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Interventional endoscopy for abdominal transplant patients

Tom K. Lin[a,b,*], Maisam Abu-El-Haija[a,b], Juan P. Gurria[c], Michelle Saad[a], David S. Vitale[a,b]

[a] Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., MLC 2010, Cincinnati, OH 45229, United States
[b] Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, OH, United States
[c] Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States

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ABSTRACT

Interventional endoscopy can play a significant role in the care and management of children pre-and post- abdominal solid organ transplantation. Such procedures primarily include endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), and balloon-assisted enteroscopy (BAE), though additional interventions are available using standard endoscopes (gastroscopes, colonoscopes) for therapeutics purposes such as endoscopic hemostasis.

The availability of pediatric practitioners with the advanced training to effectively and safely perform these procedures are most often limited to large tertiary care pediatric centers. These centers possess the necessary resources and ancillary staff to provide the comprehensive multi-disciplinary care needed for these complex patients.

In this review, we discuss the importance of interventional endoscopy in caring for transplant patients, during their clinical course preceding the potential need for solid organ transplantation and inclusion of a discussion related to endoscopic post-surgical complication management. Given the highly important role of interventional endoscopy in patients with recurrent and chronic pancreatitis, we also include a discussion related to this complex disease process leading up to those patients that may need pancreas surgery including total pancreatectomy with islet autotransplantation (TPIAT).

Introduction

Historically, surgical interventions have been the crutch of medical care, and in some situations the only option towards life-saving care for those with end-organ failure. Relative to modern standards, early surgeries may now appear to be crude and primitive. Over the last century, there has been a whirlwind of medical and surgical advances that have revolutionized medical practice today. Surgical approaches are now placing a greater emphasis on enhanced recovery protocols and minimally-invasive surgery[1] to promote shorter hospital stays, including outpatient management strategies of rehabilitation and post-operative recovery at home,[2] while maintaining favorable outcomes. Laparoscopic and robotic surgeries have been aspects that have taken hold, and so too has interventional endoscopy.[3,4]

Within the realm of pediatric gastroenterology, there are many diseases that can be fulminant or progress insidiously towards end-organ failure. Such abdominal organs encompass the liver, pancreas and small bowel. In this review, we will discuss the growing field of pediatric interventional endoscopy from its early roots to its flourishing evolution, and now as a rapidly developing field with new technologies advancing care for children.

Pediatric indications for solid organ transplants, including liver and small bowel transplant are reviewed elsewhere in *Seminars* series and will not be covered in detail within this review. Total pancreatectomy with islet autotransplantation (TPIAT) is unique in that, following complete pancreatectomy, harvested autologous islet cells are *transplanted* or infused back into the patient most often via the portal vein.[5] Patient candidates for TPIAT are those with debilitating disease from recurrent or chronic pancreatitis (CP) and may undergo pre-surgical interventional endoscopic procedures for diagnostic and therapeutic purposes. Such interventions will be discussed in detail.

From diagnostic to interventional endoscopy

Endoscopy has rapidly developed from crude, rudimentary rigid endoscopes with poor imaging capabilities to today's advanced flexible endoscopes including fully disposable endoscopes.[6] This has not come about overnight nor without many reiterations of

* Corresponding author at: Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave., MLC 2010, Cincinnati, OH 45229, United States.

E-mail address: tom.lin@cchmc.org (T.K. Lin).

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endoscopes after research and development investments into the current available endoscopic arsenal.

The adage that *necessity is the mother of invention* equally applies to gastrointestinal endoscopy. Endoscope development has gone through stages, with industry first introducing endoscopes to meet the needs of gastroenterologists to apply to adult-sized patients. These same adult-sized endoscopes have then been utilized in children despite the limitations of their original design with no proper consideration for the smaller patient in mind. Fortunately, supply and demand market forces have directed industry to develop 'pediatric-sized' endoscopes, allowing for pediatric gastroenterologists to perform diagnostic and therapeutic endoscopic interventions in patients as small as newborn babies.[7,8]

Endoscopic retrograde cholangiopancreatography (ERCP) is an advanced endoscopic intervention typically performed for therapeutic application.[9] Technologic advances have led to the development of an infant duodenoscope allowing for ERCP to now be performed in all age groups when appropriately indicated.[8]

Historically, ERCP and other interventional endoscopy procedures in pediatric patients were performed at a much smaller scale and mostly by adult gastroenterologists with advanced training in interventional endoscopic techniques. However, there has been a marked increase in pediatric providers training in and performing these procedures effectively at pediatric centers in recent years.[10,11] Under skilled expertise, ERCP can be provided for children of all sizes without limitations, with those <10 kg requiring special equipment and accessories. Better access and understanding of these procedures have led to increased utilization in pediatrics over the last 20 years.[12,13]

The newer endoscopic technologies include endoscopic ultrasound (EUS) utilizing specially designed echoendoscopes. EUS is well established in the adult population, however, its use in pediatrics is still a burgeoning field. The procedure involves an endoscopy performed utilizing an echoendoscope or a scope-based ultrasound probe that allows a transluminal sonographic evaluation of the intrabdominal organs. Standard equipment can be used in children weighing more than 15 kg, while use of endobronchial ultrasound scopes (EBUS) or through the scope probes is necessary in smaller children.[14]

Pediatric liver transplantation

Pre-transplantation

An increasing number of children are now undergoing liver transplantation because of the larger number of indications that have been identified as benefiting from the surgery.[15] In children, biliary atresia (BA) remains the most common indication, with nonalcoholic fatty liver disease becoming one of the more rapidly growing causes for transplantation in adults and adolescents. The utility of interventional endoscopy pre-transplantation is dependent upon the underlying condition. Magnetic resonance cholangiopancreatography (MRCP) has generally supplanted ERCP for diagnostic imaging of the biliary tree, but there remains a small handful of conditions whereby diagnostic ERCP can play a significant role. Neonatal cholestasis, unique to the pediatric age group, is one such condition. Though not the most common cause of neonatal cholestasis, BA is a disorder that requires a timely and accurate diagnosis due to the known clinical benefits of early diagnosis and surgical intervention.[16] ERCP can be integrated into the diagnostic algorithm for the work-up of neonatal cholestasis when other testing modalities cannot reliably rule out BA. Appropriately sized equipment and available expertise are prerequisites to safely performing ERCP in this youngest of age groups.[17]

Primary sclerosing cholangitis (PSC) is a rare, poorly understood chronic inflammatory liver disease characterized by multifocal stricturing of the biliary tree.[18] Concern for the presence of a dominant stricture will prompt the need for an ERCP with the intent of improving biliary drainage through balloon dilation with or without temporary stent placement.[19–22] As part of the ERCP procedure, due to the associated risk of cholangiocarcinoma (CCA), brush cytology and/or biopsies of the stricture should be performed, though disease progression towards the development of hepatobiliary malignancy while of pediatric age is rare.

Additional complimentary endoscopic approaches that have been potentially useful for this disease are cholangioscopy and EUS. Cholangioscopy allows direct intraductal visualization of the biliary tree employing use of a cholangioscope through the working channel of a standard adult duodenoscope.[23] Current technological advances permit single-operator management and provides improved imaging. Cholangioscopes have irrigation capabilities, visually-directed biopsies and wire guidance, electrohydraulic or laser-assisted lithotripsy, and basket accessories for retrieval of intraductal stones.[24] EUS with fine needle aspiration (FNA) or fine needle biopsy (FNB) has been used to assist with diagnosing CCA,[25] but concerns remain related to possible tumor seeding through the needle track.[18]

Due to the absence of clear disease modifying medical therapies for PSC, progression towards end-stage liver disease can be expected[26] in most patients, whereby liver transplantation is now considered the only curative treatment option.[27]

Primary liver disorders often benefit from obtaining a liver biopsy sample. Traditionally, the hepatologist has performed this procedure percutaneously with or without image guidance (ultrasound vs CT) using an array of available needles. This procedure has trended away from the hepatologist and towards the radiologist in recent years. However, with the growing availability of EUS, EUS-guided liver biopsy (EUS-LB) appears to provide key advantages over other approaches.[28] From a patient convenience standpoint, performing an EUS-LB when a concomitant endoscopic procedure is indicated can be convenient, cost saving, and allows the measurement of portal pressure and the evaluation of varices. Bilobar liver sampling is also possible via EUS, thus potentially providing for a more complete assessment of underlying liver pathology. It is unlikely that EUS-LB will monopolize the traditional percutaneous liver biopsy need in children, especially while available expertise is limited and equipment size constraints persist but is a feasible option with a growing level of interest, most especially for large tertiary care pediatric centers.

Gastroesophageal variceal management

Endoscopic management of gastroesophageal varices (GOV), esophageal and gastric, is a valuable pre-transplant modality for primary and secondary prophylaxis management of variceal bleeding. Several approaches are available but endoscopic variceal ligation (EVL) remains one of the most effective first-line approaches.[29]

Best management practices of GOV in children is sub-optimally understood and much less evidence based when compared with adult cirrhotic patients, with a gross paucity of pediatric randomized controlled trials. This is in part due to a lower prevalence of children with liver cirrhosis with the greater number of such patients being secondary to biliary atresia who often undergo early liver transplantation. Moreover, pediatric cirrhotic patients may respond differently to prophylactic therapies depending upon their primary disease. Efforts have been made towards directing needed research that will help reliably identify children with varices who are at increased risk for bleeding with proven therapies that are able to mitigate patient morbidity and mortality; however, multiple barriers exist towards accomplishing these objectives, notwithstanding the necessity for a large sample size to achieve an adequately powered study.[30] For the purpose of this review, we will present available endoscopic interventions most commonly employed in adult patients that may have pediatric application.

EVL remains one of the most effective first-line management tools for GOV. Though noninvasive esophageal capsule endoscopy is available for esophageal variceal screening and monitoring, sensitivity is lacking and thus does not replace the advantages of esophagogastroduodenoscopy (EGD). EVL, specifically band ligation, as *primary prophylaxis* prior to the onset of gastrointestinal bleeding from portal hypertension benefits patients with an elevated risk for variceal bleeding, primarily those with medium to large size varices. Nonselective ß-blocker (NSBB) usage in adult patients may prevent first variceal hemorrhage but can be medically contraindicated or poorly tolerated due to adverse side effects. Combined therapy of NSBB and EVL versus EVL alone has not been shown to be more advantageous for *primary* bleeding prophylaxis or patient mortality.[31] A small number of pediatric case series have reported the safety and benefits of the use of EVL for primary prophylaxis of variceal bleeding.[32–34]

Secondary prophylaxis of active or post-variceal bleeding benefits from an endoscopic approach. Following patient resuscitation and stabilization from an acute variceal hemorrhage, recent areas of hemorrhage may be identified endoscopically by visible active bleeding, a platelet plug or an overlying clot, and should be targeted for band ligation.[35] Red wale signs may not be reflective of a definitive bleeding source, but rather represent an area of increased bleeding risk. At times, complete endoscopic visualization may be obscured by excessive active bleeding impairing safe and directed band ligation placement. In such cases, injection sclerotherapy to control active bleeding may initially be needed to allow the ability to then perform band ligation. Studies have shown inferiority of injection sclerotherapy when compared with band ligation as first-line therapy of bleeding esophageal varices,[36] but it may be an alternate option when EVL is technically challenging such as when the presence of scar tissue limits the ability to fully deploy a band around a varix. Available pediatric literature also appears to support the advantages of EVL over sclerotherapy for secondary prophylaxis of variceal bleeding.[37,38]

Temporary placement of covered self-expandable metal stents (SEMSs) has been employed to emergently tamponade refractory esophageal variceal bleeding. Some stents can be placed with endoscopic guidance with a recent meta-analysis of such stents showing a high-rate of response (93.9%) with no reported stent-related complications.[39] More data on the safety and efficacy profile of esophageal stents is needed before it routinely employed other than in cases of refractory variceal bleeding.

Bleeding gastric varices is a much less common occurrence when compared with esophageal varices, but with gastrointestinal bleeding that can be more severe and difficult to manage with a greater level of associated morbidity and mortality. Gastric varices in adult patients have been classified according to the extension of esophageal varices into the stomach along the lesser curvature (GOV type 1) versus the greater curvature (GOV type 2), or isolated gastric varices (IGV1 – localized to the fundus; IGV2 – localized to the body, antrum or pylorus). The approach to management of GOV1 varices is like that of esophageal varices. EVL has a limited role in IGV management primarily due to the difficulty in effectively banding these varices (larger size and thicker mucosa preventing effective band ligature deployment).[35,40] As such, glue injection is the preferred method of management for gastric variceal bleeding, but adverse events can be significant including stroke and pulmonary embolism.

EUS has the ability to help guide glue injection management of gastric varices by means of improving detection of varices through thick gastric folds, but also through Doppler assessment for residual variceal blood flow which can help determine rebleeding risk.[41] EUS has also been used to guide placement of coils into gastric varices with or without glue injection with a high rate of therapeutic success and a low occurrence of procedure-associated adverse events.[42–44] Such advanced interventional endoscopic interventions should be reserved for large tertiary care referral centers with the appropriate expertise.

Post-transplantation

Following liver transplantation, interventional endoscopy has proven to be critically beneficial in managing biliary complications, the most common of which are stricture development (subcategorized into anastomotic vs non-anastomotic). Such strictures have been shown to adversely impact graft survival,[45] underlying the importance of therapeutic interventions that can effectively treat these complications.

Accessibility of the stricture(s) can be highly dependent upon the type of biliary reconstruction performed, with the two most common being choledochocholedochostomy (CC, duct-to-duct anastomosis, Fig. 1 A,B) and choledochojejunostomy (CJ). In the latter, alternative approaches may include percutaneous transhepatic cholangiography (PTC), laparoscopy assisted ERCP, or surgery. The CC anastomosis can be readily accessed by means of standard ERCP approach via the native papilla, though failed ERCP biliary access may prompt the need for rendezvous by means of PTC, or in some cases EUS when local expertise and experience is available.[46] CJ success is most often limited by the ability to deeply access the Roux limb. However, with the advent of balloon-assisted enteroscopy (BAE), this in part has provided an endoscopic approach to overcome this obstacle with reported success rates exceeding 80%.[47] An additional limitation with this approach is the limited number of therapeutic accessories of adequate length corresponding to the greater length of the enteroscope instrument. Practitioners need to continue to closely collaborate with the accessory manufacturers regarding their clinical needs in order to be able to provide the most advanced approaches/techniques in a growing world of patient complexity.

Bile leaks at the anastomosis, level of the cystic duct, or secondary to T-tube placement are additional post-liver transplant complications that can be encountered.[48–51] Diagnostic suspicion of such leaks can be initially evaluated with ultrasound or nuclear scintigraphy, but ERCP remains the diagnostic gold standard with therapeutic capability. The therapeutic objective is the redirection of biliary flow away from the leak by temporary intraductal stenting with or without biliary sphincterotomy with a high rate of success obviating the need for surgical revision.[51] Use of plastic biliary stents rather than fully-covered self-expanding metal stents (FCSEMS) is recommended due to concerns for secondary stricture development with the latter.[52]

Post-transplant stone development has been associated with biliary strictures, hyperlipidemia, and underlying biliary pathology including ischemia, infection, and acute rejection.[50,53,54] Bile casts have been associated with similar overlapping risk factors.[55,56] Standard ERCP approaches and accessories are most often successful in extracting these stones and alleviating the obstruction.

Endoscopic ultrasound in acute recurrent and chronic pancreatitis

The pancreas and peripancreatic areas can be closely examined with EUS, and in the pediatric literature, this is the most frequent indication for EUS.[57–59] As the incidence of pancreatitis is increasing in pediatrics, the utility of EUS in acute recurrent pancreatitis (ARP) and CP is evolving.[60] Cross-sectional imaging often reflects late, chronic changes to the pancreas. EUS is not well investigated in pediatric ARP and CP, but as a more sensitive imaging modality,

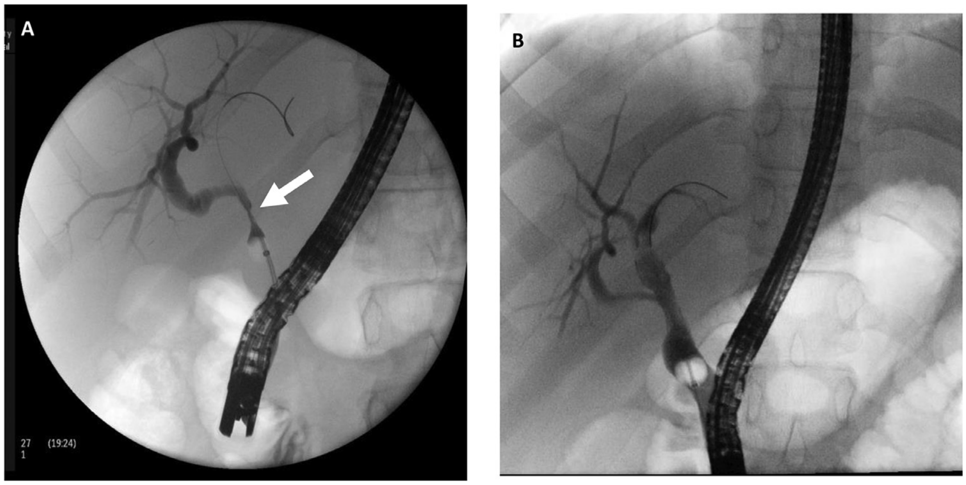

Fig. 1. (A) 13-year-old post-liver transplant recipient with anastomotic biliary stricture (arrow). (B) Stricture post serial balloon dilations via ERCP.

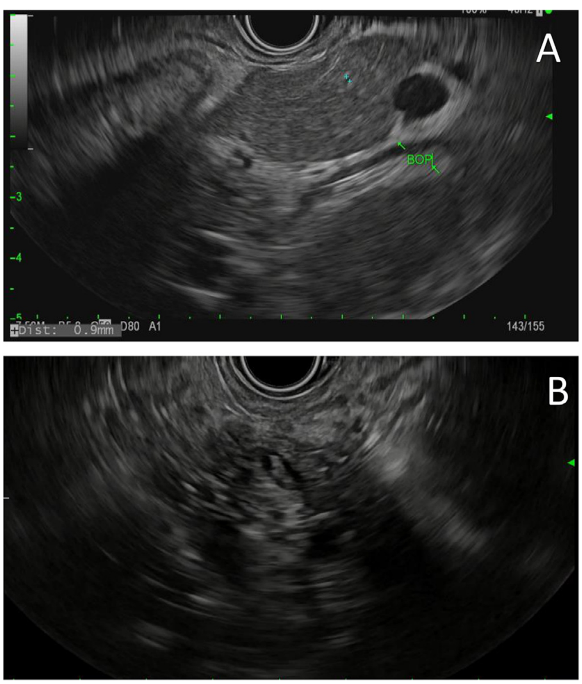

Fig. 2. (A) EUS image showing normal pancreatic parenchyma and pancreatic duct at the body of the pancreas in a 16-year-old. (B) EUS image showing chronic pancreatitis in the body of the pancreas with a dilated, ectatic pancreatic duct, stone debris within the pancreas duct and hyperechoic foci with shadowing in a 7-year-old.

its use represents an opportunity to potentially diagnose early or minimal change CP before irreversible damage occurs.

EUS has been established in adults since the 1980s and can reveal changes suggestive of CP such as calculi within the main pancreatic duct or pancreatic parenchyma, narrowing or dilation of the ducts, and parenchymal changes reported by the well accepted adult Rosemont criteria (Fig. 2 A,B).[61–63] Etiology can be identified in up to 75% of patients with idiopathic ARP.[64] In contrast, validated pediatric data remain scarce and pediatric EUS criteria for CP do not exist. EUS adult data does show benefit of EUS in ARP and CP. While EUS findings in early CP or indeterminate categories need to be correlated with clinical and functional analyses, combining MR and EUS findings can offer up to a sensitivity of 98% for CP and 100% specificity.[65,66] A recent systematic review and meta-analysis of 43 studies on the diagnostic performance of imaging in CP reported that EUS outperformed MR and CT, with a sensitivity of 81% and specificity of 90%.[67] EUS offers additional diagnostic value in pancreatic lesions or suspected autoimmune pancreatitis, allowing FNA or FNB and better evaluation of pancreatic ductal stones or choledocholithiasis. Moreover, contrast-enhanced EUS is a novel approach that recognizes and delineates necrotizing foci in the pancreas that would not enhance at an early stage.[68] Elastography through EUS is an innovative approach to assess tissue rigidity and predict fibrosis in the pancreas.[69]

Besides its diagnostic value, EUS offers multiple therapeutic benefits.[14] While most pancreatic fluid collections resolve over time without intervention, EUS adds therapeutic value in symptomatic patients who require intervention. Interventions through EUS can include the creation of a cyst-gastrostomy or cyst-duodenostomy for drainage if indicated, and are preferred to open surgical intervention, offering equal success rates, similar adverse events profile, and recurrence risks (Fig. 3 A,B,C).[14,70] Additionally, studies found that the duration of hospitalization and cost of treatment is less in the EUS transluminal drainage compared to the surgical approach.[71]

With cyst-enterostomy approach, both metal and plastic stents have been used in children for pancreatic fluid collection management with risks that include perforation, bleeding, and stent migration.[72] Use of biliary FCSEMS was associated with a high technical and clinical success rate for the management of walled-off necrosis (WON). These stents carry a risk of migration and difficulty in stent removal.[73] More recently, lumen-apposing metal stents (LAMS) have also been used with high success rates. While at present, this is the favored practice for pediatric WON requiring drainage, these stents do carry a risk of pseudo-aneurysm formation and bleeding, and removal is necessary within 4-6 weeks.[74–76] Typically the pseudocyst or WON resolve after the index procedure; however, in rare cases where necrosectomy is required due to infection or inadequate drainage, an endoscopic approach is preferred. Celiac plexus block can also be performed with EUS guidance in patients with debilitating pain from CP, with a reported 50-60% pain improvement in adults with CP and some improvement in case reports in children.[77–79]

Risks of EUS procedures include perforation, bleeding, bacteremia, and pancreatitis in patients who undergo FNA or FNB of the pancreas.[80] These risks are relatively low in diagnostic EUS, approaching similar rates of standard upper endoscopy. When accounting for interventional EUS procedures, complication rates are higher and risks versus benefits should be thoroughly discussed with families.[81]

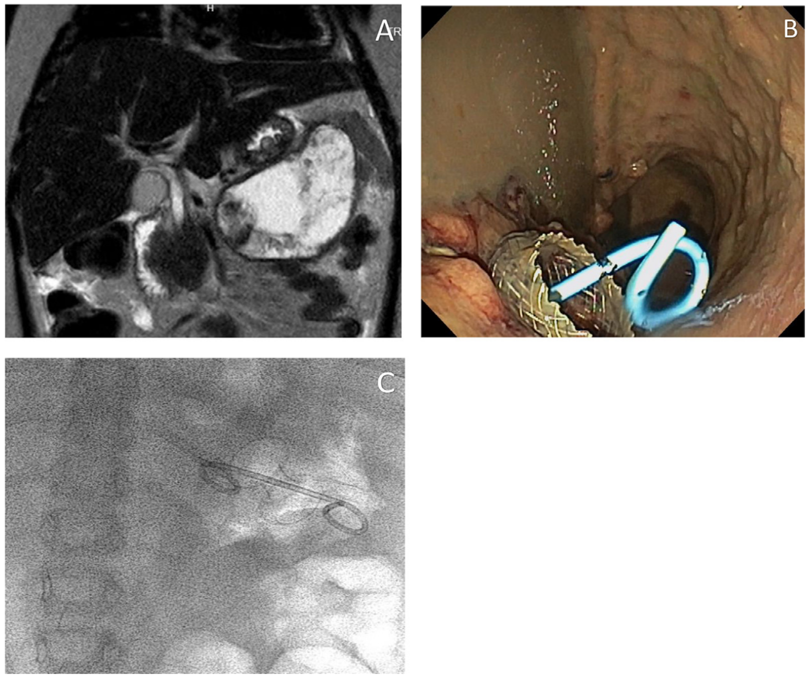

Fig. 3. (A) MRI showing pancreatic walled-off necrosis in a 9-year-old. (B) Endoscopic view of lumen-apposing metal stent placement for cyst-gastrostomy, with indwelling double pigtail plastic stent. (C) Abdominal X-ray of a lumen-apposing metal stent with a plastic double pigtail stent within its lumen for cyst-gastrostomy.

It is important to note, therapeutic EUS procedures should be performed only in high-volume tertiary care centers by interventional endoscopists (preferably with pediatric training).[14] EUS is currently underutilized in pediatric patients due to limited awareness and availability of such expertise. However, its application will only continue to grow with the pursuit to improve the care of children with ARP and CP.

Endoscopic retrograde cholangiopancreatography in acute recurrent and chronic pancreatitis

ARP and CP are some of the most frequent indications for pediatric ERCP[13,82,83]. Indications for ERCP in pediatric ARP and CP are geared towards etiologies in cases of biliary etiology, congenital anomalies (pancreas divisum, choledochal cysts, anomalous pancreaticobiliary junction), or towards the progression of the disease in cases of pancreatic duct calculi or pancreatic duct strictures.[14,84] Less well established and debatable indications include: idiopathic ARP and suspected papillary stenosis or increased sphincter pressures.[85] While adult guidelines suggest consideration of ERCP as a first-line therapy for painful uncomplicated CP, pediatric data remains scarce.[14,86,87] A study evaluating ERCP practice trends for ARP and CP from INSPPIRE (INternational Study group of Pediatric Pancreatitis: In search for a cuRE) examined practice patterns in ARP and CP, finding 65.8% of patients with CP had undergone ERCP vs 13.5% with ARP.[87]

Therapy for pancreatic duct strictures include major or minor papilla pancreatic sphincterotomy, along with possible catheter or balloon dilation of the stricture and serial pancreatic duct placements, typically over the course of approximately 12 months pending evolution of the stricture.[86] Pancreatic calculi can be treated with endoscopic sphincterotomy and subsequent stone removal utilizing extraction balloon sweep or basket retrieval methods (Fig. 4 A,B). Other methods for large calculi fracture and/or removal include extracorporeal shockwave lithotripsy and pancreatoscopy.[88] Biliary etiology of pancreatitis, typically gallstones, can be treated with ERCP with biliary sphincterotomy and stone extraction if required for cholangitis or evidence of ongoing biliary obstruction on laboratory work-up and imaging.[85,89] While MRCP is a preferred diagnostic modality, ERCP is the gold standard for the detection of anatomic pancreatic duct variants in children.[90] Pediatric studies have shown patients with ARP or CP with pancreas divisum risk factor have benefitted from minor papilla sphincterotomy and/or dorsal pancreatic duct stent placement.[91,92] In idiopathic recurrent pancreatitis without ductal dilation or with dilated pancreatic duct without obstructive factors, therapy is less well defined, with pediatric guidelines suggesting cautious utilization of ERCP after extensive counseling with family and patient.[93] While endotherapy for these issues in symptomatic pancreatitis are appropriate first-line therapies, it is important to recognize that technically successful ERCP does not always relieve a patient's symptoms.

Risks in pediatric ERCP include post-ERCP pancreatitis (PEP), bleeding, infection, and perforation.[10] PEP is the most frequently encountered risk, occurring in up to 12% of pediatric ERCPs; specifically, patients undergoing pancreatic duct cannulation and injection are at the highest risk for PEP.[94] Several studies have investigated preventative prophylactic measures for PEP in pediatric patients, with findings of decreased PEP rates with intravenous ketorolac and slightly decreased risk with intravenous ibuprofen (not reaching statistical significance).[94,95] In a multicenter registry study, in contrast to some adult studies, prophylactic pancreatic stent placement was found to increase rates of PEP in pediatric patients.[96]

The field of pediatric ERCP is continuing to evolve. As more pediatric trainees are exposed during fellowship training or choose to pursue careers in interventional endoscopy, indications, and benefits of endotherapy for pancreatitis will become increasingly recognized. Further studies are needed to better define indications and long-term outcomes of endotherapy for pediatric pancreatitis.

Surgical approach to acute recurrent and chronic pancreatitis

As outlined, endoscopic procedures can in some cases provide relief from symptoms of ARP and CP in select patients. Unfortunately, symptom relief from endoscopic interventions may be tran-

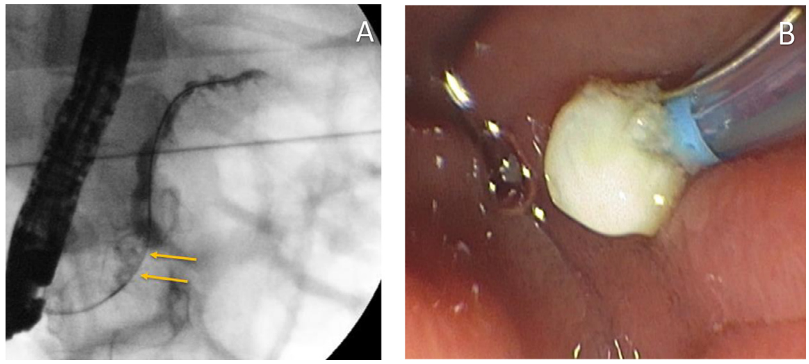

Fig. 4. (A) ERCP fluoroscopic image showing intraductal pancreatic stones (arrows). Upstream pancreatic duct is ectatic. (B) Endoscopic image of pancreatic duct stone extraction from the ampulla.

sient, especially in children with genetic risk factors leading to CP and progressive disease. Others may initially respond to therapy, such as pancreatic duct stenting for strictures; however, if the stricture persists beyond one year of serial stenting, surgical intervention should be considered.[86] Patients with ARP or CP who suffer from chronic pain despite maximized medical and endoscopic therapy, leading to recurrent hospitalizations and opioid dependence with affected quality of life, should be considered for surgical intervention. Surgical options include TPIAT or surgical drainage procedures such as lateral pancreaticojejunostomy (Puestow), or other surgical drainage variants (Frey or Beger). Rarely a focal pancreatic tail resection or pancreaticoduodenectomy (Whipple) may be considered, but indications for this in children with ARP and CP are exceedingly rare due to the limited presence of focal disease morphology (tail only or head only disease) in pediatrics.

Pediatric patients may benefit from TPIAT after a multidisciplinary team approach and extensive evaluation at a pancreas center of excellence. Total pancreatectomy alleviates pain, while islet auto-transplantation decreases the risk of difficult to control and/or brittle diabetes postoperatively. While a portion of patients is insulin-independent postoperatively, some will still require long-term exogenous insulin administration to maintain normal blood glucose. Glycemic outcomes post-TPIAT depend on the islet yield, the timing of surgery from the onset of symptoms, body mass index, pancreas mass, and fibrosis among other factors.[97] Patients will have exocrine pancreatic insufficiency (EPI) post-operatively and require pancreatic enzyme replacement therapy and nutritional monitoring.

Similarly, surgical pancreatic drainage procedures such as the Puestow procedure can offer pain relief in a subset of patients but are also of limited use in patients with hereditary pancreatitis, and pain relief is not always durable over a long-term basis.[98] Other surgeries can include partial resection or variants of a Puestow such as Frey or Beger procedures but are associated with high recurrence rates and increased exocrine and endocrine pancreatic insufficiency.[99–101]

TPIAT can offer a more durable solution than endoscopic management or pancreatic drainage surgeries. In one study, children 3-8 years of age with severe refractory CP who underwent TPIAT all had pain relief and were narcotic free post-operatively, with 82% of patients being insulin-independent compared to older age groups.[102] Some studies have shown that pain relief post-TPIAT is associated with a shorter duration of disease and fewer endoscopic interventions with ERCP.[103] Other risk factors such as pancreas divisum, obesity, higher opioid use, older age, and prior pancreatic surgeries have been associated with worse pain outcomes post-operatively.[5] Improved glycemic outcomes post-TPIAT and insulin independence in children have been associated with younger age, lack of prior drainage surgeries like Puestow, lower BSA, and higher transplanted islet yield.[104] A recent study that included 230 patients showed that preoperative ERCP, including the number of prior ERCPs, biliary or pancreatic sphincterotomy, or stent placement, had no impact on islet yield following TPIAT.[105] TPIAT is thereby a viable option for children with ARP or CP not improving with medical or endoscopic therapy and can lead to improved pain outcomes and improvement in quality of life in appropriately selected patients.

Endoscopy post pancreatic surgery

Endoscopy after pancreatic surgery is infrequently needed. However, endoscopic techniques have evolved and intestinal, pancreatic or biliary complications can often be managed endoscopically. BAE has become increasingly available, which allows deep enteroscope access in conventional or altered surgical anatomy.[106] Patients with a history of a pancreaticoduodenectomy may be successfully managed with ERCP using primarily conventional endoscopes with the availability of BAE devices as back up. Utilizing this method, success rates are reported up to 76.5% for pancreatic indications and 87.7% for biliary indications.[107] Post lateral pancreaticojejunostomy, patients can also successfully undergo ERCP.[108] Biliary and vascular complications of choledochojejunostomies or hepaticojejunostomies can be managed effectively.[106,109] While conventional endoscopes can sometimes be used, patients with Roux-en-y anatomy typically require BAE.[110]

In addition to pancreatic and biliary indications, gastrointestinal bleeding complications can occur post pancreatic surgery with altered surgical anatomy.[109] In the acute setting, GI hemorrhage can be typically treated with endoscopic therapy, pending the etiology and location of the bleeding. While endoscopic therapy for cessation of bleeding is often successful, more definitive management of sites with recurrent bleeding may need surgical intervention.

Delayed gastrointestinal motility occurs in patients with CP, specifically delayed gastric emptying (DGE) in 45–50% of patients with CP who undergo pancreatic surgery. Both classic pancreatoduodenectomy and pyloric-preserving pancreatoduodenectomy have been associated with DGE, likely due to devascularization and denervation of the pylorus, resulting in pylorospams. Duodenal resection, the length of the remaining duodenum, and post-operative decrease in motilin levels post-resection have also been reported as etiologies for DGE in this population.[111,112] Children post-TPIAT experience DGE in the early postoperative period and is persistent in some patients. A gastrojejunostomy tube is placed intraoperatively to decompress the stomach and allow distal enteral feeding through the jejunal port as soon as the small bowel ileus resolves postoperatively.[97,113] Typically, this is removed soon post-operatively as patients have transitioned to oral feeding. A subset of patients has persistent DGE symptoms or recurrent symptoms even years post TPIAT.

Studies in patients with recurrent nausea and vomiting, with or without evidence of mechanical obstruction have found unusually prolonged and intense contractions in the pylorus through endoscopic manometry.[114] The basal pyloric pressure was also elevated in patients with DGE when assessed with EndoFLIP.[115] Endoscopic botulinum toxin A (BoNT/A) administration under direct visualization into the pylorus has emerged as a method for patients with DGE refractory to diet, lifestyle modifications, and medical therapy. Symptomatic improvement at 1 month can be seen in about 64% of patients, and responders can have symptomatic improvement that lasts up to 6 months.[116] A retrospective pediatric study showed that endoscopic management of gastroparesis by balloon dilation or BoNT/A was safe and efficacious within the first few months but would require repeat interventions.[117] During TPIAT, surgeons have the option to administer BoNT/A directly into the pylorus to help alleviate the anticipated DGE post-operatively and bridge patients in the immediate post-operative period while allowing less nausea and more rapid advancement in feeds. Additionally, patients with persistent or recurrent DGE symptoms post TPIAT can be considered for endoscopic pyloric BoNT/A injection in conjunction with balloon dilation of the pylorus. Further study is needed for both intra-operative and post-operative BoNT/A pyloric injection in this patient population.

Intestinal failure

Intestinal failure (IF) is defined as a deficient functional intestinal mass below what is necessary for absorption, to adequately satisfy the nutrition, fluid and electrolyte requirements for growth in children. These patients are usually dependent on parenteral nutrition (PN).[118] The most common cause of IF in the pediatric population is short bowel syndrome (SBS), either from congenital or acquired intestinal loss. Of these, necrotizing enterocolitis is the leading cause of SBS, followed by gastroschisis and intestinal atresia.[119]

Chronic PN supports children through critical growth stages; however, the risk of intestinal failure associated liver disease (IFALD) and central line related bloodstream infections portend a significant source of morbidity and mortality. Patients with IF may eventually require an intestinal or multivisceral transplant should they develop progressive IFALD, porto-mesenteric thrombosis, loss of vascular access or recurrent central line infections, which would limit the chances of achieving enteral autonomy. Current 5-year survival after transplant is reported just under 70%.[120]

Endoscopy after intestinal transplant is often used for surveillance of rejection and infection through mucosal biopsies. Symptoms prompting endoscopic evaluation include increased stool output, diarrhea, fever, and abdominal distention with vomiting. Endoscopy may also be necessary to evaluate abdominal pain or concerns for gastrointestinal bleeding.

For patients undergoing intestinal transplant, acute cellular graft rejection is a major source of morbidity and mortality. It occurs in up to 40% of patients within a year after transplant and is the main cause of graft loss.[120] Early endoscopy is critical and represents the current gold standard for diagnosing and managing rejection. It has a significant role in the evaluation of post-transplant lymphoproliferative disease (PTLD), graft-versus-host-disease and infections.[121] Endoscopy in IF can be used for timely interventions of post-surgical complications such as gastrointestinal bleeding, fistulas, local or anastomotic strictures, gastroparesis and ischemia.[122]

To improve graft salvage rate and tailor immunosuppression accordingly, intestinal grafts should be surveilled for acute cellular graft rejection by experienced endoscopists given altered anatomy. The evaluation and diagnosis should be performed early, even if the patient is asymptomatic or has very mild symptoms of graft dysfunction like increased stool output, mild bleeding, persistent EBV or CMV viremia, or poor weight gain. It is recommended that biopsies are reviewed by experienced pathologists familiar with intestinal grafts and who are in close communication with the gastroenterologist since histologic-endoscopic correlation is not strong. Samples should be obtained from both the graft and native bowel to better discriminate infection from rejection. Studies have shown that up to 45% of histology-proven rejections can have normal-appearing endoscopies.[123] Rejection can be patchy throughout the graft, is better assessed in the ileum, and even in experienced hands, histologic findings of rejection are absent in approximately 20% of tissue samples of grafts with mild to moderate rejection.[124]

PTLD is uncommon but can bring significant morbidity and mortality to up to 16% of post intestinal transplant patients. It can present with fever, weight loss, diarrhea or recurrent gastrointestinal bleeding secondary to ulcerative nodular lesions that can be present throughout the entire graft. These lesions can also cause bowel obstruction. It is crucial to perform early endoscopic evaluation to obtain histological confirmation and start therapy.[125]

Bleeding from intestinal graft should be evaluated with upper endoscopy, colonoscopy, ileoscopy and less frequently capsule endoscopy, push enteroscopy or BAE. Most events are caused by nonspecific enteritis (erythema, ulceration with chronic inflammatory changes creating erosions); however, it can also be secondary to acute rejection, anastomotic ulceration, viral enteritis and varices. Endoscopic procedures should be performed to attempt bleeding control before surgical intervention. This can be achieved by injection of sclerosing agents or epinephrine, or bipolar electrocautery control in the case of bleeding ulcers.[126]

The most common complications from endoscopic surveillance and interventions in this patient population are perforation, hematoma, and bleeding. While procedure complications rates are reported at under 2%, they are more common than endoscopic procedures in the general population given the diverse anatomy, presence of multiple anastomoses, and immunosuppression state of these patients.[123]

Conclusion

This review of the current literature on endoscopic interventions summarizes the trajectory of pediatric interventional endoscopy as a growing field, with emerging technologies to advance the management of pre- and post- pediatric abdominal transplantation in conjunction with surgical interventions. The role of ERCP in pancreaticobiliary disorders has advanced from diagnostic to mostly therapeutic, given the improvement in cross-sectional imaging and MRCP modalities. Interventional endoscopic procedures inclusive of ERCP and EUS have implications in pre- and post-surgical management in liver transplantation, pancreatic surgeries, TPIAT, and intestinal transplantation.

In liver disease patients, indications for endoscopic interventions include biliary disease evaluation in BA, PSC, and in biliary obstruction, including stricturing disease. Cholangioscopy can be used as well in these patients. EUS has a role in diagnostic purposes, including liver biopsy. Post-surgical management of complications, such as biliary strictures or bile leaks can be managed endoscopically.

In ARP and CP patients, ERCP has a role in diagnosing and managing biliary causes, anatomic abnormalities such as annular pancreas, APBJ, and divisum, and in the progression of disease with pancreatic duct stones, strictures or duct disruption and leaks. EUS's diagnostic role in pancreatic diseases has evolved to include work up of idiopathic and/or CP, along with evaluation of and/or biopsy of pancreatic lesions and suspected autoimmune pancreatitis. Therapeutic applications include transgastric or transduodenal drainage of peripancreatic pseudocysts or WON.

In intestinal transplantation, the utility of interventional endoscopy is through the provision of timely diagnosis of graft rejection, infection, PTLD, or even management of intestinal bleeds.

In summary, interventional endoscopy has a growing application in a wide spectrum of abdominal pathology management in pediatrics. With advances in techniques and the increasing availability of skilled pediatric-trained interventional endoscopists at large pediatric centers, more patients have access to minimally invasive options that advance management and improve clinical outcomes.

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