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The Roles of Endoscopic Ultrasound and Endoscopic Retrograde Cholangiopancreatography in the Evaluation and Treatment of Chronic Pancreatitis in Children: A Position Paper From the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee

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ABSTRACT

Introduction: Pediatric chronic pancreatitis is increasingly diagnosed. Endoscopic methods [endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP)] are useful tools to diagnose and manage chronic pancreatitis. Pediatric knowledge and use of these modalities is limited and warrants dissemination.

Methods: Literature review of publications relating to use of ERCP and EUS for diagnosis and/or management of chronic pancreatitis with special attention to studies involving 0–18 years old subjects was conducted with summaries generated. Recommendations were developed and voted upon by authors.

Results: Both EUS and ERCP can be used even in small children to assist in diagnosis of chronic pancreatitis in cases where cross-sectional imaging is not sufficient to diagnose or characterize the disease. Children under 15 kg for EUS and 10 kg for ERCP can be technically challenging. These procedures should be done optimally by appropriately trained endoscopists and adult gastroenterology providers with appropriate experience treating children. EUS and ERCP-related risks both include perforation, bleeding and pancreatitis. EUS is the preferred diagnostic modality over ERCP because of lower complication rates overall. Both modalities can be used for management of chronic pancreatitis -related fluid collections. ERCP has successfully been used to manage pancreatic duct stones.

Conclusion: EUS and ERCP can be safely used to diagnose chronic pancreatitis in pediatric patients and assist in management of chronic pancreatitis-related complications. Procedure-related risks are similar to those seen in adults, with EUS having a safer risk profile overall. The recent increase in pediatric-trained specialists will improve access of these modalities for children.

Key Words: children, chronic pancreatitis, endoscopy, endoscopic retrograde cholangiopancreatography, endoscopic ultrasound, evaluation, treatment

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What Is Known

- Experience with endoscopic ultrasound and endoscopic retrograde cholangiopancreatography in pediatric patients with chronic pancreatitis is expanding.
- Recommendations for appropriate utilization are needed.

What Is New

- Recommendations are presented made with respect to size of children on which endoscopic ultrasound and endoscopic retrograde cholangiopancreatography can generally be successful, for performance by appropriately trained endoscopists; potential use of endoscopic ultrasound in diagnosis of chronic pancreatitis and its limitations; avoidance of endoscopic retrograde cholangiopancreatography solely for diagnostic purposes; utilization of endoscopic ultrasound and endoscopic retrograde cholangiopancreatography as necessary for management of chronic pancreatiti fluid collections; and endoscopic retrograde cholangiopancreatography applied helpful in management of pancreatic ductal strictures and stones.
- Nonnegligible procedural risks associated with endoscopic ultrasound and endoscopic retrograde cholangiopancreatography must be discussed with families. The risks in children are similar in type and frequency to adults. The incidence of these risks in children varies based on each particular procedure, and informed consent should be clearly documented in patients' charts.

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Children are diagnosed with pancreatitis, including chronic pancreatitis (CP) with increasing frequency. Information of CP in pediatric patients is accumulating along with recognition of the difficulties in making an accurate diagnosis and managing complications. Affected children encounter significant impact on quality of life, health care utilization and costs, pain, and nutritional consequences (1). CP in adults is frequently managed with endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) assessment and interventions, including during diagnosis of CP, assessment of localized masses, ductal strictures and stones, and management of these and other complications. EUS and ERCP are being applied increasingly in the pediatric population with increased access and pediatric expertise. Most of the available literature, however, focuses on use of EUS and ERCP in adults with CP, in whom etiologies and co-factors of CP are vastly different (eg, alcohol and cigarette smoking exposures in adults vs children) (2). Thus, an absolute need exists for physicians managing children with CP to understand the utility, benefits, limitations, risks, and complications of EUS and ERCP in pediatric patients with CP.

Although clinical trials and guidelines have historically used various definitions of CP, this manuscript defines CP in pediatric patients as per the consensus criteria established by the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium (3). CP may be diagnosed in pediatric patients when histologic features compatible with CP are identified on pancreatic specimens, which may include loss of acinar and ductal tissue, chronic inflammatory infiltrate around acini and ducts, periductular fibrosis, obstruction of ducts, perineural inflammation, with relative sparing of islets of Langerhans. More commonly, however, CP in children is diagnosed in the presence of suggestive pancreatic imaging findings along with either abdominal pain consistent with pancreatic origin, exocrine pancreatic insufficiency (EPI), or endocrine pancreatic insufficiency (3). This position paper will not review indications of EUS and ERCP for cases of acute pancreatitis (AP), discussed in a recent NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition) clinical report on management of AP in children (4). It will also not consider surgical or medical management of CP and will not address the topic of endoscopic training and competency, which has been addressed elsewhere (5). EUS is defined as endoscopy during which transluminal (typically transgastric or transduodenal) sonography and its adjuncts and guided therapies are used to evaluate the pancreas or peripancreatic regions of interest utilizing either dedicated echoendoscopes or probe-based systems. ERCP is defined as an endoscopic procedure in which the pancreatic or the biliary duct is directly interrogated in a retrograde fashion from the gastrointestinal lumen, and thus, also includes endoscopic retrograde pancreatography (ERP). The goal of this position paper is to provide practitioners, and in particular, endoscopists caring for children with CP an overview of the equipment and technology currently used to perform EUS and ERCP in children with CP, current and potential applications, and limitations, with special attention given to the unique aspects relevant to pediatric patients.

METHODS

The working group involved in the development of this NASPGHAN position paper included members of the NASPGHAN Pancreas Committee (Q.Y.L., S.B., N.P., M.A.E.H., under the leadership of Committee Vice-Chair [V.D.M.] and Chair [S.Z.H.]) and external expert members from the NASPGHAN Endoscopy and Procedures Committee (R.G., D.M.T., D.S.V.).

Three subgroups were created, headed by the 3 co-first authors (Q.Y.L., R.G., D.M.T.) under whose guidance, main topics of interest were subdivided for review of the medical literature. The literature search was performed utilizing PubMed, Embase, and the Cochrane Library databases with search terms *pancreatic diseases, chronic pancreatitis, endoscopy, ERCP, pancreatoscopy, EUS*, and relevant terms limiting to the pediatric population. The full-length relevant human studies published in English language between January 1993 and July 2018 were reviewed for relevancy. Subsequently published articles of key interest were included as warranted. Particular points of review focus revolved around patient preparation/technical aspects of the modalities, potential uses, benefits, risks, complications, and limitations of the modalities. Summaries were generated with proposed recommendations.

E-mail correspondence between the subgroup leaders and senior author led to the preparation of a draft by each subgroup leader with input of other authors. The manuscript was then shared with the remainder of the authors for review and editing before a group discussion was held via teleconference in April 2019. At this teleconference, each subgroup presented pertinent literature review, estimated strength of evidence, and proposed the statements and recommendations to vote for each element under consideration. It had been initially anticipated that the group would grade the quality of evidence to support each recommendation, utilizing the GRADE system (6). Upon review of the literature by the group, however, it was deemed that the overall quantity and quality of pediatric data were so limited that it was decided that all recommendations could only be stated to have either (1) ''low'' quality of evidence meaning that further research is likely to impact our confidence in the estimate of effect and likely to change the estimate, or (2) ''very low'' quality of evidence so that any estimate of effect is uncertain. Hence recommendations were not individually labelled with quality of evidence. The summary statements and recommendations were

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discussed and modified as indicated based on the feedback of attendees. Subsequent to group discussion, each recommendation was voted upon electronically by each of the 9 authors, using a 5-point scale (5—strongly agree; 4—agree; 3—neutral; neither agree nor disagree; 2—disagree; 1—strongly disagree) over a 10-day period. It had been previously agreed that consensus could only be reached if at least 75% of the group voted "4" (agree) or "5" (strongly agree) on a particular recommendation. Voting results were collected in an anonymous fashion, tabulated, and finalized. Statements were either labelled as supported (agreement $\geq$75% of voters) or not (agreement $<$75%) based on results. Subsequent to initial manuscript submission, 2 statements were deemed suboptimally phrased; these were re-worded and re-voted upon during the last week of September 2019 using similar criteria for voting and support. Results were updated.

The final manuscript draft was approved by all authors.

RESULTS

Patient Preparation and Technical Considerations

Children with CP frequently present with pain or recurrent attacks of AP as chief complaints, with increased health care resource utilization related to their pain (7,8). A complaint of abdominal pain, however, requires appropriate assessment to determine whether symptoms could be related to the relatively rare diagnosis of chronic pancreatic inflammation versus other more common etiologies. Investigations, such as esophagogastroduodenoscopy, colonoscopy, capsule endoscopy, transabdominal ultrasonography (TUS), or other cross-sectional imaging may be indicated. Children with either exocrine or endocrine pancreatic insufficiency similarly require thoughtful consideration as to whether CP is the most probable etiology versus alternative diagnoses.

Once an appropriate indication for an advanced endoscopic procedure for investigation or management of CP is identified, it is important to ensure that the procedure takes place in an environment that considers pediatric periprocedural and procedural care, and is performed by an appropriately trained, competent endoscopist. The unique aspects of preprocedural, intra-procedural, and postprocedural care relevant to children undergoing any endoscopic procedure, including EUS and ERCP, have been well described in position papers previously published by NASGPHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), and the American Society for Gastrointestinal Endoscopy (ASGE) (9–11). Although the technical aspect of performing EUS and ERCP in children are similar to adults, it is worth reiterating that the size of the patient is an important consideration as it influences strongly the equipment that can be used, and thus the potential interventions that can be performed. As an example, the esophageal diameter of a newborn is estimated to be approximately 6 mm by barium swallow, significantly smaller than the diameter of the standard equipment used to perform the vast majority of adult EUS and ERCP exams (12). The available literature and authors are in agreement with consensus guidelines put forth separately by the ASGE and ESPGHAN that suggest a standard adult duodenoscope can be used for ERCP in children $>$10 kg and standard adult echoendoscopes can be used for EUS in children $>$15 kg (10,11). Fortunately, the need to perform these advanced procedures in children smaller than these parameters is infrequent, particularly with respect to CP. Whenever necessary, ERCP can effectively be performed in children $<$10 kg utilizing a pediatric duodenoscope, which has an outer diameter of 7.5 mm. Similarly, for children less than 15 kg, EUS can be performed utilizing smaller echobronchoscopes. The breadth of interventions that can be performed with this smaller equipment is, however, further limited secondary to the smaller working channels, if present at all. Another factor of significant importance is that the endoscopist must be familiar with anatomic malformations and variations involving the pancreaticobiliary system that may be found more commonly when investigating a child.

Considerations of risks of anesthesia must be added to the risks of the actual intervention as the vast majority of children younger than teenagers will require general anesthesia, frequently with endotracheal tube intubation, to undergo either EUS or ERCP.

After undergoing an EUS or ERCP examination, children should be appropriately monitored for procedural tolerance and adverse events. Postprocedural throat discomfort or pain from endoscope use is frequent, in up to one-third of patients, worse 2 to 6 hours after procedure, and thus appropriate analgesia plans should be made. Follow-up plans must be clearly communicated to families and among the care providers. Although diagnostic studies typically can be performed as an outpatient, when therapeutic interventions are undertaken, particularly when implants are used, adequate communication must ensue between the performing endoscopist and the patient's primary pancreatologist on how these implants will be managed following the procedure. In particular, proposed timing for implant removal needs to be clearly discussed in advance. In addition, plans should be clear for managing potential adverse events following the procedure. This postprocedural planning is particularly important when the therapeutic endoscopist is not closely associated with the patient's primary pancreatic care institution, such as might occur when an adult trained advanced endoscopist is enlisted to help care for a child. In order to optimize outcomes, coordination of care is particularly important in these scenarios where specialists at different sites are involved. Readers are also encouraged to refer to the recently published European Society for Pediatric Gastroenterology, Hepatology and Nutritional Position Paper on Training in Pediatric Endoscopy, which discusses training for performance of EUS and ERCP, both considered level 3 advanced training for specialized endoscopic procedures (13).

Summary

Abdominal pain is an important presentation in children with CP, but many potential other differential diagnoses must be considered. Unique aspects to peri-procedural and procedural care of children undergoing EUS and ERCP exist, particularly in those with CP in whom pain may be a significant factor. The experience of performing EUS or ERCP in children, especially less than 10 to 15 kg, is importantly gained from dealing with smaller size patients, and smaller size special equipment in contrast to adult ERCP and EUS performance. This suggests the need for appropriately trained pancreaticobiliary endoscopists experienced with both the technical and medical knowledge for treating pediatric patients.

Statements/Recommendations:

1a. Utilization of EUS and ERCP to evaluate for CP in pediatric patients presenting with abdominal pain without other evidence suggestive of pancreatic pathology is discouraged and should not be routinely done.

8/9 = 89% in agreement with recommendation

Voting results: strongly agree = 2; agree = 6; neutral = 0; disagree = 1; strongly disagree = 0.

1b. EUS and ERCP in children should be performed by appropriately trained endoscopists with sufficient experience performing these procedures in children.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree = 9; agree = 0; neutral = 0; disagree = 0; strongly disagree = 0.

1c. ERCP can be routinely performed both safely and effectively in children >10 kg using standard equipment

designed for adult patients. Performing ERCP in children <10 kg typically requires utilization of specialized equipment.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree = 7; agree = 2; neutral = 0; disagree = 0; strongly disagree = 0.

1d. EUS can be routinely performed both safely and effectively in children >15 kg using standard equipment designed for adult patients. Performing EUS in children <15 kg typically requires utilization of alternative equipment not specifically designed for utilization in the GI tract.

8/9 = 89% in agreement with recommendation.

Voting results: strongly agree = 6; agree = 2; neutral = 1; disagree = 0; strongly disagree = 0.

Endoscopic Ultrasonography

EUS employs a flexible endoscope with an ultrasound transducer to obtain high-quality endosonographic images for interpretation by the endoscopist. 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 (Fig. 1A–D). EUS has recently been increasingly used in pediatric patients (14,15), in contrast to the adult population, in which EUS has been used since the 1980s (16). In the literature and throughout this manuscript, the term diagnostic EUS is used to describe applications focused on obtaining diagnostic information, such as endosonographic images and obtaining transluminal pancreatic tissue through fine needle aspiration (FNA) or biopsy (FNB). Common diagnostic indications include evaluation of idiopathic acute recurrent pancreatitis (ARP) or CP, need for FNA or FNB of pancreatic or other lesions, suspected choledocholithiasis, pancreatic ductal stones, and evaluation of submucosal lesions. The term therapeutic EUS describes applications in which endosonographic imaging is used to guide various interventions. Therapeutic applications include cyst-gastrostomy or cyst-duodenostomy for pancreatic pseudocysts or walled off necrosis, celiac plexus block and biliary drainage.

Within the pediatric literature, the most prominent indication for EUS is evaluation of pancreatic disease (14,17–21). Pancreatic calcification and dilatation of the pancreatic duct are characteristics findings of CP on noninvasive imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI) (22). 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 CP (23–29).

The best-known classifications for diagnosis of CP via EUS in adults include the Rosemont criteria (30), and the ''conventional'' criteria (Table 1), which varies the threshold for diagnosis based on patient age and indication for the procedure (30–32). The Rosemont criteria were developed by an international consensus panel in Rosemont, Illinois and published in 2009. It is important to note that these criteria were derived utilizing adult patients and are only recognized as applicable in adults. Although these current criteria are used in practice, no EUS criteria are universally accepted to diagnose CP in adults and interobserver reliability has been reported as poor in several publications (32–34). Studies directly comparing EUS and histology have shown high sensitivity (up to 83%) and specificity (up to 80%) for EUS imaging (23,35). A recent meta-analysis of 43 studies evaluating EUS, ERCP, MRCP, CT, and

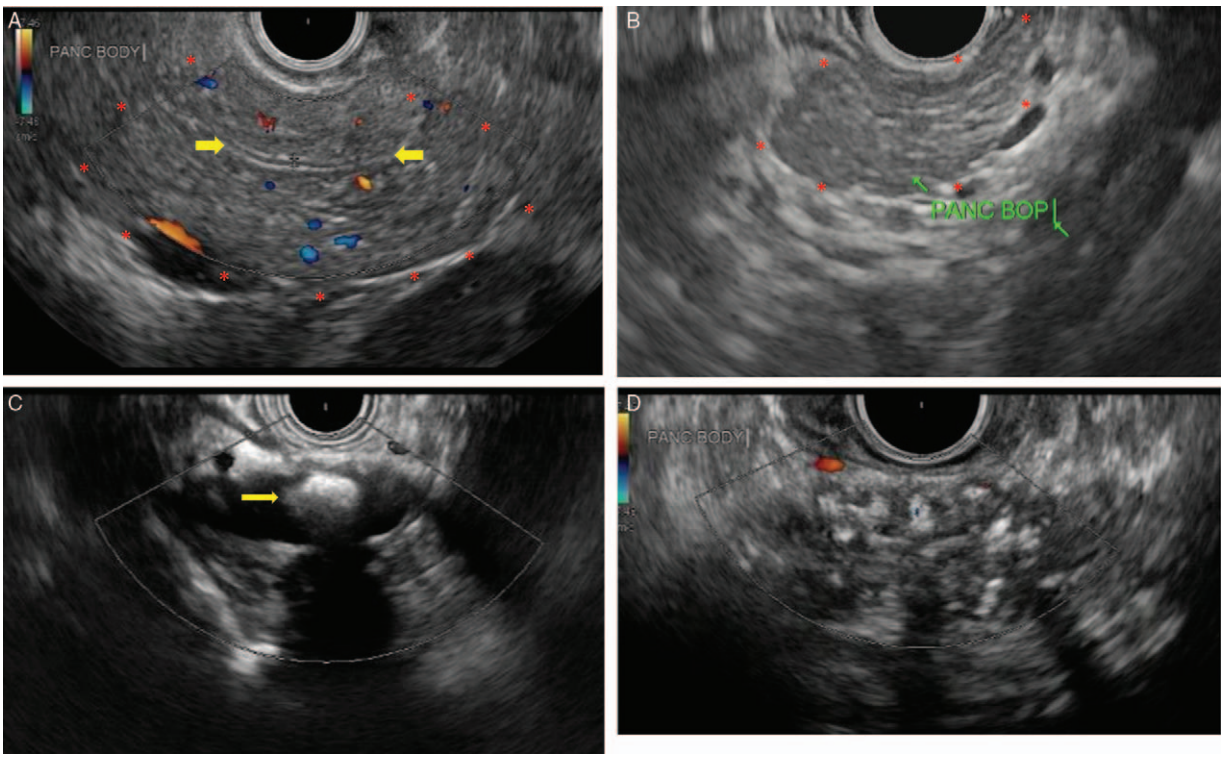

FIGURE 1. Endoscopic ultrasonography. (A) EUS with Doppler image of a 13-year-old with a normal pancreas duct (bracketed by yellow arrows) and pancreas parenchyma (outlined by red asterisks). (B) EUS image of a 4-year-old demonstrating normal body of pancreas parenchyma (outlined by red asterisks). (C) EUS image of a 16-year-old with cystic fibrosis transmembrane conductance regulator, who has a pancreatic duct calculi (arrow) with shadowing effect. (D) EUS imaging of a 7-year-old with calcific pancreatic parenchyma as demonstrated by shadowing hyperechoic foci. EUS = endoscopic ultrasonography.

TABLE 1. Criteria to diagnose chronic pancreatitis via endoscopic ultrasonography

Rosemont criteria	Conventional criteria
Major A criteria	Parenchymal abnormalities
Hyperechoic foci with shadowing	hyperechoic strands,
Main pancreatic duct calculi	hyperechoic foci,
	lobulation or
	cysts
Major B criteria	Ductal abnormalities
Lobularity with honeycombing	main pancreatic duct dilation,
	ductal irregularity,
	visible side branches,
	hyperechoic ductal margins or
	stones
Minor criteria/features	
Cysts	
Dilated ducts ≥3.5 mm	
Irregular pancreatic ducts	
Dilated side branches ≥1 mm	
Stranding	
Hyperechoic duct walls	
Nonshadowing hyperechoic foci	
Lobularity with noncontiguous lobules	
Diagnosis of CP based on Rosemont Criteria ''consistent with CP''	Diagnosis of CP based on Conventional Criteria
2 major A criteria or	≥ 5 criteria: high probability of CP
1 major A and 1 major B criteria or	3–4 criteria: ''indeterminant'' for CP
1 major A and ≥3 minor criteria	
''Suggestive of CP''	
1 major A and 3 minor features or	
1 major B +/- 3 minor features or	
≥5 minor features	
''Indeterminant for CP''	
3–4 minor features only	
1 major B +/- <3 minor features	
Potential limitations/concerns to use in pediatrics:	Potential limitations/concerns to use in pediatrics:
Dilation of ductal duct defined as ≥3.5 mm	Uncertainty whether CP EUS findings in children are identical to/and have similar significance to CP findings in adults
Definition of dilated side branches defined as >1 mm	
Uncertainty whether CP EUS findings in children are identical to and have similar significance to CP findings in adults	

See refs. (32–36). CP = chronic pancreatitis; EUS = endoscopic ultrasound.

transabdominal US in diagnosis of CP concluded EUS and ERCP outperformed other modalities (36). Currently, no pediatric EUS criteria exist for diagnosis of CP. Hence, in practice, the Rosemont and conventional criteria are used for pediatric patients. Very importantly, the etiology of pancreatitis in children, however, differs substantially from adults (37), and the pathophysiology and early changes of CP may differ as well (1,38). It is imperative that definitive EUS criteria specifically for CP in pediatric patients be developed.

Summary

EUS appears superior to CT and MRI scans for diagnosis of CP in adult patients. Published criteria of EUS findings suggestive and diagnostic of CP in adults include the Rosemont criteria and the Conventional criteria, and these are commonly extrapolated to EUS CP assessment in children.

Endoscopic Ultrasonography-based Emerging Technologies

Newer techniques have emerged within the realm of EUS: contrast-enhanced EUS (CE-EUS), and EUS elastography (39–42).

CE-EUS is a novel approach where the usual high resolution of ultrasound is intensified by contrast agents (43). Contrast agents consist of gas-filled microbubbles, encapsulated by a phospholipid or albumin shell injected into peripheral veins. CE-EUS helps recognize and delineate necrotizing foci of AP, which ordinarily are not enhanced at a very early stage (39). CE-EUS provides a more detailed vascular image of a target lesion and uses the contrast agents to intensify more vascularized tissue to differentiate lesion(s) (44,45). Several publications of the use of these techniques in adults have shown benefits in evaluating and distinguishing pancreatic lesions, such as adenocarcinoma, neuroendocrine tumors, and autoimmune pancreatitis.

Elastography is a method to assess tissue rigidity in real time. Elastography can be done in conjunction with EUS to generate real-time elastographic data, using the degree of deformation as an index of tissue rigidity to evaluate for the presence of CP (24). In a study by Dominguez-Muñoz et al (46), elastography was used to predict pancreatic fibrosis and quantify the probability of EPI in adult patients with CP.

Summary

CE-EUS and EUS-elastography are recent developments that may assist in the evaluation of pancreatic lesions, the diagnosis of CP, and the quantification of pancreatic fibrosis; however, little data exist on their use in pediatrics.

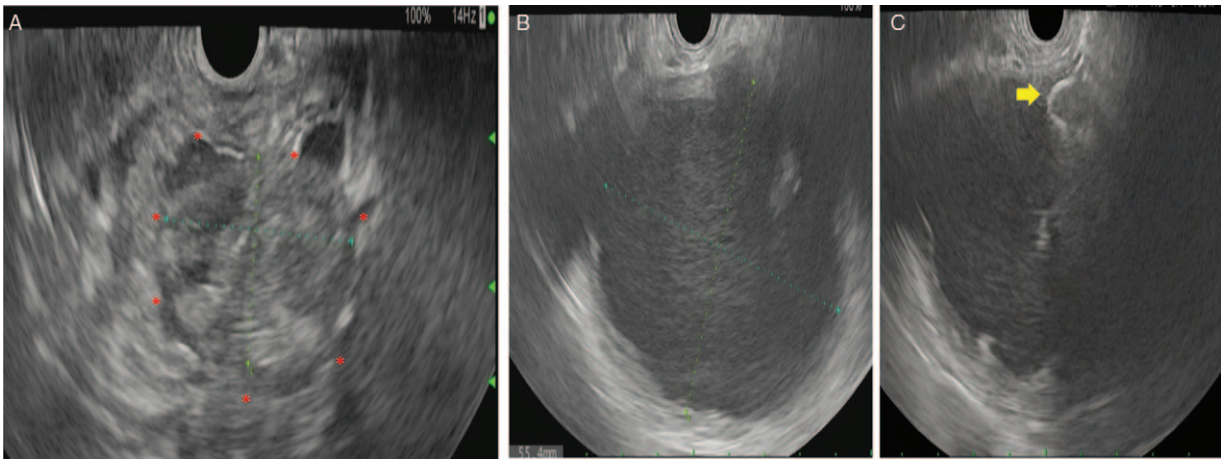

FIGURE 2. Endoscopic ultrasonography. (A) EUS image of 3-year-old child with walled-off pancreatic necrosis (i outlined by asterisks). (B) EUS image of a 14-year-old child with pancreatic pseudocyst. (C) EUS image of the same 14-year-old child with pancreatic pseudocyst with placement of a luminal apposing metal stent (arrow). EUS = endoscopic ultrasonography.

Endoscopic Ultrasonography-guided Therapeutic Interventions

Therapeutic EUS-guided applications in pediatric patients with CP include management of pancreatic pseudocysts and walled off necrosis. Although percutaneous drainage and intervention are still widely accepted as possible first-line therapies in adult literature, endoscopic-based interventions are also increasingly used as first line in adults requiring intervention for walled off necrosis or pseudocysts, with EUS-based interventions being less costly (47,48). Both plastic and metal stents have been used in pediatric reports, with the largest series describing 30 pediatric patients with pancreatic fluid collections managed with plastic pigtail stents via cystgastrostomy. Long-term follow-up of >2 years was achieved, with only 2 recurrences (49). Three adverse events, however, were reported including perforation and bleeding requiring interventions. Use of biliary fully-covered metal stents for treatment of walled-off necrosis has also been reported in a small series of children with a clinical success of 95%; however, these stents carried a risk of migration (50). Lumen apposing metal stents (LAMS) are used in adults with good technical and clinical success (51,52), and there have been case reports of successful use in pediatrics (53,54). LAMS, while having less migration complications, do carry a risk of pseudoaneurysm and bleeding, and are generally removed within 4 to 6 weeks. The indication for intervention in any particular patient must be carefully considered. Acute peripancreatic fluid collections, pseudocysts and pancreatic necrosis often resolve without any intervention, and hence it is important to emphasize that management of these complications of CP should involve a tertiary care center with expert pediatric experience when feasible (see Fig. 2 A–C).

EUS-guided celiac plexus block with injection of steroid and anesthetic can be used in patients with CP pain, with reports of success in pediatrics (55,56). Celiac neurolysis is generally reserved for malignant processes, thus extremely rarely indicated in children.

Summary

A growing list of publications detail series of children in whom EUS has been used for therapeutic indications in CP including placement of plastic and metal stents for management of pseudocysts and walled-off necrosis. Risks, such as stent migration, perforation, and bleeding exist, but are comparable with adult series. In adults, EUS-based procedures have been shown to be less costly than surgical-based procedures. Fluid collections, pseudocysts, and necrosis may resolve without intervention, and thus careful pre-procedural assessment of patient factors and evaluation of local expertise and comfort in performing EUS in pediatric patients are necessary.

Statements/Recommendations:

2a. EUS should be considered in the evaluation of pediatric patients with suspected CP when cross-sectional imaging is insufficient to pose a diagnosis, determine etiology, or establish extent of the disease.

9/9 = 100% in agreement with recommendation

Voting results: strongly agree= 5; agree= 4; neutral= 0; disagree= 0; strongly disagree= 0.

2b. Rosemont and Conventional criteria for diagnosis of CP can only be used to support and guide interpretation of EUS in children as these criteria are adult-based.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree= 6; agree= 3; neutral= 0; disagree= 0; strongly disagree= 0.

2c. CE-EUS and EUS-elastography need to be further studied before their widespread use can be supported in pediatric patients with CP.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree = 5; agree = 4; neutral = 0; disagree = 0; strongly disagree = 5.

2d. Watchful waiting for resolution of CP-associated fluid collections should always be considered, as many collections resolve on their own, and nonnegligible risks of stent migration, perforation, and bleeding exists with EUS-based interventions.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree = 4; agree = 5; neutral = 0; disagree = 0; strongly disagree = 0.

2e. When intervention is required, EUS should preferentially be considered for management of CP fluid collections before surgical/open interventions.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree = 8; agree = 1; neutral = 0; disagree = 0; strongly disagree = 0.

In summary, EUS is an emerging endoscopic diagnostic and therapeutic tool within pediatrics. Its use in patients with CP is well

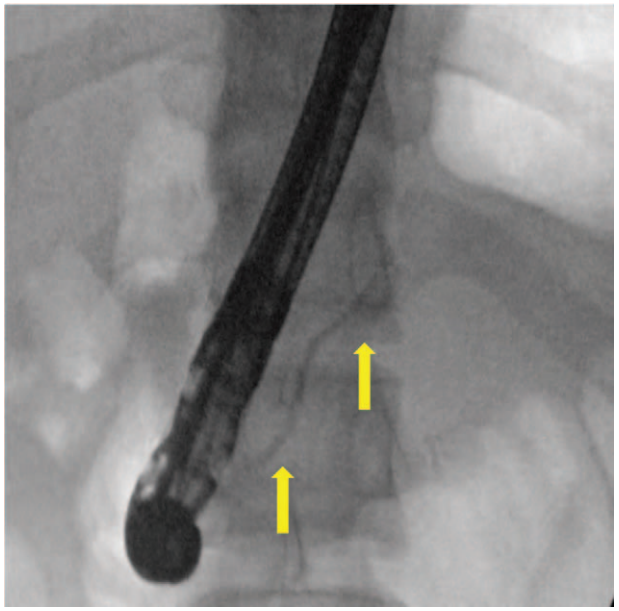

FIGURE 3. Endoscopic retrograde cholangiopancreatography. Pancreaticogram showing a normal pancreas duct (arrows) during ERCP in a 2-month-old child. ERCP = endoscopic retrograde cholangiopancreatography.

defined in adults and is becoming more recognized and applied in pediatrics. Whenever possible, endoscopic evaluation with EUS or other therapeutic endoscopy for children with CP should be deferred to tertiary care centers with pediatric therapeutic endoscopy expertise. Further studies are needed to continue to establish and support the efficacy and safety of EUS in pediatric patients with CP.

Endoscopic Retrograde Cholangiopancreatography

Cross-sectional imaging has become the first line tool for diagnosis of CP, replacing the use of risk-associated ERCP for diagnostic purposes. ERCP, however, can be considered if imaging cannot clearly diagnose CP. ERCP provides excellent fluoroscopic-based imaging of the pancreatic ductal system (Fig. 3). Key ductal findings in CP that can be seen via ERCP include beading, dilated side branch radicals, enlargement of the main pancreatic duct, and dystrophic intraductal calcifications (57) (see Fig. 4A–C). The Cambridge criteria were developed decades ago to better characterize the extent of CP when using endoscopic pancreatogram as ductular imaging to enable result comparisons between different centers (58). Importantly, these criteria have significant limitations with respect to use in pediatrics (Table 2).

Because of TUS limitations for evaluating the entire pancreatic parenchyma and radiation exposure during CT (59), the pediatric community has shifted towards using MRI, and specifically towards MRI cholangiopancreatography (MRCP) for CP imaging. MRCP has similar diagnostic capabilities compared with ERCP without procedure-related risks (60). Yet the Cambridge classification cannot be directly applied to MRCP because of their different methodologies, including the direct injection of contrast into the pancreatic ductal system during ERCP (61). A pediatric study in Poland shows that patients with pancreatic disorders who had both MRCP and ERCP have similar findings (62). Of 41 children with CP, MRCP had a sensitivity of 77.1%, positive-predictive value of 90%, and specificity of 50%, with negative-predictive value of 27.3% compared with ERCP.

Although MRCP and EUS are now being used more than ERCP for the diagnostic evaluation of CP, ERCP may still have a role in the diagnostic evaluation in pancreas divisum (PD), a risk factor for pancreatitis (63). A study of children with ARP and CP from the INSPPIRE multicenter cohort found that PD was reported

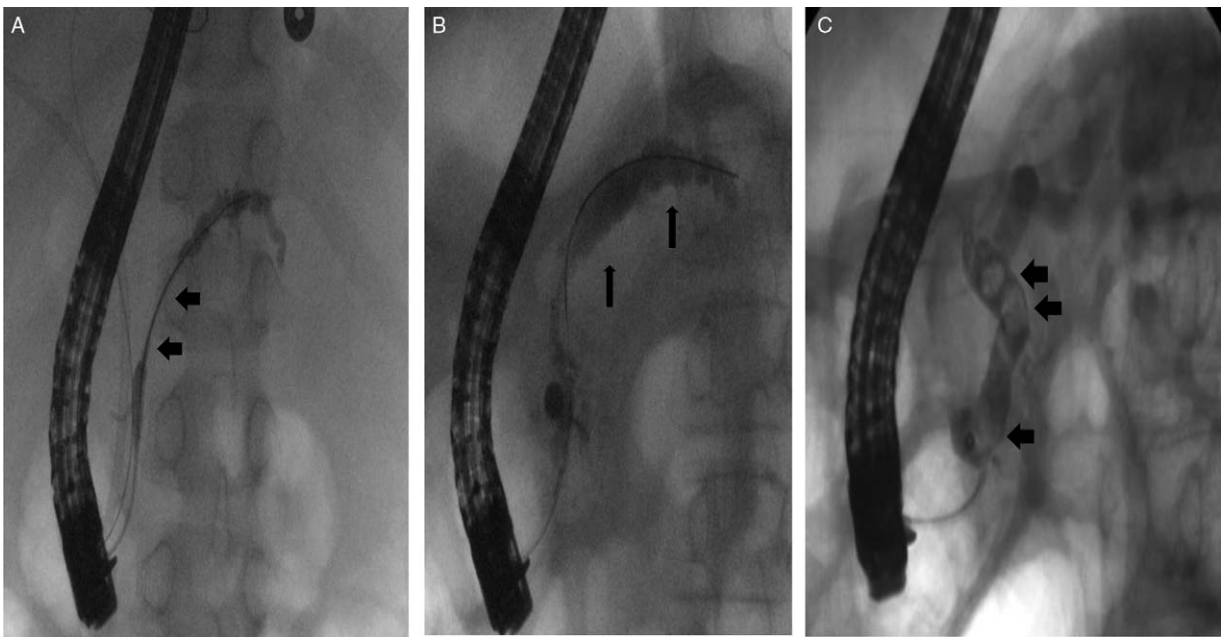

FIGURE 4. Endoscopic retrograde cholangiopancreatography. (A) Thirteen-year-old patient with pancreatic duct stricture (arrows) with upstream pancreatic duct dilation and irregularity as seen via ERC. (B) Thirteen-year-old with dilated and irregular pancreatic duct of the body and tail (arrows). (C) Thirteen-year-old patient with cystic fibrosis transmembrane conductance regulator mutation and pancreatic duct stones (arrows). ERCP = endoscopic retrograde cholangiopancreatography.

TABLE 2. Diagnosis of chronic pancreatitis: endoscopic retrograde cholangiopancreatography (Cambridge) and pediatric considerations

Factor/criterion	Cambridge historical criteria [see reference (58)]	Pediatric considerations
Main duct	Search for dilatation, structuring, irregularity with active filling of duct with contrast (note: tail PD may be difficult to distend if downstream stricture)	No clear characterization of what is abnormal Considerations of different normal sizes based on age
Side branches	Search for dilated side branches (with 3 being the cutoff criterion)	No clear characterization of what is abnormal Different normal sizes based on age
Additional	Cavities (''large'' being >10 mm) Intraductal filling defects and calculi Ductal obstruction or strictures ?Gross irregularity ?Contiguous organ invasion ?Severe dilatation PD	No clear characterization of what is abnormal based on age
Criteria to diagnose CP	Marked/severe CP >3 abnormal side branches and abnormal main duct with calculi, obstruction, or cavity Moderate CP > 3 abnormal side branches and abnormal main pancreatic duct Mild CP >3 abnormal side branches and normal main pancreatic duct Equivocal for CP: three or fewer abnormal side branches and normal main pancreatic duct	Unclear whether these diagnostic criteria are applicable to children Need for high-quality pancreatogram including filling the main pancreatic duct with sufficient contrast to opacify the pancreas tail duct and duct branches. This may be difficult to achieve especially in smaller children with smaller ducts.

CP = chronic pancreatitis; ERCP = endoscopic retrograde cholangiopancreatography; PD = pancreatic duct.

more frequently with ERCP than with MRCP, although the difference was not significant (ERCP 90% vs MRCP 68%, $P = 0.06$). Although ERCP is not statistically superior to MRCP, ERCP may identify patients with PD that MRCP may miss, and in this scenario, pancreatic minor papillotomy might be performed in the appropriate clinical setting (minor papillotomy was performed in 54% of the PD group in the INSPPIRE cohort). ERCP in this context functioned both as an imaging/diagnostic and therapeutic modality within 1 intervention.

Summary

Trans-abdominal ultrasonography has significant limitations in identifying pancreatic ductular abnormalities that can be seen in pediatric patients with CP. MRCP is the preferred cross-sectional imaging because of lack of radiation and detailed outline of pancreatic anatomy. ERCP typically is comparable to MRCP but may have advantages of ability to distend the ductular system via contrast injection for better delineation. No pediatric-specific criteria are available to diagnose CP via ERCP. ERCP may also be beneficial as both an imaging and therapeutic intervention within 1 session, particularly in the context of pancreas divisum with duct obstruction.

Endoscopic Retrograde Cholangiopancreatography-based Therapeutic Interventions

Although ERCP has a minimal role in the diagnosis of CP, it has a major impact in its management. Various studies have reported CP as the indication or associated diagnosis for 4% to 26% of ERCPs performed in children (64–66). In the large INSPPIRE cohort of children with ARP and CP, 65% of children with CP had undergone at least 1 ERCP compared with 13% in children with ARP (67).

The purpose of therapeutic ERCP in CP is in the management of the anatomical chronic ductal or sphincter changes, such as pancreatic duct strictures, ductal leaks into fluid collections and pancreatic duct stones. Studies have shown the efficacy of pancreatic duct stenting for pancreatic duct strictures in children for the goal of relieving symptoms and decreasing the frequency of pancreatitis attacks (68,69). Oracz et al (68) showed that long-term pancreatic duct stenting for various etiologies of CP and duct stricture was effective. In their retrospective study, 72 children had 223 ERCP stenting procedures. The median number of stent replacement procedures was 3 with median interval between stent replacement 4.5 months. Stenting was shown to decrease the median number of AP attacks from 1.75 to 0.23 episodes per year.

ERCP appears most effective when used to remove pancreatic duct stones in contrast to other therapeutic maneuvers, such as pancreatic sphincterotomy and stenting. The INSPPIRE cohort reported that of 18 children with pancreatic duct stones who had therapeutic ERCP for clearance, all 18 (100%) reported improvement after ERCP, compared with 33/66 (50%) who improved with pancreatic sphincterotomy, and 28/57 (49%) who improved with pancreatic duct stenting (67). Li et al (70) reported the application of ERCP for complete and partial removal of pancreatic duct stones was successful in 20 children, and 67.9% of the children experienced symptom improvement. When pancreatic duct stones are either too large or calcified for initial endotherapy removal, pancreatic extracorporeal shock wave lithotripsy (ESWL) is recommended in conjunction with ERCP for stone clearance (71). ESWL has been shown to be both technically successful and safe for children with a complication rate similar to adult data (69,72,73). Wang et al (73) performed a prospective observation study on 72 children undergoing ESWL followed by ERCP for pancreatic duct stones and reported a 11.1% complication rate (post-ERCP pancreatitis or pain because of pancreas contusion). Complete pain relief was reported in 77.6% of the children over a 3-year follow-up period. Their results demonstrate that ESWL is as safe and effective in children compared with adults with pancreatic stone disease. Agarwal et al (69) conducted a prospective study in India of ERCPs for 76 children with duct stones in which 50 children had duct stones greater than 5 mm requiring ESWL. In a smaller retrospective study involving 15 ERCP procedures in 12 children (3 children requiring

2 procedures over time), Oracz et al (72) showed that ESWL followed by ERCP was also technically successful in all, with 3 (25%) children having an acute chronic pancreatitis episode after an ESWL-ERCP session, and 4 having recurrence of pancreatic duct stones.

Although EUS-guided therapy for pancreatic fluid or necrotic collections is usually preferred, ERCP may still be used to assist with fluid collection management. The role of ERCP in this context is to treat any pancreatic duct leak or fistula feeding a fluid collection, or to place a transpapillary stent directly into a fluid collection. This can be done in addition to, or in lieu of, EUS-guided stent drainage. In a child with a very small pancreatic duct diameter in which only a 3-French pancreatic duct stent would be appropriate to place, drainage may be suboptimal because of the small diameter of the stent. Transpapillary stenting of pancreatic fluid collections in children can be a safe and successful treatment (69,74), yet its effectiveness compared with EUS-guided drainage has not been well studied in pediatrics.

Overall application of ERCP for pediatric patients with CP to improve symptoms is favorable. Li et al (70) reported symptom improvement in 37 children who had a total of 110 ERCPs for CP from various etiologies. After a 61-month follow-up period, 81.1% of the children reported improvement in pain, with 64.9% of the children reporting complete resolution of the pain. Arvanitakis et al(75) reported long-term improvement over a 72-month follow-up in children with CP after therapeutic ERCP by demonstrating decrease in median frequency of hospital admissions per year from 3 before endotherapy to 0.66 after endotherapy ($P = 0.001$). Hsu et al (76) also demonstrated fewer health care encounters and improvement in patient pain and general condition after therapeutic ERCP for pancreatic disease in children in a 6-month follow-up period (76). Prospective, randomized trials of ERCP in the management of CP complications versus other therapeutic options are necessary.

Summary

Several publications detail therapeutic ERCP in children with CP for management of pancreatic duct strictures and/or dilatations, ductal fluid leaks, and pancreatic ductal stones. ERCP may be used to perform pancreatic ductal sphincterotomy, pancreatic ductal stent placement, or ERCP-assisted removal of ductal stones (with or without ESWL). ERCP management of the above CP complications has been shown to successfully reduce pain in children with CP. Complication rates in pediatric patients with CP are similar to adult rates. EUS is generally preferred to ERCP for drainage of pancreatic fluid collections. Limited ERCP roles for pancreatic fluid collections include placement of transpapillary stents into fluid collections or evaluation for pancreatic duct leaks. Concerns include stent-associated ductal trauma in smaller-sized pancreatic ducts, infections secondary to stent occlusion and the generally higher procedural risks of ERCP compared to EUS.

Statements/Recommendations

3a. With the advent of safer diagnostic alternatives, ERCP should not be routinely used solely to diagnose CP in pediatric patients. Rather, its utilization should be reserved for situations where endotherapy is likely to be undertaken.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree = 8; agree = 1; neutral = 0; disagree = 0; strongly disagree = 0.

3b. ERCP can be beneficial in management of pancreatic ductal strictures and stones in pediatric patients with CP.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree = 6; agree = 3; neutral = 0; disagree = 0; strongly disagree = 0.

3c. ERCP should be considered in the management of pediatric patients with CP-associated pancreatic fluid collections if EUS management would be suboptimal or not possible, or to supplement therapeutic EUS management.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree = 5; agree = 4; neutral = 0; disagree = 0; strongly disagree = 0.

Procedure-related Risks

Endoscopic Ultrasonography-related Risks

Multiple studies have addressed efficacy and safety of EUS in pediatrics (17–20,77). The risks associated with pediatric EUS are less than 1% and include infection, perforation, bleeding, and pancreatitis (78). Risk rates appear similar to those reported in adults. Similarly, with a duodenoscope, esophageal intubation with EUS endoscopes is performed blindly, and the longer tip has raised concern of cervical esophageal perforation, especially in smaller children. A prospective study of 4894 patients undergoing upper EUS found a cervical esophageal perforation rate of 0.06% (79). It is not known whether different specifications found in different EUS models might affect complication rates. Overall risk, including pancreatitis and infection, associated with EUS-guided FNA of cystic lesions, such as pancreatic fluid collections have been reported up to 2.2% in adults (80). A recent meta-analysis of 51 studies found a rate of EUS-FNA-related pancreatitis of 0.44% (81).

Summary

Risks of EUS in children appear comparable with those in adults, with less than 1% risk of infection, perforation, bleeding, and pancreatitis.

Endoscopic Retrograde Cholangiopancreatography-related Risks

ERCP is limited by the risk for bleeding, perforation, infection, and pancreatitis (82). Multiple pediatric studies have demonstrated ERCP complication rates to be similar to (83) adult studies (69,83), although 1 study showed a higher incidence of post-ERCP pain (14.6%) in children with CP (84). The risk of bleeding is lower than 1% in most studies, but can present late as melena, which should raise suspicion for bleeding from a sphincterotomy site. Perforation can also occur at a rate of approximately 1% with retroperitoneal duodenal perforations from sphincterotomies as most common. Perforation of the pancreatic duct can occur following dilation of a stricture, forceful cannulation, guidewire insertion, stent migration, or difficult stone extraction. In smaller children, the shortening of the duodenoscope should be performed with more care to avoid duodenal wall perforation. Stent occlusions may cause infections (cholangitis or pancreatitis) and very rarely retroperitoneal perforations could lead to abscesses. Occasionally, retention of endoscopic accessories can occur, such as when a stone retrieval basket is trapped on a stone beyond a pancreatic duct stricture and cannot be withdrawn. Plastic stents used for pancreatic strictures, leaks, and pseudocysts, can migrate upstream, cause duct injury, and duct scarring over time if not removed within a prescribed timeframe. In addition to technical risks related to ERCP, other risks include radiation exposure because of fluoroscopy, reactions to fluoroscopy contrast agents, anesthesia risks, and the potential for multiple endoscopic procedures. Increase risk for radiation exposure has been shown to be higher in children undergoing ERCP for pancreas-related indications in comparison to biliary indications (85).

Post-ERCP Pancreatitis (PEP) is the most common complication from ERCP, ranging from 5% to 10% of procedures, with severe pancreatitis occurring in 0.3% to 0.5% of cases (65,69,83,86). Risk factors for PEP include prolonged manipulation of the papillary orifice, instrumentation of the pancreatic duct, and contrast injection of pancreatic duct causing hydrostatic injury. To reduce the risk of PEP, several strategies have been studied including, minimizing cannulation attempts and contrast injection of pancreatic duct, use of carbon dioxide for insufflation, placement of prophylactic pancreatic stents, intravenous hydration with lactated ringers, and rectally administered indomethacin. Most of these strategies have been supported by clinical studies in adults (87). In contrast to the benefit reported in adults, prophylactic pancreatic duct stents are associated with increased risk of PEP in children. This finding highlights the need for larger, prospective studies to determine the effect of stenting on PEP in children and the potential dangers of extrapolation from adult practice without pediatric data (65,86). More recently, concern has surfaced regarding transmission of resistant bacteria from a contaminated duodenal side-viewing endoscope, which is currently being studied with high priority by several professional gastroenterology societies. Guidelines continue to evolve to address duodenoscope (and linear echoendoscope) reprocessing techniques and development of disposable endoscopy technology (88–91).

Summary

Despite having definite potential benefits in the management of complication of CP, with aim to provide pain relief, several complications are described with use of ERCP. Bleeding, perforations, stent migrations, cholangitis/abscesses, pancreatitis, radiation, allergic reactions to contrast agents and other sedation, multiple procedures and anesthesia, risks of retained foreign bodies, and need for hospitalization, are all reported.

Statements/Recommendations:

4a. EUS for diagnosis of CP in pediatric patients is considered safe overall, with complication rates similar to esophago-gastro-duodenoscopy in adults.

8/9 = 89% in agreement with recommendation.

Voting results: strongly agree = 7; agree = 1; neutral = 1; disagree = 0; strongly disagree = 0.

4b. When interventions are performed, EUS risks increase and include infection, perforation, bleeding, and pancreatitis. These risks must clearly be outlined to families before performing EUS in management of pediatric patients with CP.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree = 8; agree = 1; neutral = 0; disagree = 0; strongly disagree = 0.

4c. ERCP for pediatric patients with CP should only be undertaken subsequent to detailed discussion with patients/families regarding significant potential risks that include, but are not limited to: bleeding, perforation, infections, radiation exposure, allergic reactions to contrast, iatrogenic foreign bodies, post-ERCP pancreatitis, and potential need for multiple interventions and sedation/anesthesia events.

9/9 = 100% in agreement with recommendation.

Voting results: strongly agree = 8; agree = 1; neutral = 0; disagree = 0; strongly disagree = 0.

Summary of Recommendations

Please refer to Table 3 for a summary of recommendations, all of which were supported by the voting authorship.

TABLE 3. Summary of recommendations

EUS/ERCP in CP: recommendations
1a. Utilization of EUS and ERCP to evaluate for CP in pediatric patients presenting with abdominal pain without other evidence suggestive of pancreatic pathology is discouraged and should not be routinely done.
1b. EUS and ERCP in children should be performed by appropriately trained endoscopists with sufficient experience performing these procedures in children.
1c. ERCP can be routinely performed both safely and effectively in children >10 kg using standard equipment designed for adult patients. Performing ERCP in children <10 kg typically requires utilization of specialized equipment.
1d. EUS can be routinely performed both safely and effectively in children >15 kg using standard equipment designed for adult patients. Performing EUS in children <15 kg typically requires utilization of alternative equipment not specifically designed for utilization in the GI tract.
2a. EUS should be considered in the evaluation of pediatric patients with suspected CP when cross-sectional imaging is insufficient to pose a diagnosis, determine etiology, or establish extent of the disease.
2b. Rosemont and Conventional criteria for diagnosis of CP can only be used to support and guide interpretation of EUS in children as these criteria are adult-based.
2c. CE-EUS and EUS-elastography need to be further studied before their widespread use can be supported in pediatric patients with CP.
2d. Watchful waiting for resolution of CP-associated fluid collections should always be considered, as many collections resolve on their own, and nonnegligible risks of stent migration, perforation, and bleeding exists with EUS-based interventions.
2e. When intervention is required, EUS should preferentially be considered for management of CP fluid collections before surgical/open interventions.
3a. With the advent of safer diagnostic alternatives, ERCP should not be routinely used solely to diagnose CP in pediatric patients. Rather, its utilization should be reserved for situations where endotherapy is likely to be undertaken.
3b. ERCP can be beneficial in management of pancreatic ductal strictures and stones in pediatric patients with CP.
3c. ERCP should be considered in the management of pediatric patients with CP-associated pancreatic fluid collections if EUS management would be suboptimal or not possible, or to supplement therapeutic EUS management.
4a. EUS for diagnosis of CP in pediatric patients is considered safe overall, with complication rates similar to esophagogastroduodenoscopy in adults.
4b. When interventions are performed, EUS risks increase and include infection, perforation, bleeding, and pancreatitis. These risks must clearly be outlined to families before performing EUS in management of pediatric patients with CP.
4c. ERCP for pediatric patients with CP should only be undertaken subsequent to detailed discussion with patients/families regarding significant potential risks that include, but are not limited to: bleeding, perforation, infections, radiation exposure, allergic reactions to contrast, iatrogenic foreign bodies, post-ERCP pancreatitis, and potential need for multiple interventions and sedation/anesthesia events.

Summary of recommendations is supported via anonymous voting. Please refer to text for detailed summaries of literature reviews relating to each statement.
CE = contrast-enhanced; CP = chronic pancreatitis; ERCP = endoscopic retrograde cholangiopancreatography; EUS = endoscopic ultrasonography.

FUTURE DIRECTIONS/CONCLUSIONS

Historically, even large pediatric referral centers managed relatively small cohorts of patients with CP and most had poor access to advanced endoscopic procedures, such as EUS and ERCP. These factors have hindered the ability of the pediatric community to adequately study the utility of advanced endoscopic procedures in the setting of CP.

This document's statements and recommendations serve to situate the current position of EUS and ERCP in the workup and management of CP in pediatric patients as reviewed by a NASPGHAN expert working group. Many questions, however, remain unanswered, and this review exercise highlights the paucity of research and literature available in pediatric EUS and ERCP. The recommendations are thus based on low to very low quality of evidence, and primarily represent consensus expert opinions. Some of the most urgent issues that need to be addressed relating to advanced endoscopic procedures in children with CP include:

1. Development of equipment allowing for the full breadth of EUS- and ERCP-guided endotherapy across the pediatric age range.
2. Increasing and optimizing the probability that a child undergoing EUS or ERCP is managed by an endoscopist with expertise performing these interventions in children.
3. Developing and validating pediatric-specific EUS criteria for the identification of CP in children.
4. Developing and validating pediatric-specific ERCP criteria for the identification of CP in children.
5. Determining the usefulness of EUS-associated modalities in the management of pediatric patients with CP, including contrast-enhanced EUS and EUS-elastography.
6. Formation of procedural collaboratives capable of evaluating not only technical outcomes, but clinical outcomes of EUS and ERCP being performed in children with CP (pain, exocrine function, endocrine function, recurrence of pancreatitis, progression of fibrosis, etc).
7. Prospective trials evaluating the utility of EUS and ERCP interventions to treat CP, particularly in relation to other interventions such as surgery or total pancreatectomy-islet cell autotransplantation (TP-IAT).
8. Determining what the minimum training requirements should be for a pancreaticobiliary endoscopist to be considered adequately trained to perform pediatric cases.

Well-organized and well-supported consortiums with track records for continued productivity, such as the INSPPIRE consortium, are rapidly shedding light on the etiology and disease burden of CP in children. They are also collecting data from multiple centers regarding use of EUS and ERCP in CP, including benefits and complications for the patients. Other international groups and consortia are collecting similar data in different pediatric populations. In addition, access to and availability of advanced endoscopic procedures is increasing in children, both because of an increasing willingness of adult trained endoscopists to treat children and an increased number of pediatric gastroenterologists fully trained in EUS and/or ERCP. The combination of these efforts is anticipated to lead to significant advancements in knowledge and address various gaps in the knowledge and utilization of EUS and ERCP to diagnose and manage pediatric patients with CP.

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