The emerging role of endoscopic ultrasound for pancreaticobiliary diseases in the pediatric population

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Review article

Background: **Endoscopic ultrasound (EUS) is a useful diagnostic and therapeutic tool in the pediatric population. Given the high accuracy and sensitivity of EUS, it is particularly effective in evaluating pancreaticobiliary disease. Published literature in the use of pediatric EUS is limited. Therefore we aimed to review the current literature for EUS indications, safety, and effectiveness for the pediatric population.**

Data sources: **English language articles on the use of pediatric endoscopic ultrasound in evaluating pancreaticobiliary diseases were retrieved from PubMed/MEDLINE.**

Results: **We analyzed various retrospective studies and case series publications. Data were extrapolated for pediatric patients with pancreaticobiliary diseases.**

Conclusions: **EUS offers superior imaging. It is comparible to magnetic resonance imaging and/or pancreatic-protocol computed tomography. In the current literature, there are a variety of pancreaticobiliary conditions where EUS was utilized to make a diagnosis. These include recurrent pancreatitis, congenital anomalies, microlithiasis, pancreatic pseudocysts, and pancreatic mass lesions. EUS was shown to be a safe and cost-effective modality with both diagnostic and therapeutic capabilities in the pediatric population. EUS is now increasingly being recognized as a standard of care when evaluating pancreaticobiliary conditions in children.**

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Introduction

Evaluating pancreaticobiliary conditions in children often requires the specialty of a gastroenterologist. Endoscopic ultrasound (EUS) is becoming a more popular diagnostic and therapeutic tool for gastroenterologists, and can be effectively utilized in the pediatric population. The close proximity of the gastric and duodenal lumen to the pancreas and biliary tract results in high-resolution images. EUS offers superior imaging with performance comparable to magnetic resonance imaging (MRI) and pancreatic-protocol computed tomography (CT). Although endoscopic retrograde cholangiopancreatography (ERCP) has traditionally been used in the evaluation of different pancreaticobiliary diseases, it is invasive with 2.5% to 11% complication rate in children.[1] This article will review the emerging role of EUS in different pancreaticobiliary conditions in the pediatric population.

Equipment

EUS was first introduced in the 1980s.[2] A special ultrasound probe was installed to the tip of an endoscope, and a water-filled balloon surrounds the ultrasound transducer to enhance the acoustic coupling. Due to the close proximity of the pancreas to the upper gastrointestinal tract, it was first used in adults to help detect pancreatic cancer. With increased experience, gastroenterologists were able to expand its use to diagnose other conditions, including pancreatitis, cholelithiasis, and other cancers. Later, with even more experience, and better technology, gastroenterologists were able to use these devices in the pediatric population.[3]

For most children weighing over 25 kg, adult echoendoscopes can be used safely.[4] Smaller children and infants can be accommodated by using an ultrasonographic miniprobe that is passed through the working channel of a standard pediatric endoscope.[5,6] Initially, radial scanning echoendoscopes were available (Supplemental Fig. 1).[7] These scopes have a perpendicular scanning direction and a rotation range of 300-360 degrees. The radial echoendoscope is useful for its full circumferential

viewing range. Later, the linear echoendoscopes were developed (Supplemental Fig. 2).[7] These scopes have a longitudinal/parallel scanning direction and a range of 100-180 degrees.[8] The benefit of this type of echoendoscope is its ability to allow therapeutic intervention. Linear array echoendoscopes are now the preferred scope and widely used in clinical practice.

Both echoendoscopes operate at a frequency between 5 and 10 MHz with 3-100 mm depth of field. Higher frequencies achieve higher resolution, while lower frequencies achieve deeper tissue penetration.[9] The proximity gives EUS a unique ability to differentiate all five gut layers by alternating hyperechoic and hypoechoic bands.[10] In addition, fine needle aspiration (Supplemental Fig. 3)[7] as well as a Tru-cut biopsy, can be included during the EUS procedure. These modalities are of additive value in diagnosing conditions by providing tissue sampling for cytology and histopathology.

Indications

EUS has various applications and has grown to be a useful modality in the evaluation of the pancreaticobiliary system. Pancreaticobiliary disease is the most common reason for EUS referrals in the pediatric population (Table 1).[3,4,11]

Inflammatory conditions

Acute pancreatitis

Estimates suggest that there are 3.6 to 13.2 pediatric cases per 100 000 individuals of acute pancreatitis per year, which approximates the incidence in adults.[12] The most common causes of acute pancreatitis in children are blunt trauma, systemic disease, and anatomical anomalies.[13,14] EUS can be diagnostic in cases with an unknown etiology of pancreatitis. Current medical literature suggests the most common indication for EUS is recurrent pancreatitis. Table 2 summarizes different studies done in children where EUS was utilized in the management of recurrent pancreatitis. The most common EUS finding in such cases were chronic idiopathic pancreatitis, autoimmune pancreatitis, microlithiasis, and pancreas divisum.

Chronic pancreatitis

EUS criteria established for chronic pancreatitis include both ductal and parenchymal criteria.[21] Ductal criteria include dilation of the main pancreatic duct (>3 mm), tortuous pancreatic duct, intraductal echogenic foci, echogenic ductal wall, and ectatic side branches. Parenchymal criteria include inhomogeneous echo pattern, foci of reduced or increased echogenicity, prominent interlobular septa, lobular outer gland margin,

Table 1. Pancreaticobiliary indications for endoscopic ultrasound[3,4,11]

Inflammatory conditions	Congenital conditions	Cystic lesions	Neoplastic conditions
Suspected choledocholithiasis/microlithiasis	Choledochal cyst	Pancreatic pseudocyst	Neuroendocrine tumors
Recurrent pancreatitis	Anomalous pancreaticobiliary junction	Mucinous cystic neoplasms	Solid pseudopapillary tumor
Chronic pancreatitis	Pancreas divisum	Serous cystic neoplasms	Lymphoma
Autoimmune pancreatitis	Duodenal duplication		
	Ectopic pancreas		

Table 2. Summary of literature for pediatric patients with recurrent pancreatitis and their overall diagnoses and treatments

Studies	*n*	EUS findings and diagnoses	Treatments
Attila et al, 2009[15]	11	5 normal 4 chronic pancreatitis 1 acute pancreatitis, no ductal dilatation 1 chronic pancreatitis, 30 mm pseudocyst	
Al-Rashdan et al, 2010[16]	20	Chronic pancreatitis	3 transgastric core biopsy, chronic idiopathic pancreatitis
Varadarajulu et al, 2005[17]	6	2 chronic pancreatitis 1 idiopathic fibrosing pancreatitis 1 pancreas divisum 1 duodenal duplication cyst 1 normal	3 ERCP, sphincterotomy & stent (1 for pancreas divisum, 1 for sphincter of Oddi dysfunction, 1 for stricture of pancreatic duct at head of pancreas); 2 precluded need for ERCP; 1 surgical excision for duodenal duplication cyst
Cohen et al, 2008[6]	9	4 microlithiasis	4 cholecystectomy
Bjerring et al, 2008[18]	5	3 normal 1 large calcification in body, ductal dilation of tail 1 lobulated pancreas	1 surgical resection of pancreatic tail for calcification in body, ductal dilation of tail
Fujii et al, 2013[19]	9	7 autoimmune pancreatitis (type 2) 2 normal	4 prednisone therapy
Scheers et al, 2015[20]	14	9 chronic pancreatitis 4 pancreatic pseudocyst 4 pancreatic stones 1 duplication cyst	8 ERCP, sphincterotomy & stone extraction & pancreatic duct stenting; 5 EUS-guided pseudocyst drainage; 3 surgery

EUS: endoscopic ultrasound; ERCP: endoscopic retrograde cholangio pancreatography.

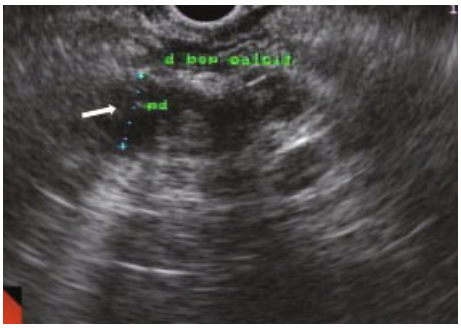

Fig. 1. Endoscopic ultrasound image of chronic pancreatitis with pancreatic duct dilatation (white arrow), multiple areas of calcifications, and atrophic parenchyma.

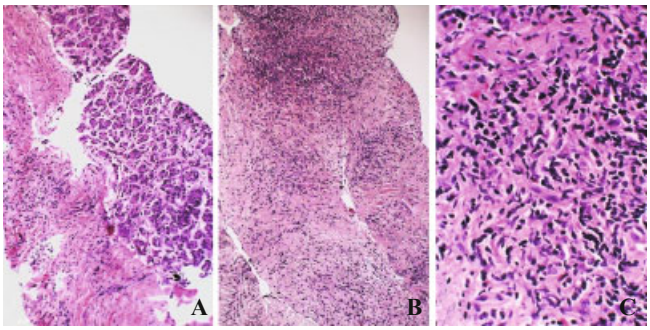

Fig. 3. Fine needle aspiration results from a patient with autoimmune pancreatitis showing sclerotic parenchyma compared to an intact acinar parenchyma (**A**), infiltrated by inflammatory cells (**B**), and consisting predominantly of lymphocytes and rare eosinophils (**C**) (with permission from Iqbal, et al).[7]

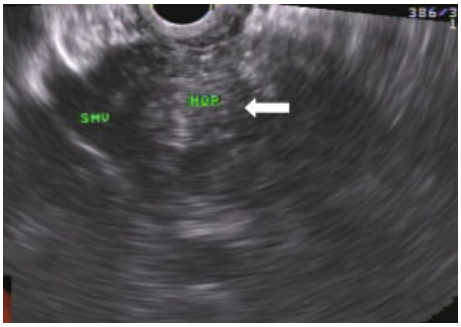

Fig. 2. Endoscopic ultrasound example of autoimmune pancreatitis. The pancreas (white arrow) is diffusely enlarged, lobulated, and hypoechoic in appearance with coarse echogenic foci (with permission from Iqbal, et al).[7]

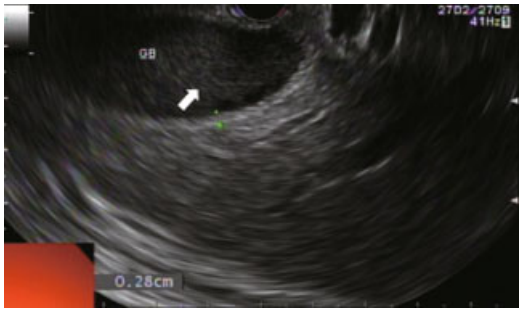

Fig. 4. Endoscopic ultrasound image demonstrating sludge as mobile hyperechoic foci/strands (white arrow) within the gallbladder.

and large echo-free cavities (>5 mm). Fig. 1 demonstrates an example of chronic pancreatitis on EUS.

EUS is useful in patients with chronic pancreatitis. In one retrospective study,[16] 20 patients received a new diagnosis of chronic pancreatitis after undergoing EUS where previous imaging with CT or MRI was non-diagnostic. "This is due to excellent visualization with EUS from the stomach and duodenum."[22,23]

Autoimmune pancreatitis

In addition to the characteristic appearance (Figs. 2 and 3),[7] EUS can also be helpful by providing a biopsy for tissue sampling for the accurate diagnosis of autoimmune pancreatitis. In one study in the pediatric population, Tru-cut biopsy was used due to its ability to obtain larger tissue sample and preserved tissue architecture.[19] The diagnostic yield of 86% was comparable to that in adults.

Microlithiasis

Biliary microlithiasis is described as gallstones less than 3 mm in size. EUS has been shown to be 95% to 100% accurate for diagnosing such diseases as suspected choledocholithiasis and microlithiasis.[6] Although small, they can still cause the same clinical manifestations as cholelithiasis.[24]

Due to their small size, they are difficult to be imaged by conventional means. Transabdominal ultrasound cannot detect the small microliths.[25] EUS has a higher resolution, and is therefore more sensitive for microlithiasis when compared to hepatobiliary iminodiacetic acid scan, magnetic resonance cholangiopancreatography, or CT.[25,26] Fig. 4 illustrates a patient diagnosed with gallbladder sludge and microlithiasis on EUS. Microlithiasis has been shown to be implicated more often as the underlying cause of cholecystitis or idiopathic pancreatitis given the higher sensitivity of EUS. Children with EUS showing no evidence of microlithiasis can potentially avoid unnecessary cholecystectomy or ERCP. One study demonstrated that ERCP was precluded in 13 out of 17 children due to findings noted on EUS.[20]

Congenital anomalies

Choledochal cyst

Anomalies of the pancreaticobiliary system are the second most common cause of pancreatitis, contributing to 15% of

cases.[27] Choledochal cyst (CC) is one congenital anomaly involving cystic dilation (>10 mm) in the biliary tract. Most cases, approximately 80%, present before 10 years of age.[28] It is associated with biliary cancer, primarily cholangiocarcinoma in 9%-28% of cases.[29,30] EUS has diagnostic utility for both CC and to evaluate for potential carcinoma as well. EUS is sensitive in detecting cystic ductal dilatation, which can potentially suggest neoplastic transformation.[31,32] When comparing EUS to ERCP, a prospective blinded study demonstrated that EUS was as effective in diagnosing CC, while avoiding the potential complications of ERCP.[31]

Anomalous pancreaticobiliary junction

Anomalous pancreaticobiliary junction (APBJ) is a congenital anomaly defined as a markedly long common channel (formed by the pancreatic and bile ducts outside the duodenal wall) usually greater than 15 mm. Because of this, the sphincter of Oddi does not function properly causing reflux of pancreaticobiliary fluid. Secondary to the reflux, CC is commonly seen in patients with APBJ. It has been reported that around 90%-100% of patients with CC have APBJ.[33,34] APBJ results in a high incidence of biliary cancer likely because of this reflux pathophysiology.[35] Although ERCP is a gold standard in diagnosing APBJ, EUS is proving to be both specific and sensitive for detection.[33,35] In instances where the common channel is not extensive, EUS can detect the common channel and the confluence of the pancreatic and bile ducts via the proximal portion of the duodenal wall.

Duodenal duplication

Duodenal duplication (DD) is a wall duplication of the alimentary tract, sometimes causing an outpouching cyst with possible involvement with the biliary tree. DD occurs in approximately 5% of all the gastrointestinal duplications, which is one out of every 4500 autopsies.[36] One study demonstrated how EUS using a miniprobe could safely diagnose and treat a patient with DD.[37] The wall of the DD is identified via EUS by being composed of a smooth muscle layer lined by epithelium. With this diagnostic tool, four of the six cases were identified as having an anechoic lesion without ducts or vessels in the common wall, and were treated with endocavitary surgical techniques. Of those four, three had the common wall excised by sphincterotomy, and one via needle-knife sphincterotomy.[37] Overall, this demonstrates how EUS can be used for diagnostic imaging and leading to a therapeutic intervention.

Pancreas divisum

Pancreas divisum is the most common pancreatic congenital anomaly. It is seen in up to 14% of autopsies.[38-40] In one retrospective evaluation, 14% of patients with chronic pancreatitis who underwent EUS were diagnosed with pancreas divisum.[41] EUS can be used reliably to trace the pancreatic duct from the head to body in order to exclude pancreas divisum with a sensitivity of 100% and specificity of 96%.

Pancreatic pseudocyst

One potential complication of severe necrotizing pancreatitis is the development of a pseudocyst. Most resolve spontaneously with conservative medical management. However, symptomatic pseudocysts eventually require drainage.[42,43] Although, surgical drainage is the gold standard of treatment, it has a 35% morbidity and 10% mortality.[44] With the development of EUS, endoscopy is evolving as the primary modality for drainage. EUS identifies a suitable puncture site and eliminates the need to identify a visible luminal bulge.[45,46] EUS can also identify intervening blood vessels and optimize the puncture site for drainage and/or stent placement.[47] Fig. 5 demonstrates a patient with a pseudocyst that was treated successfully with EUS-guided cystgastrostomy.

One study demonstrated the usefulness of EUS-guided pseudocyst drainage in ten symptomatic pediatric cases that failed conservative management.[47] Eight children had double-pigtailed stents successfully placed, while two had complete cyst collapse with EUS-FNA alone. Two children in another study had safe and effective EUS-guided pancreatic pseudocyst drainage.[6] As in the adult population, EUS-guided pseudocyst drainage is becoming the primary treatment modality in children.

Pancreatic masses

In the literature, EUS has proven to be both sensitive and specific in pediatric patients with pancreatic masses. Overall, EUS obtained adequate tissue in 98% of cases with an 87% accuracy.[48] It is superior to transabdominal ultrasound or CT scan for discovery of a pancreatic mass, especially in cases where the size is less than 2-3 cm.[49-52] EUS can also be performed after an initial CT or MRI result for sampling and staging as the first-line diagnostic test.[50,53] Table 3 summarizes different studies where EUS was used to assess pancreatic mass lesions in the pediatric population. The most common causes of pancreatic mass lesions in children with EUS were pancreatic necrosis, solid pseudopapillary tumor (Fig. 6), neuroendocrine tumor, and lymphoma. EUS findings subsequently lead to the appropriate intervention, including Whipple procedure.[15]

Table 3. Summary of literature for pediatric patients undergoing EUS for pancreatic masses and their findings

Studies	*n*	Indications	EUS findings
Bjerring et al, 2008[18]	9	1 recurrent teratoma on CT	No tumor found
		1 recurrent non-resectable Wilm tumor on CT/MRI/US	Surgically resectable Wilm's tumor
		1 Burkitt lymphoma relapse on CT	No recurrence with normal biopsy
		1 hypoglycemia with normal octreotide scan & MRI	Insulinoma found (surgically resected)
		3 abdominal pain	1 gastric leiomyoma, 1 benign tumor, 1 no tumor
		2 jaundice tumor on imaging	1 retroperitoneal tumor, 1 no tumor noted
Al-Rashdan et al, 2010[16]	9	Pancreatic mass	3 pancreatic pseudocyst, 2 solid pseudopapillary tumor of the pancreas, 2 retroperitoneal cyst/hematoma, 1 carcinoid, 1 gastric lipoma (8 FNA)
Attila et al, 2009[15]	7	Pancreatic mass	4 pancreatitis
			1 B-cell lymphoma, chemo
			1 islet cell tumor, Whipple
			1 normal
Cohen et al, 2008[6]	4	Pancreatic mass	2 pseudocyst
			1 lymphoma
			1 GI stromal tumor

EUS: endoscopic ultrasound; CT: computed tomography; MRI: magnetic resonance imaging; FNA: fine needle aspiration; GI: gastrointestinal.

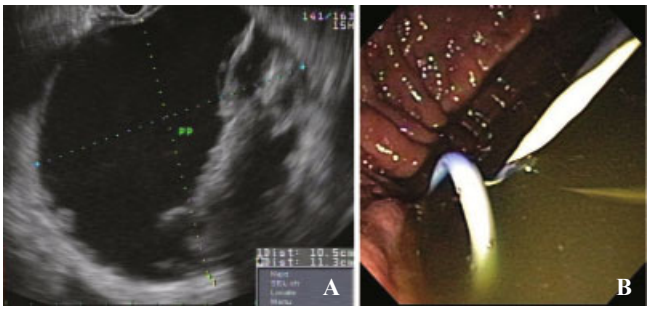

Fig. 5. Endoscopic ultrasound (EUS) drainage of a symptomatic pancreatic pseudocyst causing pain and bloating. **A:** EUS image of peripancreatic pseudocyst, measuring 10.5×11.3 cm; **B:** An endoscopic view of the stomach after drainage and placement of a cystgastrostomy tube.

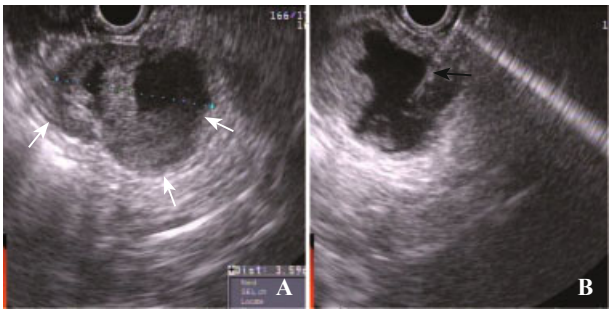

Fig. 6. Endoscopic ultrasound example of a solid pseudopapillary tumor. **A:** It shows a 36 mm anechoic, cystic lesion with a hypoechoic thick irregular rim (white arrows) and a solid polypoid component in the pancreatic head/body junction; **B:** The cystic and solid components were separately biopsied using a 19-gauge FNA needle (black arrow) via transgasric approach (with permission from Iqbal, et al).[7] FNA: fine needle aspiration.

Safety

EUS can be done safely in the outpatient setting. Contrary to early beliefs, advanced endoscopic procedures, such as EUS, do not require general anesthesia.[16,18] The majority of EUS procedures can safely be done under intravenous sedation with propofol and/or midazolam on outpatient basis.[6,16,18] Adult EUS scopes have been used in the pediatric population with good outcomes and without increased complications.[5] Compared to the 2.5% to 11% complication rate in ERCP, the complication rate for EUS is less than 1%, making EUS the more favorable diagnostic procedure.[54] The role of ERCP has now been limited to a therapeutic modality in different pancreaticobiliary conditions.

EUS also reduces the risk associated with imaging modalities, specifically CT scan. "Radiation dose is magnified in children owing to their smaller size, increased radiosensitivity, and long life expectancy with which to develop a radiation-induced malignancy".[55] EUS can replace CT scanning for diagnosis and follow-up imaging. This alternative can minimize the risk of radiation-induced solid cancer associated with abdominal CT scans.[56]

Overall, EUS-related complications are extremely rare. Pancreatitis, bleeding, infection, and perforation have been documented and can be extrapolated from adults.[57] Pancreatitis can be a complication of EUS-FNA. A meta-analysis found a rate of 0.44%, with the majority classified as mild pancreatitis.[58] Hemorrhage from EUS-FNA has been reported in the same meta-analysis at a rate of 0.13%.[58] Infection rates are approximately 0.3% for EUS-FNA, which are comparable to EUS-alone or diagnostic endoscopy.[57] EUS-FNA of cystic lesions seems to carry a higher infection rate, and prophylactic antibiotics are suggested. The risk of perforation is also comparable to standard endoscopy, at a rate of 0.03%.[58-60] Bile peritonitis and malignant tumor seeding have been documented in rare cases.[57,61,62]

Conclusions

EUS is now being more commonly performed in the pediatric population. Due to its high sensitivity and

accuracy, it is an effective diagnostic tool for different pancreaticobiliary conditions. The diagnostic accuracy of EUS exceeds 90% for diseases such as suspected choledocholithiasis (microlithiasis), chronic pancreatitis, and pancreaticobiliary mass lesions.[17] It is complimentary to MRI and/or pancreatic-protocol CT scan. Compared to ERCP, it is a safe modality with minimal risk.[1,11,25] It has both diagnostic as well as therapeutic roles in children, like EUS-guided cyst-gastrostomy for pancreatic pseudocyst. With increased expertise, the role of EUS will continue to expand in the pediatric population.

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