosing and treating pathology encountered during an endoscopic exam. A recent analysis has indicated that almost 200,000 EUS exams were performed in 2015, which represent approximately 1% of all upper endoscopies and a smaller proportion of colonoscopies[1]. Fortune business insights reports that the global endoscopic ultrasound market was 831 million in 2018 and is projected to increase to 1.376 billion by 2026. Many adult gastroenterology training fellowships have begun to incorporate EUS into the curriculum. However, the expanding need for this technology has resulted in the ASGE and Olympus Corporation of the Americas partnering in a joint effort to provide "post graduate" training for gastroenterologists that will increase the number of endosonographers to meet the increased need. In addition to diagnostic EUS, the major thrust of clinical practice, research papers, and training is therapeutic EUS, including but not limited to the aspiration of fluid from pancreatic cysts, drainage of pancreatic fluid collections, or biopsies of pancreatic masses and subepithelial gastric lesions.

Simultaneously, POCUS or point of care ultrasound has heralded the incorporation of ultrasound into a variety of medical applications and has been the subject of a recent review article in the New England Journal of Medicine[2], which had updated an earlier review[3]. EUS shares a central feature with POCUS as both technologies center around the physician responsible for the patient personally acquiring the images utilized in their care. POCUS has been employed to guide interventions such as central line placement and trauma victim triage, as described above for EUS. However, POCUS is also being increasingly employed to characterize anatomic features that aid in diagnosis, as with emergency room POCUS echocardiography[2]. EUS is similarly capable of adding an immediate three-dimensional appreciation of any subepithelial pathology, which could also guide clinical decision making.

The present review will focus on the initial, present, and future of anatomic, diagnostic, applications of endoscopic POCUS, (E-POCUS). For the purposes of this review, E-POCUS is the acquisition of EUS images which are necessary to make or confirm a diagnosis at the time of the endoscopy. While the emphasis will be on pediatric applications, the significant contributions of adult gastroenterology to the field will be recognized. The goal of E-POCUS is to provide comprehensive, anatomical characterization of any encountered subepithelial pathology which can then be discussed with the patient immediately after the endoscopy. Rapid appreciation of the nuances of full thickness gastrointestinal pathology in a safe, noninvasive, cost effective manner, is analogous to the introduction of echocardiography to the field of cardiology. This review will focus on several transmural gastrointestinal diseases where EUS is beginning to be introduced into clinical care, esophageal EUS for eosinophilic esophagitis and intestinal EUS for inflammatory bowel disease. The final portion of the review will look into the technical advancements that will further enhance the capabilities of EUS.

Equally intriguing is the principle that any form of endoscopy that is presently designed to evaluate mucosal disease will have situations where an understanding of subepithelial pathology will be beneficial. Specific examples include colonoscopy (fibrosis/inflammation in inflammatory bowel disease, microvasculature inadequacies in ischemic bowel disease), bronchoscopy (airway remodeling in asthma and chronic obstructive pulmonary disease), laparoscopy (abdominal tumors), intraductal (primary sclerosing cholangitis, biliary tumors), laryngoscopy (laryngeal tumors), cystoscopy (renal stones), and hysteroscopy (pelvic inflammatory disease). All are potential candidates to improve clinical outcomes through the inclusion of E-POCUS.

Early History

The early history and the development of endoscopic ultrasound (EUS) has been summarized by its pioneer Dr. DiMagno[4]. Briefly, Dr. DiMagno, was part of the team that developed the technology, tested the first EUS instrument in dogs, and then performed the first application in humans. The initial impetus was that transcutaneous ultrasound of the pancreas was not accurate enough and that by placing the probe closer to the gland, superior imaging of the pancreas could be obtained. Along the way his group established that transesophageal echocardiography provided higher resolution imaging of the dog's heart compared to transthoracic echocardiography. Their early studies demonstrated that EUS could distinguish mucosal from intramural or extramural pathology and that they could obtain high resolution images of structures 1-2mm[5]. Being a true visionary, he even postulated how artificial intelligence could improve the ability of EUS images

to discriminate between pancreatic malignancy and inflammation, and how elastography could be added to EUS. As he predicted, the diagnostic implications of EUS has dramatically increased and is currently involved in the evaluation of cancers of the esophagus, stomach, and rectum, gastric lymphoma, subepithelial lesions, fecal incontinence, perianal disease, lymphadenopathy, and cardiac and vascular pathology[6].

Present Applications of Endosocpic Ultrasound In Pediatrics

Approximately 15 years ago, articles began to describe the use of EUS in pediatric patients. Single center publications described experiences by mainly adult gastroenterologists performing procedures that were already being routinely performed on adults. These include a series of 58 cases in 56 patients (median age 16 years) to investigate acute or recurrent pancreatitis, abdominal pain of suspected pancreaticobiliary origin, suspected biliary obstruction, upper GI mucosal/submucosal lesions, and evaluation of pancreatic abnormalities seen on prior imaging. Five procedures included therapeutic interventions and 44 (67%) yielded a new diagnosis[7]. Another series described 40 studies, in 38 children (mean age 13.5 years) for various indications. Pancreaticobiliary indications were for pancreatitis (n = 10), solid pancreatic mass (n = 7), cystic pancreatic mass (n = 1), cyst in the setting of chronic pancreatitis (n = 1), suspected annular pancreas (n = 1), celiac plexus block (n = 1), suspected common bile duct stone (n = 1), abdominal pain and atrophic pancreas (n = 1), ampullary adenoma (n = 1), and abnormal MRCP in a patient with jaundice (n = 1). The indications for gastric EUS were mucosal lesions (n = 2) and subepithelial lesions (n = 4). The indications for mediastinal endosonography were evaluation of mediastinal masses and/or lymph nodes (n = 5). The remaining evaluations were performed for esophageal stricture (n = 1), unexplained abdominal pain (n = 1), unexplained abdominal pain with celiac axis block (n = 1), and a perirectal fluid collection (n = 1). EUS-guided FNA (EUS-FNA) was performed in 12 (30%) cases and established the correct diagnosis in 9 (75%). EUS-guided fine-needle injections for celiac axis block were performed in 2 (5%) cases[8]. A third group of surgeons retrospectively reviewed their EUS experience with 18 patients (12 boys, 6 girls; median age 12 years, range 0.5-15). The indications were as follows: tumor (9), epigastric pain (3), recurrent pancreatitis (2), unexplained jaundice (2), hypoglycemia (1), and von Hippel-Lindau disease (1). They concluded that EUS had a significant impact in 78% of the cases[9].

However, pediatric gastroenterologists were also beginning to publish on their experiences in EUS which included younger patients. One series described 32 children (range 1.5-18 years, mean 12 years of age) in which the indications in the pancreas and biliary tract group were recurrent pancreatitis in 9, cyst or mass in 6, and obstructive jaundice in 4. In the esophageal group, 4 children with esophageal stenosis, 2 with suspected duplication, and 2 with an esophageal mass were evaluated. Seven cases were described with fine needle aspiration and EUS changed the diagnosis or therapy in 14 (44%)[10]. In the last few years, there have been multiple reports describing larger single center EUS experiences in children by pediatric gastroenterologists (see table)[11-18]. The table illustrates that in most series the vast majority of applications would be considered endoscopic Point of Care Ultrasound (E-POCUS) and that the indications are similar to the earlier studies mentioned above. There has also been a comprehensive review of previously published pediatric EUS series[19] and a clinical guidelines paper published by North American Society Pediatric Gastroenterology Hepatology and Nutrition[20].

In the largest published single center series of patients, 306 EUS procedures, using radial or linear array echoendoscopes, were performed from 2009 to 2020 on 279 patients 18 years or younger[11]. The majority (93.8%) occurred during upper endoscopy but 19 (6.2%) were performed during colonoscopy. Two hundred and twenty-nine procedures were diagnostic (74.8%) and 77 were therapeutic (25.2%). The majority of EUS procedure indications were related to evaluation and therapy of the pancreaticobiliary region (231 procedures, 75.5%). Smaller subsets of EUS procedures were performed for evaluation/sampling of subepithelial or regional lesions (54 patients, 17.8%), celiac plexus block (19, 6.2%), and hemostasis (14, 4.5%).

Table: Prevalence of E-POCUS in Pediatric EUS publications

Study	Cases	Diagnostic	Therapeutic	Indications	Impacts on Diagnosis/ Treatment
Barakat et al. (2022) [11]	306 EUS	122 (40%) E-POCUS 55 (18%) FNA/FNB 52 (17%) not classified. Overall 229 (75%)	77 (25%)	Pancreaticobiliary (75.5%), Subepithelial lesions (17.8%), Celiac plexus block (6.2%), Hemostasis (4.5%) Others *	93% clinical care influenced by EUS 99% of procedures successful Diagnostic yield 94% FNA/FNB
Ragab et al. (2022) [12]	29 EUS	13 (45%) E-POCUS 11 (38%) had FNA/FNB	5 (17.2%)	Pancreatic mass (10.3%), Pancreatic cyst (6.9%), Chronic pancreatitis (31.0%), PPC (17.2%), Subepithelial lesions (13.8%), Bile duct mass (3.4%), Mediastinal mass (3.4%), Pelvic mass (3.4%), Mass at splenic hilum (3.4%)	EUS-guided cysto-gastrostomy (100% success). EUS diagnosed 21 out of 24 patients (87.5%). EUS-guided tissue acquisition yielded definitive histopathological diagnosis in 10 of 11 patients (91%)
Dalal et al. (2022) [13]	92 EUS	87 (95%) E-POCUS	5 (5%)	Abdominal pain (52.9%), Jaundice/cholangitis (17.6%), Others	Meaningful impact 69 (81.2%)
Piester & Liu (2021) [14]	98 EUS	56 (57%) E-POCUS Additional 18 (18%) for pancreatic fluid removal and 15 (15%): FNA/FNB	9 (9%)	Choledocholithiasis (31.6%), Pancreatic fluid collections (18.4%), Chronic and acute recurrent pancreatitis (14.3%), Acute pancreatitis characterization (13.3%), pancreatic mass (6.1%) and luminal lesions/strictures 6.1%)	Procedure success rate 100% Changed management 17%
Demirbaş et al. (2021) [15]	41 EUS	41 (100%) E-POCUS	0	Biliary colic (51.2%), Suspected chronic pancreatitis (29.2%), Cholecystitis/cholangitis (12.2%), Acute pancreatitis (7.4%)	EUS influenced treatment decisions (43.9%). EUS may prevent unnecessary cholecystectomy or ERCP in children with no evidence of microlithiasis and was more sensitive for some than MRCP or Ultrasound
Téllez-Ávila et al (2019) [16]	54 EUS	48 (89%) E-POCUS 2 FNB/FNA (4%)	4 (7.4%)	Pancreatitis (57%) Choledocholithiasis (9.3%), Insulinoma (5.6%), Pancreatic neoplasia (5.6%), Peripancreatic collection (5.6%), Subepithelial lesion (3.7%), Choledochal cyst (3.7%), Rectal polyp (1.9%), gastric compression (1.9%), Jaundice (1.9%), Dilated biliary tract (1.9%), Papillary adenoma (1.9%)	EUS is a useful and safe tool in the pediatric population with pancreatobiliary diseases: Microlithiasis (gallbladder or common bile duct) was the most common diagnosis. In suspected malignancy, EUS confirmed the finding in 4/8 (50%) and disproved it in 4/8 (50%).
Garcia et al. (2022) [17]	107 EUS	64(58%) E-POCUS	43(42%)	Pancreatobiliary (76%), Gastric (13%), Rectal (4.6%), Esophageal (2.8%), Duodenal (1.8%), Mediastinal (1.8%) diseases	Significant clinical impact (81% of children)

* Therapeutic ablation of congenital cystic anomalies (eg, a bronchogenic cyst), endosonographic evaluation of duplication cysts and endosonographic evaluation of congenital esophageal stenosis
PPC: *Pancreatic pseudocyst; FNA/FNB fine needle aspirate or biopsy; E-POCUS: EUS procedures in which imaging alone was employed to make the diagnosis*

Twelve patients underwent EUS for more than one of these indications. Lower EUS indications included evaluation of peri-rectal lesions and sub-epithelial lesions in the vicinity of the rectum. Diagnostic sampling was performed in 52 of these EUS procedures, with a 96.2% diagnostic yield. The review reported that 98.7% of the pediatric therapeutic procedures were technically successful and that there were no significant adverse events. The authors noted that some unique applications for EUS are noteworthy within the pediatric population. These included E-POCUS indications such as evaluation of congenital cystic anomalies (eg, a bronchogenic cyst), duplication cysts, and congenital esophageal stenosis, which was able to determine the appropriate next step in management. The authors concluded that EUS is an appropriate tool to differentiate the GI wall layers, identify mucosal and submucosal lesions, and clearly distinguish between solid and cystic lesions and direct their management[11].

A comprehensive review of the pediatric literature found 19 articles that described a total of 643 EUS procedures on 571 patients with a median age of 12.7 years[19]. As with the large series, the majority of EUS procedures investigated the pancreaticobiliary tract (77,7%) followed by the upper GI tract, including the evaluation of the esophagus, stomach and duodenum (15,4%), and the rectum (4%), and other miscellaneous indication (such as evaluation of lymph nodes, mediastinal/abdominal mass) (2.9%). Most studies showed a high positive impact on management with a median value of 81.7%, leading the authors to conclude that EUS is an emerging modality even in pediatrics that provides detailed evaluation of the pancreatic parenchyma and gastrointestinal tract due to its high sensitivity and accuracy.

The roles of EUS (and endoscopic retrograde cholangiopancreatography, (ERCP)) in the evaluation and treatment of chronic pancreatitis in children were summarized in a recent position paper from NASPGHAN[20]. The committee members concluded that EUS provides high-resolution transluminal ultrasound images of the pancreas and surrounding intra-abdominal structures, providing excellent detailed information of both the pancreatic parenchyma and ductal structures, and is being increasingly used in pediatric patients. As previously noted, EUS is focused on obtaining diagnostic information, such as endosonographic images and obtaining transluminal pancreatic tissue through fine needle aspiration or biopsy. The utility of EUS stems from its capacity to demonstrate subtle alterations in pancreatic parenchyma and ductal structures that escape traditional imaging and laboratory tests of pancreatic function. EUS has been amply compared with noninvasive cross-sectional imaging and ERCP in terms of accuracy in diagnosing chronic pancreatitis. The authors describe how the future of EUS will be further enhanced which is discussed below.

Furthering the Spectrum of Published Endoscopic Ultrtasound Indications

There is an increasing list of indications for EUS in gastroenterology. The opportunities to employ EUS are determined by the anatomic conditions and the technical capabilities of the endosonographer and the equipment. The high-resolution capacity and low penetration depth of EUS enables highly detailed imaging of the gastrointestinal wall and nearby tissue. The depth of visualization will be dependent on the actual instrument as discussed below. Important examples for diagnostic E-POCUS include staging of cancer, especially gastric and rectal, and characterizing gastrointestinal subepithelial lesions, as well as adjacent mediastinal and retroperitoneal masses. Therapeutic EUS can be performed for fine needle biopsy or drainage (biliary and cyst drainage), fine needle injection (celiac plexus block or neurolysis, tattooing, and placement of lumen apposing stents (gallbladder and pseudocyst drainage)[21].
Novel anorectal pediatric applications include evaluation of anorectal anomalies, anal sphincter defects in children with congenital anorectal malformations[22], rectal adenocarcinoma[23], and visualization of the anal sphincter complex to assist in the injection of botulinum toxin for the treatment of refractory idiopathic constipation in children[24].

E-POCUS can often distinguish benign from malignant subepithelial gastric lesions. Beyond the endoscopic size, shape, color, mobility, consistency, and appearance of the overlying mucosa, EUS can identify the layer of the lesion and whether it is hypoechoic, anechoic, or hyperechoic. These features have assisted adult gastroenterologists, who encounter these lesions much more frequently, to choose between endoscopic resection, fine needle aspiration, or core biopsy[25].

E-POCUS has been able to identify distal common duct biliary stones that were not seen on abdominal ultrasound or MRCP, features of chronic pancreatitis that were not seen on MRCP, and assisted in the evaluation of pediatric patients with biliary colic, acute and chronic pancreatitis and cholangitis[15].
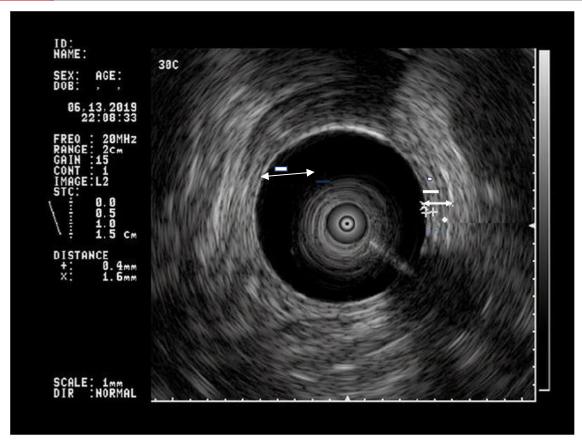
Figure: EUS of the Esophageal Wall.

E-POCUS performed after therapeutic interventions of esophageal varices was able to identify large peri-esophageal collateral veins and the existence of perforating veins as being significantly associated with the recurrence of esophageal varices (p<0.0001 and P<0.001, respectively). With a cut-off value of peri-esophageal collateral veins diameter of 3.5 mm, the specificity of predicting rebleeding in one year was 86% and the sensitivity was 45%[26].

Endoscopic Ultrasound of the Esophagus

The normal esophageal wall is comprised of a mucosa, submucosa, circular and longitudinal muscle, and a thin adventitia. Using radial echosonography, the probe is seen in the center, surrounded by a black ring (the lumen) with the esophageal wall appearing as a series of concentric circles which define its layers.

Moving outward from the black shadow, the first of the two contiguous cursors is the luminal border of the esophageal wall and the hyperechoic (brighter) layer in between the two contiguous cursors defines the mucosa. A thin hypoechoic (dark line) is marked by both the outermost of the two contiguous cursors and the luminal border of the solid white bar in the

figure. This corresponds to the muscularis mucosa. Moving further outward, the next hyperechoic (brighter) layer, defined by the solid bar in the figure, is the submucosa. The hyperechoic layer that starts at the end of the bar and goes to the second arrowhead is the muscularis propria. In certain portions of the image a feint dividing line between the innermost circular layer and outermost longitudinal muscle layer can be distinguished. The periphery of the muscularis is the adventitia and is indicated by the outermost arrowhead on the double arrow line, superimposed on the two separated cursors. The double arrow line indicates the diameter of the entire eosinophilic esophagitis wall, which is referred to as the total wall thickness (TWT).

Endoscopic Ultrasound in Eosinophilic Esophagitis

Endoscopic Ultrasound was initially employed in a seminal study of EoE in 2003 by Fox and coworkers which demonstrated that 11 pediatric EoE patients had thickened esophageal walls compared to 8 controls of similar ages. The cohorts were similarly aged and consisted of nine boys and two girls with EoE (mean age 9.5 years, range 3.4-18.2 years) and 8 controls (6 boys, 2 girls; mean age 9.3 years, range 2.0-15.3 years, mean age, $p = 0.869$)[27].

EUS was performed by a single investigator using a 20-MHz, 2.4-mm diameter catheter US probe (UM-3R, Olympus) and US processor (EU-M30, Olympus). Significant differences were found between EoE and control patients comparing mean values for total wall thickness (TWT) (2.8 vs. 2.1 mm; $p = 0.004$), mucosa plus submucosa (1.6 vs. 1.1 mm; $p = 0.001$), and muscularis propria (1.2 vs. 1.0 mm; $p = 0.043$). Mean values for circular muscle thickness (0.5 mm) were the same for EE and control patients ($p = 0.836$).

A second group confirmed the earlier observation of increasing esophageal diameter based on EUS measurements in EoE, which became a secondary outcome measure in their study of prolonged low dose steroid therapy for EoE[28]. Adults and adolescents older than 14 years, with clinically, endoscopically, and histologically confirmed EoE, who were initially brought into remission with high-dose (2 mg/d) budesonide, were studied. Each participant received an additional year of low dose (0.5mg/d) budesonide or placebo. EUS was performed before and after treatment in 13 budesonide and 11 placebo patients with an echoendoscope. Before budesonide induction treatment the active EoE patients had a significant thickening of all of the esophageal wall layers when compared with healthy controls: TWT (4.16 ± 1.20 mm vs 2.18 ± 0.35 mm; $P < .0001$), mucosa (0.75 ± 0.42 mm vs 0.36 ± 0.10 mm; $P < .0001$), submucosa (1.31 ± 0.77 mm vs 0.45 ± 0.12 mm; $P < .0001$), and the muscularis propria (0.82 ± 0.25 mm vs 0.55 ± 0.12 mm; $P < .0001$). After the year of low dose budesonide, the TWT decreased, with the most impressive reduction occurring in the mucosa from a mean of 0.75mm to 0.45mm ($P = .025$). Decreases in the deeper wall structures were less pronounced (submucosa, 1.31 to 1.08 mm; $P = .191$; muscularis propria, 0.82 to 0.76 mm; $P = .719$) and did not reach statistical significance. Of note, the individual wall layers and TWT still remained thickened in the EoE patients after one year of low dose budesonide, compared to their controls. In the placebo group, no significant changes were observed during the observation period. The widening that was described is now generally recognized as esophageal remodeling, the essence of EoE pathogenesis[29].

However, for EUS to be employed in children as a tool to evaluate esophageal wall thickening, normal values of thickness need be obtained. The literature has unfortunately not provided reliable measurements as has been previously summarized[30]. Until the completion of puberty, a child's body will be growing, including the esophageal wall. A single study has attempted to address this question and has found that the diameter of the esophageal TWT increases in both the mid and distal esophagus as a function of both age and height (p < 0.001 for both age and height at both sites)[30]. Using data obtained from their cohort, a preliminary equation to determine the average TWT as a function of age was determined. There were no significant differences in either the TWT or the diameters of the individual layers between the mid and distal esophagus (all p > 0.05). The diameters of the mucosa and the submucosa were comparable and together they were slightly thicker than the muscularis propria, thus contributing more than half of the TWT. Similar to the TWT, the diameters of each of the individual layers in both the mid and distal esophagus all correlated significantly with height and age.

Since the original paper by Fox and co-workers, only abstracts have been presented to confirm these results in children[31,32]. An ongoing prospective IRB approved study in our center has extended these preliminary observations. The esophageal wall diameters in both the mid and distal esophagus of older patients with active EoE were significantly increased compared to similarly aged controls and to similarly aged EoE children in remission. Multiple layers appeared to contribute to the increase and patients in remission had their esophageal wall measurements return to values similar to controls. These results demonstrate that E-POCUS can characterize both the esophageal wall changes that develop in active EoE and their resolution with appropriate therapy.

Most significantly, a couple of anecdotal reports have suggested that the resolution of symptoms, endoscopic abnormalities, and esophageal eosinophilia occur prior to the normalization of the EUS observed esophageal wall thickening in EoE[33,34]. A recent review article on the utilization of EUS in EoE has concluded that preliminary data "suggest that EUS and TWT measurement may become an important test in diagnostics, monitoring the effectiveness of therapy, assessing disease progression, and in individualizing the method and duration of EoE treatment in children"[35].

Roles for Endoscopic Ultrasound in Inflammatory Bowel Disease

Like EoE, inflammatory bowel disease (IBD) is a chronic illness that can result in the fibrotic remodeling of the gastrointestinal wall, and resolution of these changes is a therapeutic goal. As such it is an ideal candidate for E-POCUS to enable the clinician to augment clinical and mucosal observations with an appreciation of subepithelial anatomy. The recent introduction of POCUS in the

form of intraabdominal ultrasound to the office visits of IBD patients has provided convincing preliminary data and has resulted in the creation of guidelines to allow extension of this technique (see below). However, incorporation of EUS into the serial colonoscopies performed on IBD patients should be able to complement the traditional abdominal wall ultrasounds[36].

Perianal/Rectal Endsoscopic Point of Care Ultrasound

Rectal endoscopic ultrasound (EUS) presents the unique advantage of assessing concurrent endoscopic mucosal anomalies and sonographic alterations within the region most affected by ulcerative colitis (UC). Sonographic changes occurring beneath the superficial mucosa, or the presence of hyperemia could potentially serve as indicators of persistent inflammation. EUS can permit more accurate evaluation of perianal Crohn fistula as the transducer can be placed directly against the wall harboring the fistulae. EUS utilizing a miniprobe[37] can potentially be employed in all portions of the colon and proximal small bowel that can be reached by the endoscope including those that are retroperitoneal. In addition, EUS can be directly performed at the exact site of any significant endoscopic findings. For the evaluation of the anal canal, a radial echoendoscope is preferred, and for the rectal and pararectal regions, the linear echoendoscope is recommended[38]. EUS of the entire colon can be performed with either a forward-viewing linear echoendoscope or during conventional colonoscopy with an EUS mini probe. The advantages of each approach are described below.

The most widely utilized application of E-POCUS in Crohn disease has been the characterization of perianal fistula, because of its good sensitivity. It also has the advantage of assessing the macroscopic aspect of the recto-colonic mucosa and the ability to identify the internal orifice of the fistulous tract. EUS has limitations in identifying supra sphincteric and posteriorly located fistulous trajectories, while MRI has difficulty evaluating short, superficial, anteriorly located or anovaginal trajectories[39]. A study that compared the effectiveness of three methods (examination under anesthesia, MRI and EUS) for the evaluation of perianal CD patients included 34 patients (40 fistulas and 13 abscesses) and found no significant differences between the three methods. Each had an accuracy of between 87% and 91% and when any two of the three methods were combined, the accuracy approached 100%[40].

Differentiating Crohn Disease from Ulcerative Colitis

While the two forms of IBD, Crohn Disease (CD) and Ulcerative Colitis (UC), differ in both their distribution and depth of inflammation, there is still an appreciable minority of IBD patients that cannot be definitively distinguished and are referred to as indeterminate colitis. As E-POCUS can visualize the individual layers of the gastrointestinal wall, endosonographers have attempted to evaluate it as a means of distinguishing these entities. In one study mucosal, submucosal, and total wall thickness (TWT), along with regional lymph nodes (LN), were evaluated using forward viewing EUS[41]. The TWT was then compared with the macroscopic scores for inflammatory bowel disease (IBD) and the histological inflammation scores. TWT in controls (1.71 $\pm$ 0.02 mm)) was significantly less than in either form of active IBD (3.51 $\pm$ 0.15 mm). Furthermore, in *active UC, there was significant thickening of the mucosa*, while the submucosa and muscularis propria were mostly normal. *Conversely, in active CD, the submucosal layer was significantly thicker,* while the mucosa and muscularis propria appeared nearly normal. Another group also showed that active CD had thicker submucosa and TWT in their rectal and cecal walls, while active UC had increases in their TWT and in their mucosa but not submucosa or muscularis propria layers. Comparing active CD to active UC, rectal submucosa was significantly thicker in active CD (median, 1.80 mm [IQR, 1.40-2.00] vs 0.55 mm [IQR, 0.40-0.75], respectively, P < .01).[37]

As there is a significant impact on prognosis as TWT can be secondary to various etiologies including the edema of acute inflammation verses fibrosis, EUS elastography (see below) holds promise in distinguishing these conditions. Transrectal endoscopic ultrasound (TRUS) elastography has been employed to demonstrate key distinctions between CD and UC. A notably elevated strain ratio within the rectal wall and adjacent tissue was seen in active CD compared to active UC. This suggests a potential predictive capability of TRUS to identify CD patients who might eventually experience rectal involvement[42].

Monitoring Ulcerative Colitis Activity

Earlier EUS observations separated UC patterns into smooth, irregular, and blurred based on the degree of delineation between the individual wall layers which correlated with the degrees of severity[43]. Subsequently, another group developed an EUS scoring system that quantitatively assessed UC severity based on TWT, the layers that are involved, depth of the inflammatory process, and

hyperemia as measured by Doppler examination[44]. In a more comprehensive study, a third group described a significant positive correlation between their EUS scores and two clinical scoring systems (Truelove and Witts, Mayo) and with an endoscopic severity score. EUS-UC scores were higher in moderate Mayo index cases than in mild cases and were highest in severe cases. The same correlation of EUS scores with severity were also noted when patients were stratified by the Truelove and Witts scores ($P < 0.05$). After 2 months and 6 months of treatment, EUS scores were repeated and had significantly decreased from their baseline ($P < 0.05$)[45].

Identifying Extramural Tumor in Inflammatory Bowel Disease

EUS can assist in managing IBD complicated by tumors by enhancing diagnosis[46] or by accurately assessing the depth of invasion. This POCUS data can then be employed to select patients who may benefit from less invasive therapeutic methods, such as endoscopic resection[47].

Insights into Inflammatory Bowel Disease Derived from Endoscopic Point of Care Ultrasound

Two intriguing studies highlight how EUS may provide novel insights into IBD pathophysiology that were not previously appreciated. While UC is universally considered a mucosal disease, a group has described how hypoechoic changes in a group of severely affected UC patients extended into the muscularis propria. They defined EUS in active UC as follows: UC-M—intact parietal layer with thickened intestinal wall (limited to mucosal inflammation); UC-SM—hypoechoic changes extending to the superficial submucosal inflammation; UC-SMdeep—hypoechoic changes penetrating more deeply into the submucosal inflammation; UC-MP—hypoechoic changes extending up to the level of the muscularis propria inflammation; and UC-SS/SE—hypoechoic changes including the muscularis propria. The authors proposed vigilant monitoring for patients showing UC-SMdeep, UC-MP, or UC-SS/SE as they found that most UC patients requiring future surgery exhibited these advanced EUS features[48]. In another series of rectal EUS performed on 17 patients with acute infectious colitis of various etiologies, 15 patients had normal EUS wall features and no pathological lymph nodes. The other two patients with pathological lymph nodes went on to develop UC over the next few weeks[49].

Intrabdominal Ultrasound in Inflammatory Bowel Disease

Presently, the most effective application of ultrasound in IBD patients is not via EUS, but through transabdominal point of care ultrasonography performed during routine office visits in some centers[50]. A consensus group has generated specific guidelines to create a standard approach to the technique[51]. This form of POCUS adds valuable imaging of the intestinal wall without the need for a prep, a colonoscopy, sedation, or radiation, and is thus amenable to repeated examinations to follow the course of the disease and its response to therapy. However, the insights into the sonographic features of IBD patients can be adapted to improve the yield of EUS that could be performed during routine IBD colonoscopies. In both, bowel wall thickness (BWT) with particular attention to the layers that are primarily involved are the key determinants of disease activity. BWT varies by bowel region and by the degree of bowel distension, but a cut-off of <3 mm is generally used to differentiate normal bowel from pathologic bowel[50]. Future reports in both applications may include more sophisticated imaging of complex fistulae, phlegmon, abscesses, and mesenteric fat content. Adaptations of new EUS developments (see below) should enhance understanding of hyperemia via color Doppler signals and contrast enhanced UES, and distinguishing the nature of bowel wall thickening through elastography.

Challenges in Diagnostic Endoscopic Ultrasound of the Esophagus

Ultrasound is often referred to as an operator dependent technique because of potential variations in both acquisition of images and their subsequent interpretation. While diagnostic EUS can provide insights into the deeper organization of any healthy or diseased gastrointestinal tract wall, clinical utilization requires a single, uniform approach. The above referenced adult EUS study on EoE patients included a cohort of controls. Their mean esophageal wall TWT of 2.18 ± 0.35 mm[27], is very similar to the controls in the pediatric EoE study[28], even though TWT correlates with age. However, the actual reported sum of the individual layers in the adult controls (mucosa + submucosa + muscularis) equaled 1.4 mm, virtually identical to the values reported in the study of pediatric controls[30]. The authors recognize this disparity and state that "the total wall thickness included entry and exit signals and therefore exceeded the sum of the three single layer signals". Two smaller published series have also yielded EUS TWT results in EoE patients that emphasize the need for a single,

universal methodology in order to compare and interpret these measurements. Among ten Japanese adults with clinical, histologic, and multiple endoscopic features of active EoE that included a cobblestone-like appearance in five patients, only a single patient had increased TWT[52]. In a small study of 29 Danish children, the mean TWT (3.4 mm distally and 3.2 mm proximally)[53] were considerably greater than the corresponding values reported in the control adults in the EoE study referenced above[28].

Several areas of potential controversy were uncovered while performing 130 diagnostic EUS investigations on 100 pediatric patients with suspected, newly diagnosed or treated EoE in our center. These include issues surrounding obtaining the sonographic images and their interpretation. Initially, we attempted to obtain the most reproducible images, however in the course of our study we found that images that were physiologically relevant were not being considered. Specifically, in patients with furrowing there can be a dramatic increase in the wall diameter in the presence of the furrow. Addition potential sources of controversy have previously been summarized[54]. These include: determining how high above the endoscopic LES to measure (we have gone to 3 cm or more) to avoid the physiologic thickening of the lower esophageal sphincter; technical difficulties in distinguishing the mucosa and the submucosa interface, especially in younger children; and the precise locations to utilize for the mid and proximal measurements.

Besides those variables listed above, since acoustic coupling in ultrasound requires a water air interphase, another fundamental issue is if water should be added to yield passive or maximal distension of the lumen. In addition, adding and maintaining the water itself to allow coupling can be formidable. For example, in the distal esophagus relaxation of the lower esophageal sphincter rapidly evacuates the added water. A recent series of 1598 EUS cases performed to evaluate gastric wall cancer in adults, reported that the procedure required the addition of 300-800ml of water into the stomach[55]. While maximal distension can theoretically be a more reproducible end point, it can also yield a slight decrease in wall thickness secondary to the distension itself. In our center we have been able to overcome this issue of passive *vs.* maximal distension with the utilization of a balloon sheath which can fit over the Olympus miniprobe. Filling the balloon with water creates the acoustic interface, avoiding the need to add free water to the lumen, and the problem of seeing the water go through a relaxed lower esophageal sphincter thus requiring a repetition of the process. We have employed a pre-assembled Olympus ultrasound miniprobe (UM-BS20-26R) inside of an Olympus latex balloon sheath (MAJ-643R) filled with water and advanced it through the 2.8mm working channel of a GIF-Q180 or GIF-160 standard pediatric Olympus endoscope. EUS was performed using acoustic coupling from the water in the latex balloon sheath, obviating the need for adding free water or suctioning the air out of the esophagus. With this approach values of the mucosa, mucosa plus submucosa, and the total esophageal wall were able to be obtained from both the mid and distal esophagus in an average of less than 8 ½ minutes (Rabinowitz et al, unpublished results).

A final issue that will need to be determined is whether measurements obtained with different EUS instruments, are all equivalent. Presently, there are no guidelines describing the recommended conditions to guide the performance of EUS in EoE patients. It has been recommended that a panel be convened consisting of experts in the field of EUS to address these[54]. A consensus guideline can be created and then disseminated with representative EUS images to illustrate the principles. This will permit clinical clarity when reporting EUS characterization of subepithelial pathology. In addition, multicentric scientific investigations using a single technique may then provide evidence-based recommendations.

Different Endosonography Instruments and Techniques

The typical EUS study in adults is performed with a thicker, specialized instrument, an echoendoscope. These are also typically employed for therapeutic studies in children. Alternatively, an EUS miniprobe can be placed through the biopsy channel of a standard endoscope to provide the images. Echoendoscopes typically scan over a limited frequency range of 5 to 12 MHz, whereas miniprobes allow scanning at higher frequency (usually up to 20 but now available to 30 MHz). Scanning at higher frequencies limits the penetration (i.e. depth) of the ultrasound beam, but improves resolution. Thus, higher frequencies allow for better image resolution of near objects (2 cm from the transducer), whereas lower frequencies allow better EUS penetration and imaging of structures up to 12 cm from the transducer.

Echoendoscopes have the probe incorporated into the tip of the scope and thus are thicker than standard endoscopes. They can be radial-array or linear. The radial-array transducers are oriented

around the distal tip in a 360-degree radial array, producing an image in a plane perpendicular to the long axis of the echoendoscope. Radial-array echoendoscopes are used only for diagnostic EUS examinations and thus have limited applications because tissue sampling and therapeutic interventions are not possible. Linear echoendoscope's images are in a plane parallel to the long axis of the echoendoscope, usually in a sector between 100 and 180 degrees. These images are analogous to images from transabdominal US scanning. The image orientation in the linear-array echoendoscope supports tissue acquisition and therapeutic interventions as EUS needles are advanced from the distal tip of the echoendoscope in the same plane as the US image. This allows for simultaneous visualization of the target lesion and the EUS needle as it is advanced. Accurate control of the depth and position of the needle into the target lesion is therefore possible under linear EUS guidance. In addition, all curvilinear-array instruments incorporate an elevator at the distal end of the working channel that allows limited control of the angle of exit of EUS needles or other devices from the working channel[56]. The primary problem for pediatric endosonographers is their relatively large size (see below).

EUS can alternatively be performed with an ancillary miniprobe (EUS-MP) that passes through the biopsy channel of a standard endoscope or colonoscope, as utilized in the pediatric EoE study[27]. Thus, EUS-MP could have wider applications, reaching areas of the gastrointestinal tract that are only accessible to a narrower scope [57] and potentially being available during any endoscopic procedure. Miniprobes are available with 12 or 20 MHz frequency. The 20 MHz probe provides higher resolution imaging and can yield more anatomical details. While the higher frequency sensor limits penetration to ~20 mm[58], this still permits imaging of the full thickness of almost any portion of the gastrointestinal tract reached by the endosonographer.

Safety, Value, And Cost

Multiple review articles have shown that the cumulative body of literature attests to the safety of diagnostic EUS [18-20,56]. One comprehensive review of the published pediatric EUS literature reported that there were no major complications in the included studies and that five studies reported minor complications ranging from 2 to 22%, with a mean value of 2%[18].

While there is no significant series that examines non-interventional diagnostic EUS (i.e. with only

image acquisition and without sampling of fluids and /or tissue) the risks would be even lower and likely similar to those observed in routine endoscopy without the addition of the endosonography. The NASPGHAN position paper on pancreatic EUS and ERCP stated regarding the use of EUS to primarily diagnose pancreatic abnormalities and to obtain fluid and or tissue for analysis, found that the risks associated with pediatric EUS are less than 1% and include infection, perforation, bleeding, and pancreatitis and that the risk rates appear similar to those reported in adults[20]. Esophageal intubation of a small child with a larger EUS echoendoscope carries an increased risk of cervical esophageal perforation. Some authors have reported successful EUS in children <1 year of age, as small as 15 kg, while one group has reported successful therapeutic EUS in children as small as 12 kg[14].

Regarding the cost-effectiveness, adult studies showed that EUS, when incorporated into a diagnostic algorithm, is cost-effective, especially in conjunction with fine needle guided procedures and when compared with other imaging modalities (e.g., CT and magnetic resonance imaging) and/or surgery. However, when considering the cost of EUS procedures, maintenance and repair of EUS equipment is highly expensive, and should be taken into consideration. [21]

In pediatric studies, several of those listed in the table have attested to the value of EUS in their clinical experience. In the most focused analysis, EUS led to a new diagnosis in 34 of 43 (79%) patients and prompted further intervention in 24 of 51 (47%) procedures[18]. The largest review concluded that EUS played a significant role in establishing a definitive diagnosis and managing pediatric disorders with an important clinical impact ranging from 35.5-100%, with a median value of 81.7%. The authors explain that the possible reason for the individual study with the lowest (35.5%) impact was likely related to their lack of follow up in recurrent acute pancreatitis. Utilizing EUS to rule out the presence of biliary stones and thus avoiding ERCP was felt to be a positive impact in management[19].

Future Frontiers of Endoscopic Point of Care Ultrasound

E-POCUS in pediatrics continues to evolve to incorporate novel applications in children, following the path of EUS in adult patients[56]. This will lead to clinical patterns of care that would have been inconceivable a short time ago, such as the recommendation of endosonography as the initial procedure for mediastinal node biopsy in certain forms of lung cancer from the European

Respiratory, Thoracic Surgeons, and Gastrointestinal Endoscopy societies[59]. One recent application of E-POCUS describes how a 1.5 cm gastric antral tumor noted on endoscopy was characterized as a submucosal tumor of the muscular layer that did not penetrate the serosa and had no perigastric nodes. Surgical removal was performed and revealed a benign gastric myoadenoma[60].

Just as laparoscopic surgery has created a less invasive alternative to traditional laparotomy, utilizing EUS to gain a deeper appreciation of anatomical relationships, has provided surgeons with an even less invasive approach. Dr. Luigi Dall'Oglio, a pediatric surgeon, has recently shared some of his experiences. A 17-year-old boy with severe neurological impairment requiring jejunal feedings, was plagued by repeated dislodgement of the percutaneous gastrojejunal feeding tube. Utilizing EUS and fluoroscopy a gastrojejunostomy was created with a metal stent and several months later after it had matured, the feeding tube was modified to go directly from the stomach into the jejunum. A second child was referred with superior mesenteric artery syndrome after multiple attempts to pass a feeding tube were unsuccessful because of proximal duodenal dilation. EUS was initially employed to measure the aortomesenteric angle (which is a valuable both for diagnosis of the syndrome and for monitoring the progressive weight regain). In the same sedation, utilizing EUS to identify a safe site without risk of complications from the abnormal vasculature, a gastropexy was performed. The team then was able to use the fistula to introduce a small scope into the distal duodenum and then place a feeding tube beyond the obstruction. A third case involved EUS to treat a child with a large pancreatic cyst that had created a gastric outlet obstruction. In this child EUS allowed for drainage of the cyst into the stomach and subsequent endoscopic placement of a nasal jejunal tube to allow the child to begin feeding while the cyst was resolving[61].

Two novel techniques that will improve the resolution and utility of E-POCUS, to appreciate vascular dynamics and tissue inflammation, are contrast enhanced ultrasound (CEU) and elastography[20]. On conventional ultrasound images, blood flow characteristics cannot be readily assessed so vessels appear black. Contrast enhance EUS uses gas-filled microbubbles injected intravenously during the EUS exam after baseline images have been obtained [57,62]. CEU images are obtained from the arterial (10 to 20 seconds after injection) to the venous phases (30-45 seconds after injection). The relatively large size (similar to erythrocytes) of the microbubbles employed in CEU ensures that they remain intravascular, so they function as red blood cell tracers. For parenchymal organs, a longer and higher parenchymal/venous phase enhancement is visible followed by a progressive decrease in enhancement until the microbubbles are no longer seen. Different enhancement patterns can help identify a lesion's vascular composition, which can assist with identifying inflammation, angiogenesis, and thrombus formation. Furthermore, microbubbles are surrounded by a thin phospholipid bio-compatible encapsulation which permits the introduction of endothelial markers. This allows CEU to provide an appreciation of the roles that CAM-1, VCAM-1, and integrins (which have already been incorporated into microbubbles) are playing in pathology and in the response to therapy. The diversity of potential markers is just being realized suggesting a potentially new wave of personalized medicine[62]. The next technological advancement to be realized will be the utilization of nanobubbles, which will further extend the ability to visualize microvascular dynamics in a variety of gastrointestinal diseases.

Tissue elastic imaging allows the calculation of tissue stiffness as a non-invasive marker of fibrosis. Elastography can be paired with E-POCUS to measure relative tissue stiffness by creating a color map image that reflects fibrotic changes in the gut wall. The accuracy and potential of this approach is demonstrated by a recent investigation which was able to correlate pancreatic fibrosis, measured by elastography, to pancreatic exocrine insufficiency in chronic pancreatitis[63].

However, the innovation that will bring all ultrasound, especially E-POCUS, to an entirely new level of accuracy and reproducibility will be the incorporation of artificial intelligence (AI) into the field. Presently, there are limitations in all branches of ultrasound related to image-related interpretation such as overlap of various diagnoses, interobserver variability, false positives, and false negatives. Recent improvements in deep learning techniques and computing power have made computer-aided diagnosis systems a useful tool in the field of medical imaging[64]. One clinical setting in which this is already having an impact is with pancreatic cancer. AI models have been successfully integrated with EUS to yield earlier detection of pancreatic cancer, thereby expediting management, reducing the risk of mortality, and decreasing the overall healthcare burden on individuals and healthcare systems across the globe[65]. Early results from the application of AI to the interpretation of EUS imaging in inflammatory bowel disease and celiac disease have added to

the enthusiasm regarding the future of this technology[66,67].

Conclusions

EUS has evolved into an added resource for gastrointestinal endoscopists which has led to structured programs to teach the technique to assure adequate availability. Presently, the focus has been on guiding the removal of fluid or tissue for clinical therapy as well as diagnostic analysis. Simultaneously, the value of point of care ultrasound (POCUS) imaging has also dramatically increased and a similar program to train physicians to develop expertise in this domain is underway. Gastroenterologists routinely attempt to analyze luminal disease by their endoscopic appearance. The ability to go from a superficial analysis of an encountered lesion to a three-dimensional detailed understanding of its anatomy and physiology, that can be immediately discussed with the patient, represents a significant improvement in the medical care of subepithelial gastrointestinal pathology. Incorporating recent and future technological advancements is expected to further improve the accuracy of these diagnoses and positively impact patient care and satisfaction.

Acknowledgement

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