Specialized Imaging and Procedures in Pediatric Pancreatology: A North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Clinical Report

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ABSTRACT

Objectives: An increasing number of children are being diagnosed with pancreatitis and other pancreatic abnormalities. Dissemination of the information regarding existing imaging techniques and endoscopic modalities to diagnose and manage pancreatic disorders in children is sorely needed.

Methods: We conducted a review of the medical literature on the use of the following imaging and procedural modalities in pediatric pancreatology: transabdominal ultrasonography (TUS), computed tomography (CT), magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS), and endoscopic retrograde cholangiopancreatography (ERCP). Recommendations for current use and future research were identified.

Results: TUS offers noninvasive images of the pancreas but has limitations to details of parenchyma and ductal structures. CT offers improved detail of pancreatic parenchyma, solid masses, and traumatic injuries, but requires relatively high levels of ionizing radiation and does not adequately assess ductal anatomy. MRI/MRCP offers detailed intrinsic tissue assessment and pancreatic ductal characterization, but requires longer image acquisition time and is relatively poor at imaging calcifications. EUS provides excellent evaluation of pancreatic parenchyma and ductal anatomy, but can be subjective and operator dependent and requires sedation or anesthesia. EUS offers the capacity to obtain tissue samples and drain fluid collections and ERCP offers the ability to improve drainage by performing sphincterotomy or placing pancreatic stents across duct injuries and strictures.

Conclusions: Various imaging modalities may be used in pediatric pancreatology, but TUS and MRI/MRCP are favored. Interventional therapeutic maneuvers primarily involve use of ERCP and EUS. Future research is necessary to optimize equipment, expertise, and appropriate indications.

Key Words: computed tomography, endoscopic retrograde cholangiopancreatography, transabdominal and endoscopic ultrasonography, magnetic resonance cholangiopancreatography, pancreas, pediatrics

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What Is Known

- Transabdominal ultrasonography, computed tomography, magnetic resonance imaging/magnetic resonance cholangiopancreatography, endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography are all modalities used to evaluate (adult) pancreaticohepatobiliary abnormalities and disorders.
- The literature is limited on the use of these technologies for pediatric pancreatology indications.

What Is New

- This article reviews the pediatric literature regarding the diagnostic and therapeutic uses, benefits and limitations, and recommendations for use and future study for transabdominal ultrasonography, computed tomography, magnetic resonance imaging/magnetic resonance cholangiopancreatography, endoscopic ultrasonography, and endoscopic retrograde cholangiopancreatography in pediatric pancreatology.

Pancreatic pathologies in children represent a substantial worldwide problem, with etiologies such as acute and chronic pancreatitis, anatomic abnormalities, and neoplasms being responsible for significant morbidity and mortality. Knowledge regarding presentations, investigations, diagnostic methods, and treatment modalities has expanded in recent decades, but has primarily

emanated from reports within adult patient populations, with technologies developed and used to investigate and treat adult-sized patients and disorders (1–4).

Published reports in the past several years document an increasing number of children diagnosed with acute pancreatitis (AP), acute recurrent pancreatitis (ARP), chronic pancreatitis (CP), exocrine pancreatic insufficiency (EPI), and other abnormalities of the pancreas (5–11). The field of pediatric pancreatology has thus emerged as a distinct entity; however, advances within this field continue to lag behind the adults. Given the relation of gallstones with both acute and recurrent pancreatic disease, pediatric pancreatology has also frequently been included within discussions of hepatobiliary diseases. But despite the presence of shared pathologies, pancreatic-specific problems are often independent and necessitate individual attention. As such, it is now imperative for pediatric gastroenterologists and hospital-based pediatricians to become more familiar with imaging techniques and procedures that are useful in the diagnosis and treatment of pediatric pancreatic disease.

Imaging and therapy for the pancreas in children may be accomplished through a variety of techniques including transabdominal ultrasonography (TUS), computed tomography (CT), magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP), endoscopic ultrasonography (EUS), and endoscopic retrograde cholangiopancreatography (ERCP). The latter 2 technologies are of particular interest, as they offer not only diagnostic but therapeutic capabilities. Significant knowledge and evidence gaps exist in the pediatric literature regarding the use of these modalities. The aim of this clinical review is to highlight the particularities of the above diagnostic and therapeutic modalities, including benefits and limitations, with specific focus on their use in pediatric pancreatology based on the available pediatric literature and expert opinion.

METHODS

An ad hoc special interest group was assembled from the NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition) Pancreas Committee with aim to review the literature and experience pertaining to various imaging and therapeutic interventions specific to pediatric pancreatology (concept: committee chair V.M.; members T.K.L., B.B., V.F.). Special outreach was undertaken to the NASPGHAN Endoscopy Committee for additional expertise (D.M.T., D.F.) and external pediatric pancreatology radiology expertise (D.W.).

Discussions were held via e-mail, teleconferences, and face-to-face meetings. Workload was subdivided among the 3 main first authors (T.K.L., D.M.T., and D.W.), all with specific pediatric expertise in their respective fields of review. The main authors conducted literature reviews using electronic medical search engines for appropriate English language literature on the relevant technologies for imaging and therapeutics germane to pediatric pancreatology, to generate manuscript subsections. The following key words were used: pediatrics, pancreatology, TUS, CT, MRI, MRCP, EUS/ultrasound, endoscopic retrograde pancreatography (ERP), and endoscopic retrograde cholangiopancreatography. Articles selected for content included review articles with a focus on peer-reviewed journals, included a review of clinical trial articles. Key information contained was noted and summarized. Articles written in languages other than English were excluded from review. Recommendations were made based on available medical literature. Areas lacking evidence and topics for future progress and study were identified. Subsections were reviewed and a manuscript was designed and assembled by the senior author. The preliminary draft was then circulated among the secondary list of authors for critical review and editing. The subsequent drafts underwent a process of review and editing among all participating authors to create a final draft.

RESULTS

Imaging Techniques
Radiologic Pancreatic Imaging

Noninvasive imaging plays a vital role in the evaluation of children with known or suspected pancreatic disorders. As a complement to clinical and laboratory findings, imaging is able to accurately diagnose and monitor a wide range of pancreatic diseases as well as assess for associated complications. The primary modalities used in the radiologic evaluation include TUS, CT, and MRI, with each having its own advantages and disadvantages in the pediatric population.

Transabdominal Ultrasound

Ultrasound uses high-frequency sound waves to create grayscale images of the pancreas and surrounding structures. Doppler imaging can evaluate the peripancreatic vasculature and assess for areas of regional hypo- or hyperemia. The spatial resolution of TUS exceeds that of CT and MRI, making it a more improved modality to evaluate small structures. TUS is relatively inexpensive, widely available and lacks ionizing radiation. TUS also offers an excellent evaluation of the biliary system and gallbladder in which culpable pathology is frequently identified in pediatric patients with pancreatic disease. In an appropriately fasted patient, the gallbladder, common hepatic duct, and most if not all of the common bile duct can be routinely identified. Dilation of the biliary system can be a clue that distal obstruction or a choledochal cyst is present and guide providers to the next appropriate imaging modality or intervention. For these reasons, TUS is often the initial diagnostic examination of choice in children with a suspected pancreatic disorder.

Clinicians should, however, be aware of limitations of TUS in the assessment of the pancreas (12). The pancreas is a relatively small organ with an elongated shape and is predominantly located within the retroperitoneum. Although the entire pancreas may be visible in the hands of an experienced sonographer with proper attention to technique, size and location can make the pancreas somewhat difficult to fully evaluate. In particular, air within the stomach and intestines frequently interferes with acoustic wave transmission to portions of the body and tail of the pancreas. Visualization of the head of the pancreas and its ventral portion may be limited. Differentiation of normal from abnormal pancreas parenchyma can also be challenging. For example, in AP the parenchyma can maintain normal echogenicity or become hypoechoic and/or hyperechoic. In addition to this, while fluid-filled masses are readily visible, small soft tissue masses can be difficult to distinguish from adjacent normal parenchyma. Although abnormal ductal enlargement is well visualized, TUS is usually inadequate for defining ductal anatomy when searching for anatomic variants. Obese body habitus will limit quality of image acquisition. Despite these limitations, TUS remains the primary tool for initial noninvasive imaging of the pancreas. Readers may refer to a review by van Rijn and Nievelstein (13) of the role of ultrasound in pancreatic disorders.

Computed Tomography

High-resolution images provided by CT allow global assessment of the pancreas. The remainder of the abdomen is also visualized with this single scan, with the images acquired in a few seconds. Administration of intravenous (IV) contrast during CT evaluation of the pancreas will optimize the examination.

Precontrast imaging can detect pancreatic calcifications (as can be seen in CP). Images obtained during pancreatic contrast enhancement help to identify hyper- and hypovascular pancreatic lesions and vascular involvement by inflammatory processes or tumors. For example, hypoenhancing or nonenhancing parenchyma is readily visible with contrast, seen in various inflammatory, ischemic, and traumatic disorders. Solid pancreatic masses are well defined, particularly when imaged in arterial, portal venous, and late venous phases. CT has superior sensitivity for detecting calcific densities within ducts and soft tissue or pancreatic parenchyma. However, CT has poor sensitivity for defining ductal anatomy in the presence of a nondilated system.

The main drawback of CT is the use of ionizing radiation, which has gained increasing attention as evidence mounts regarding the associated increased cancer risk from repeated radiation exposure. These concerns are particularly important in children, in which cells have been shown to have a greater susceptibility to radiation injury (14,15). Fortunately, advances in CT hardware and radiation dose-reduction strategies have significantly lowered the patient exposure (16). Although the risk remains small, clinicians must consider potential long-term and cumulative effects of CT radiation exposure, particularly when multiple follow-up examinations are anticipated, against the potential need for sedation or anesthesia needed to perform other modalities.

Magnetic Resonance Imaging

With MRI, the interaction of high-strength electromagnetic fields with protons in human tissue allows tomographic images to be acquired in multiple planes without the risk of ionizing radiation. Relative to the other modalities, MRI provides excellent intrinsic tissue characterization. Normal pancreas should have mildly higher T1 signal and similar T2 signal relative to the liver. Areas of pancreatic inflammation will have high T2 and low T1 signal compared with uninvolved parenchyma. Differentiation of normal from abnormal tissue is further aided by the addition of gadolinium-based IV contrast with the performance of multiphase imaging. MRI is, however, relatively insensitive for detecting pancreatic calcifications (17).

A primary disadvantage of MRI is the long scan duration, which may take up to an hour and require patients to hold their breath for short periods for optimal image quality. For this reason, infants and young children (under 4–5 years of age) frequently require general anesthesia. Varying strengths of the scanner magnets may influence the picture output. Those with certain device implants, such as pacemakers, heart valves, aneurysm clips, or neurostimulators, may not undergo this modality depending on their MRI safety profile. Metallic implants and surgical material, even when safe for MRI, can cause substantial artifact and degrade image quality. Image quality may also be diminished in patients with ascites.

MRCP facilitates imaging of the biliary and pancreatic ductal systems. This examination is usually performed without IV contrast injection, though contrast-enhanced imaging may be added if it is necessary to assess for acute infection, pancreatic or peripancreatic fluid collection, or pancreatic mass. High-resolution, heavily T2-weighted fluid-sensitive sequences offer enhanced visualization of the ducts, even in a nondilated system. These sequences provide accurate determination of variant ductal anatomy, such as pancreas divisum, and ductal pathology, although accuracy may be compromised in younger children. MRCP is often performed in conjunction with synthetic secretin administration, which stimulates bicarbonate secretion into the pancreatic duct (PD). Secretin is typically injected (dose $= 0.2\,\mu$g/kg) slowly more than 1 minute. Increased fluid secretion enhances visualization of the ductal system and improves diagnostic accuracy for identifying anatomic variants (17). A drawback is that the medication can lead to flushing, vomiting, or diarrhea. Although secretin does improve PD visualization, MRCP without secretin provides adequate image quality and spatial resolution to allow definition of ductal anatomy and pathology. Trout et al (18) compared MRCP sequences obtained in pediatric patients before and after secretin administration and found an increase in PD diameter with secretin but no significant difference in image quality or duct visibility.

Other methods have been described to enhance the quality of MRCP, including administration of certain fruit juices as negative contrast agents (19). These alternatives may be of particular interest in countries in which secretin is not readily available. Readers may also wish to refer to the 2008 review on pediatric MRCP by Chavhan et al. (20).

Endoscopic Pancreatic Imaging

Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) (21) has historically been considered the criterion standard for pancreatic ductal imaging. Diagnostic capabilities are limited to duct-related abnormalities with an inability to evaluate the pancreatic parenchyma. The majority of pediatric case series on ERCP have favored a greater frequency of biliary indications, yet a few studies are available specific to pancreatic indications in children (22–24). Similar principles for determining ''when'' to perform ERP in adults have been applied in children (25). The benefit of ERCP/ERP includes detailed evaluation of the pancreatic ductal system, with the capacity to inject contrast under pressure to better delineate anatomy, including demonstration of duct leakage or disruption, or continuity with cystic lesions. Injection of iodinated contrast agent into the PD can help assess an underlying or primary pancreatic process causing AP, ARP, CP, pancreatic cystic lesions, ductal injury from pancreatic trauma and biliary abnormalities (eg, biliary stricture secondary to CP) (26). Communicating pancreatic fluid collections and ductal disruptions from abdominal trauma can also be reliably identified or ruled out. Drawbacks of the technology are its invasive nature including endoscope insertion (requiring sedation or general anesthesia), exposure to fluoroscopic radiation, and procedural related complications such as post-ERCP pancreatitis (PEP), which is directly associated with injection of contrast or passage of catheters or guide wires into the PD (27,28). Owing to these limitations, ERCP has evolved from an adjunct diagnostic tool to primarily a therapeutic modality allowing for pancreatic-specific therapeutic interventions. Recent reviews of the application of ERCP in children include those by Lin and Barth (26) and Troendle et al (29).

Endoscopic Ultrasound

Available since the 1980s, EUS allows detailed anatomical evaluation of the pancreas and surrounding organ and tissues, including the layered walls of the gastrointestinal (GI) tract (30). Benefits include absence of ionized radiation exposure, excellent axial resolution providing detailed real-time imaging of pancreatic parenchyma and ducts including calcifications, and the capacity to sample tissue and fluid collections via fine needle aspiration (FNA) and fine needle biopsy. For adult patients with GI malignancies, including pancreaticobiliary (PB) cancers, this capability to image not only the pancreas but also surrounding tissues and organs has proven invaluable in staging of disease (31). Well established as a valuable diagnostic and therapeutic technique in the management of adult patients with PB disease (30,32), EUS has only recently been shown to be equally safe and effective in the care of children (33–36). Several factors may explain the delayed adoption of EUS for children with PB diseases: lower incidence of malignancies, size limitations of EUS equipment relative to pediatric anatomy, scarce

number of skilled pediatric endoscopists with EUS expertise, need for sedation or anesthesia, and limited awareness among pediatric practitioners of EUS diagnostic and therapeutic capabilities (36,37). A recent manuscript by Lakhole and Liu (38) reviews the role of EUS in pediatrics.

Clinical Application of Imaging Techniques (Radiologic and Endoscopic)

Normal Anatomy and Variants

Normal morphology of the pancreatic parenchyma to exclude entities such as dorsal pancreatic agenesis or focal hypoplasia can be performed with TUS (39). A more complete evaluation for coexistent syndromic abnormalities, including splenic malformations, liver, vascular, and intestinal abnormalities may require CT or MRI (Fig. 1).

A ring of tissue (which may be extremely thin or incomplete) encircling the second portion of duodenum may be difficult to detect by TUS to diagnose an annular pancreas. This malformation is often initially suggested in infants by the presence of a ''double bubble'' on abdominal radiographs with duodenal narrowing found on subsequent upper GI fluoroscopic examination. Both findings can be seen with other anatomic abnormalities, most frequently duodenal atresia or stenosis. As such, confirmation is usually obtained at surgery. Less severe forms of annular pancreas may escape early detection and are frequently discovered by an upper GI series or CT/MRI performed later in life.

Pancreas divisum is the most common variant of pancreatic ductal anatomy and is present in an estimated 5% to 10% of the general population (40). Diagnosis is important as it may play a role in ''idiopathic'' AP and CP (41). ERP remains the criterion standard for the diagnosis of pancreas divisum, but because of its invasiveness and the technical expertise required to perform the procedure, it is typically reserved for cases in which less invasive diagnostic modalities are nondiagnostic or therapy is planned. MRCP is the most accurate noninvasive imaging modality to identify separate drainage of the main PD to the duodenum through the minor papilla via the duct of Santorini, rather than through the major papilla via the duct of Wirsung (42,43) (Fig. 2A and B). At times, a Santorinicele may be found, which is a cystic dilatation of the distal dorsal duct just proximal to the minor papilla. Visualization of a Santorinicele, which is suggestive of more significantly compromised drainage, is well depicted by MRCP (43), although this may be best identified via ERCP with direct endoscopic visualization (author B.B., expert opinion) (Fig. 2C and D).

Early experience with EUS suggests that it may be comparable with MRCP for identifying pancreas divisum in the hands of experienced endoscopists (44). As it does not carry the same risks associated with ERP, EUS may represent a more preferable option for patients who require sedation for MRCP as EUS offers the opportunity for sequential therapeutic ERP during the same anesthetic session if pancreas divisum is indeed confirmed and believed to be pathologic for that patient.

Pancreaticobiliary maljunction (or malunion) occurs when an abnormally long common channel (usually >15 mm in adults) of the distal common bile duct and duct of Wirsung is present just proximal to the major papilla (45) (Fig. 2E). In a series of 264 ERCP studies, the upper limit of normal in children younger than 1 year was found to be 3 mm, increasing with age to an upper limit of normal of 5 mm in adolescents (46). The prevalence of PB maljunction is estimated to be 1.5% to 3.2% in adults (47) and up to 4.4% in children (46). Associated complications include bile salts refluxing into the PD or an obstruction at the common channel resulting in pancreatitis and gallbladder carcinoma related to the biliary reflux (47,48). Similar to pancreas divisum, this anatomic abnormality is thought to be best imaged noninvasively with MRCP, having an accuracy comparable with ERCP (49), although diagnostic EUS may ultimately prove equal or superior (50,51).

Pancreas Imaging in Primary Exocrine Insufficient Conditions

Cystic fibrosis is the most common cause of EPI in children, primarily as a result of plugging of the ducts with inspissated secretions (52). Morphologic abnormalities visible on imaging include gland atrophy with fatty replacement of the parenchyma, pancreatic calcifications, and cystosis (refer to section Neoplasms and Cysts). Shwachman-Diamond syndrome represents the second most frequent cause of EPI in children. This disease is characterized by diffuse fatty replacement of the pancreatic glandular tissue. Findings in both of these conditions are well visualized by TUS, CT, MRI/MRCP, and EUS, and hence TUS is frequently used as initial modality.

Inflammatory Disorders

The diagnosis of pediatric AP is based on a combination of clinical, laboratory, and/or imaging findings (8). Imaging is particularly useful to assess for complications. In most cases, TUS is sufficient to detect acute pancreatic/peripancreatic fluid collections and to monitor their evolution. TUS has also been used to follow the appearance and size of the PD in AP (53). In more severe AP, patients may develop necrosis, hemorrhage, thrombosis, pseudoaneurysm, or other complications. In these cases, CT or MRI is preferred for a more definitive assessment (Fig. 3). In the acute setting, CT is usually most appropriate primarily due to the much shorter imaging duration in patients unable to lay still for the much
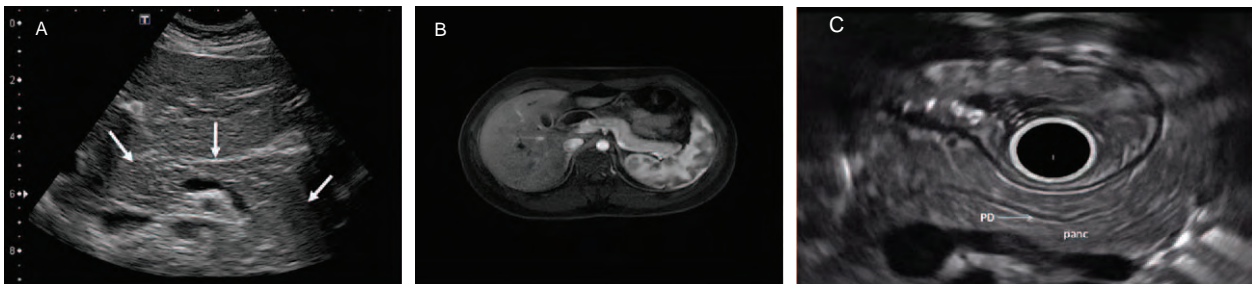

FIGURE 1. Normal pancreas imaging. A, Transabdominal ultrasonography (TUS) pancreatic head, body, and partially obscured tail. B, Magnetic resonance imaging (MRI) axial T1 image with contrast. C, Endoscopic ultrasonography (EUS) normal pancreatic body with pancreatic duct coursing through center.
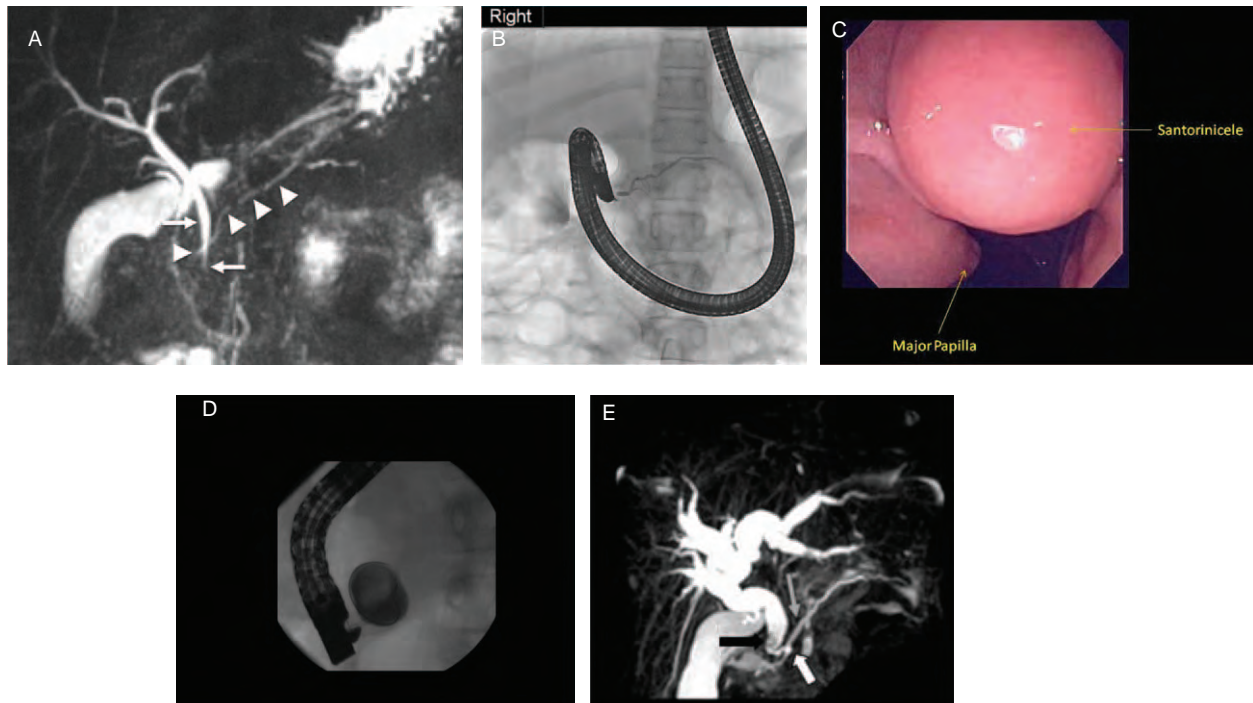
FIGURE 2. Pancreas ductal variants and anomalies. A, Magnetic resonance cholangiopancreatography (MRCP) demonstrating pancreas divisum: coronal oblique image shows the pancreatic duct (arrowheads) crossing the distal common bile duct (arrows) and draining to the expected location of the minor papilla. The common bile duct drains separately to the major papilla more inferiorly. B, Endoscopic retrograde cholangiopancreatography (ERCP) diagnosis of pancreas divisum: with endoscope in typical long position with a cannula engaging the minor papilla, ERCP-contrast injection via minor papilla confirms complete pancreas divisum. C, ERCP endoscopic view of Santorinicele. D, ERCP image of Santorinicele: fluoroscopic image demonstrating cystic dilation filled with contrast following injection and passage of guide wire through the abnormal papillary orifice on the surface of the Santorinicele. E, Pancreaticobiliary maljunction: long common channel with choledochal cyst and stone. Black arrow (common bile duct stone within a choledochal cyst), gray arrow (pancreatic duct), and white arrow pointed at junction of pancreatic and bile duct. Courtesy of Dr Richard Braverman.

longer imaging acquisition required with MRI. The 2012 revision of the Atlanta classification of AP in adults uses contrast-enhanced CT as the modality of choice to delineate and diagnose various inflammatory conditions that may be associated with AP. This includes interstitial edematous pancreatitis, necrotizing pancreatitis, acute peripancreatic fluid collections, pancreatic pseudocyst, acute necrotic collections, and walled-off necrosis (54). In 2013, the International Association of Pancreatology and the American Pancreatic Association published guidelines regarding the management of adult AP that recommend using CT in cases of diagnostic uncertainty or for assessment of AP severity 72 to 96 hours after onset of symptoms (55). Of importance, these guidelines for imaging are only validated in adults, although they are frequently extrapolated to pediatric patients because of the paucity of recommendations for children. The most obvious drawback to following these guidelines is the associated ionizing radiation exposure.

In adult patients with suspected choledocholithiasis as a cause of pancreatitis, EUS is an alternative to cross-sectional imaging. Several studies have identified superiority to conventional imaging in detecting biliary stones/sludge (56,57).

CP in children has numerous potential causes and may be reliably diagnosed via imaging with the characteristic findings (8,11). Imaging aids in the diagnosis of CP with visualization of associated pancreatic atrophy, calcifications, main and side branch ductal enlargement, strictures, pancreatic fluid collections and lithiasis. Imaging is also helpful in excluding an underlying structural cause. Overall, with the exception of parenchymal

calcifications, MRI/MRCP provides the best noninvasive imaging of these findings. EUS is a more invasive alternative that can be considered in patients requiring sedation for MRCP or those in whom EUS-guided tissue acquisition or intervention, and/or sequential ERP is anticipated to be likely (Fig. 4).

Although uncommon in children, autoimmune pancreatitis (AIP) can be the cause of CP that may benefit from noninvasive imaging for diagnosis (58,59). Classic radiologic appearance has been described as the appearance of a diffuse or focally enlarged pancreas with loss of the normal lobular contour. The pancreas is typically low attenuation on CT and has low T1 signal on MRI delayed enhancement after administration of IV contrast. A thin capsule, representing inflammatory cell infiltration, without significant mesenteric involvement is highly specific for this entity though seen in only a minority of cases (60). Ductal abnormalities, including strictures or diffuse narrowing, can also be accessed via MRI/MRCP. EUS is an alternative imaging modality with the ability to identify characteristics of AIP including diffuse hypoechoic pancreatic enlargement and occasionally findings of a solitary mass in the head of the pancreas (61). Ultimately, the most definitive diagnostic test to establish the diagnosis of AIP is pancreatic tissue sampling attainable at the time of EUS by FNA (54) or by a more recent technique of trucut biopsy (62,63). Please refer to section Image-Guided Interventions and Therapeutics for further details.

The Cambridge classification is a widely accepted ERCP scoring system for identifying changes suggestive of CP but is a tool
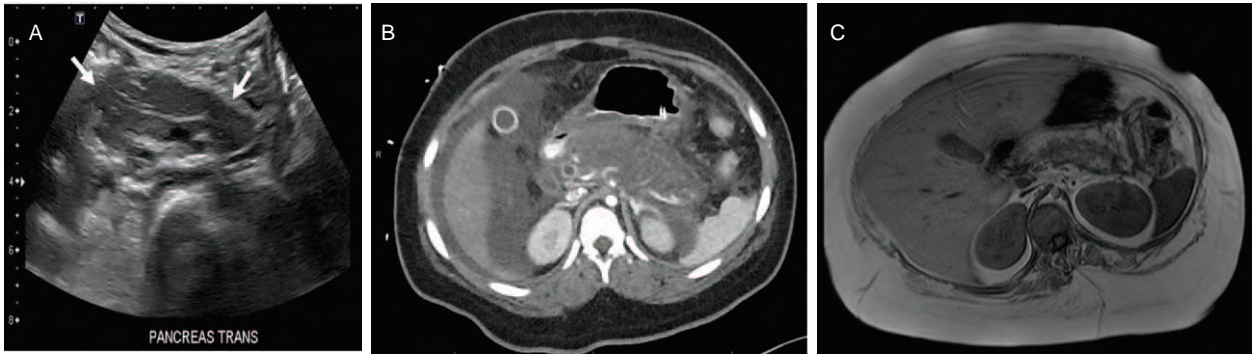
FIGURE 3. Acute pancreatitis and complications. A, Transabdominal ultrasonography (TUS) images of enlarged and hypoechoic pancreas. B, Computed tomography (CT) severe acute pancreatitis (AP): nonenhancement of pancreas confirming necrotizing pancreatitis. C, Magnetic resonance imaging (MRI): severe pancreatic necrosis T1 image.

primarily used in adults (64). This classification grades the severity of chronic pancreatic structural changes based on findings such as abnormal side branches, main duct changes, large cavities, and ductal obstructions or dilations as seen on ERCP.

Endosonographic characteristics for diagnosing CP have been developed for adult patients and referred to as the Rosemont classification (65). This classification evaluates for a combination of parenchymal (hyperechoic foci or strands, cysts, lobularity) and ductal changes (dilatation, irregularity, calculi, side branch dilatations, hyperechoic walls) suggestive of CP when specific criteria are met (65). These criteria have recently been applied in the diagnosis of CP in children but currently lack validation (36). The importance of establishing validated EUS CP criteria specific to children cannot be overemphasized especially when considering that the primary risk factors for CP in children, genetic and obstructive factors (11), differ significantly from that in adults in which alcohol is a more predominant risk factor (66). As it relates to EUS as a method for diagnosing CP, the greatest limitation in the Rosemont classification system is the relatively poor interobserver agreement (67).

Trauma

The pancreas is susceptible to injury in blunt abdominal trauma because of its fixed retroperitoneal position, with children even more vulnerable than adults due to their underdeveloped abdominal wall musculature (68). Pancreatic injury occurs in an estimated 3% to 12% of children with blunt abdominal trauma, most commonly from a handlebar injury (69). Nonaccidental trauma should be suspected when a history of injury is questionable.

Traumatic pancreatic injury is best imaged initially with contrast-enhanced CT. Contusions are visible as focal areas of low attenuation, usually with varying degrees of adjacent fluid, edema, or hematoma. Pancreatic laceration and transection are higher grades of injury that may require surgical intervention depending on their size, location, and whether the PD is disrupted (70); hence, detailed imaging is critical. Duct disruption is suggested in the setting of a fluid collection extending into the pancreatic parenchyma or progressive increase in size of a peripancreatic fluid collection after abdominal trauma. In cases in which ductal integrity remains indeterminate, ERCP is the criterion
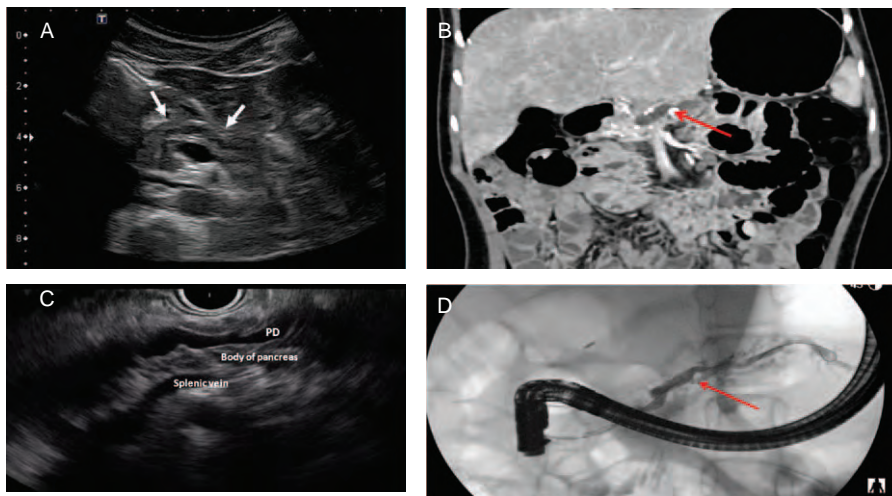
FIGURE 4. Chronic pancreatitis. A, Transabdominal ultrasonography (TUS) severely atrophic pancreas with only thin rim of tissue surrounding dilated main pancreatic duct (PD). B, Computed tomography (CT) showing several pancreatic parenchymal calcifications, extremely dilated PD, and large intraductal calcification (red arrow). C, Endoscopic ultrasonography (EUS) showing extremely dilated PD and abnormal parenchyma. D, Endoscopic retrograde cholangiopancreatography (ERCP) showing large parenchymal calcification with mass effect on PD (red arrow). Dilated PD and side branches visualized.

standard for diagnosis, and may offer therapeutic advantage (Fig. 5). MRCP, however, also appears to be highly accurate in detecting duct injury, with an accuracy of 94% in a recent study (71).

Neoplasms and Cysts

Pancreatic neoplasms are rare in children, with malignant tumors having an estimated incidence of 0.02 per 100,000 (72,73). Pancreatoblastoma is the most common pancreatic tumor in young children, usually seen in patients less than 10 years of age. On CT and MRI, the mass is usually large, well circumscribed and hypoenhances relative to the adjacent pancreatic parenchyma. Solid pseudopapillary tumor is a neoplasm with low malignant potential more common in postpubertal girls. This lesion also is character- istically large and well circumscribed with an enhancing capsule. Internal contents may be primarily solid or cystic/necrotic and calcifications are frequently present. Neuroendocrine tumors, chiefly insulinoma and gastrinoma, are more frequently seen in patients older than 10 years of age. Patients with multiple endocrine neoplasia type 1 tend to present in young adulthood, with a mean age at diagnosis of 25 years (74); however, some patients can present earlier within the pediatric age range. Syndromic tumors are usually seen as a small arterial enhancing mass, whereas nonsyn- dromic tumors are frequently much larger and more heterogeneous at diagnosis. Ductal adenocarcinomas rarely present in adolescence and carry a poor prognosis. Most pediatric pancreatic tumors other than insulinomas are large enough to be detected by ultrasound, particularly if the mass contains cystic or necrotic components allowing easier distinction from the adjacent normal parenchyma. Subsequently, CT or MRI is usually performed to evaluate the full extent of the tumor and look for metastases wherever applicable. Insulinomas and other functional neuroendocrine tumors most often present at a smaller size because of their secretion of a hormonally active polypeptide (75). Functional tumors should be imaged with multiphase CT or MRI as they usually are best seen in the arterial phase of contrast enhancement.

Cystic lesions of the pancreas may represent benign or malignant processes and may be identified incidentally during abdominal cross-sectional imaging or TUS performed for other indications. Cystic fibrosis patients may develop various degrees of pancreatic cystosis, which may be visualized through TUS, CT, or MRI/MRCP. When cysts are typical and asymptomatic, TUS can be adequate for follow-up without the need for repeat CT or MRCP (76). Pancreatic cysts may also be found as part of certain syn- dromes such as Von Hippel-Lindau, or as a congenital anomaly. Pancreatic pseudocysts are not true ''cysts.'' They lack an epithelial lining, but are identified relatively more frequently than other cysts, developing most commonly after blunt pancreatic injury in up to 44% of cases (77). EUS has the ability to characterize pancreatic cystic lesions and, when performed in combination with FNA, can allow for discrimination of the various types of cysts.

Newer EUS techniques of contrast-enhanced harmonic EUS and EUS elastography are not widely used but represent the forefront of advances for diagnosing pancreatic masses (78,79) and may prove to be valuable adjuncts for CP imaging (80).

Image-Guided Interventions and Therapeutics

Endoscopic Retrograde Cholangiopancreatography

Therapeutic indications for ERCP in adult biliary and pan- creatic disorders have previously been presented in guideline form (3). Pancreatic-specific therapies in children include pancreatic
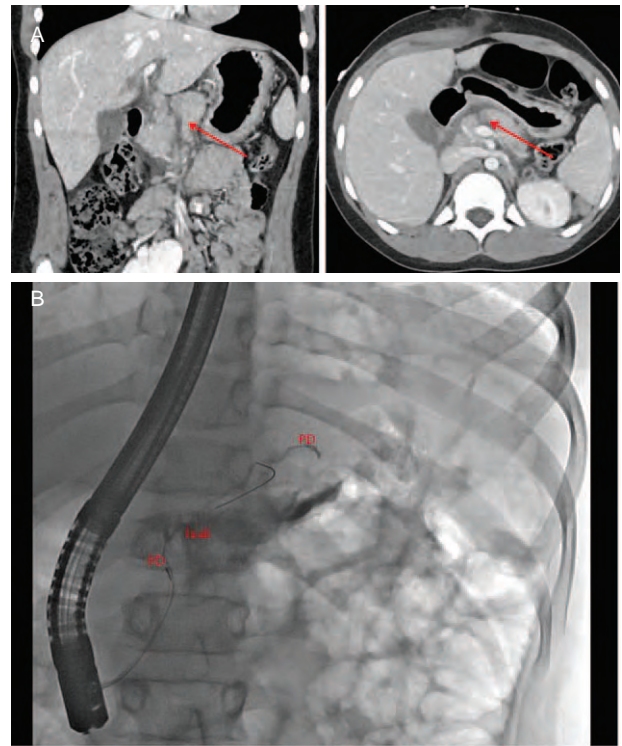

FIGURE 5. Pancreatic trauma. A, Computed tomography (CT) demonstrating pancreatic laceration secondary to handlebar injury. B, Endoscopic retrograde cholangiopancreatography (ERCP) demon- strating pancreatic duct leak at site of laceration, with guide wire outside of the pancreas.

sphincterotomy (PS), main pancreatic ductal dilation with stenting across a stricture, ductal stenting as prophylaxis against PEP, and stone removal (26). Stenting may also be used for PD leaks by transpapillary drainage or in cases of duct disruption to attempt to bridge such defects to restore ductal continuity, redirect flow of pancreatic fluid into the duodenum, and resolve a pancreatic fluid collection (81,82).

Compared with adult data, the literature on the efficacy of pediatric therapeutic ERCP as it relates to the pancreas has been limited to single-center case series that have primarily reflected procedural outcomes (22,83–87). No children-specific randomized control trials of pancreatic therapeutic endoscopic interventions have been reported. Supported by available literature, such thera- pies are, however, generally accepted to be similarly effective in children as they are in adult patients (22,84,87). Recently, Oracz et al (23) retrospectively reviewed their outcome of PD stenting as ''therapy'' for children specifically with CP for the purpose of identifying the efficacy of this intervention. In this study, PD stenting was most frequently performed in children with CP sec- ondary to hereditary pancreatitis (*PRSS1 cationic trypsinogen* gene mutation) and in those with pancreatic ductal anomalies. The authors found that ''therapeutic'' stenting resulted in an overall significant decrease in the frequency of pancreatitis episodes per year, supporting its utility for this age group. Other published pediatric ERCP case series have identified no significant compli- cations from stenting, but neither did they identify any clearly defined benefit from such stenting (84,87). Of note, however, benefit from therapeutic pancreatic stenting was not the primary aim of these series.

An alternative concern has been that PD stenting in children under specific circumstances could be more harmful than beneficial. As an example, a recent report on the effect of ''prophylactic'' PD stenting in children found that such stenting may fail to prevent severe occurrences of PEP and in high-risk patients may actually contribute to its development (27). Clearly, more data are necessary to either confirm or invalidate this report. If accurate, this observation may not represent a new phenomenon, but rather reflect an outcome that has previously gone unrecognized because of the paucity of literature attempting to answer such specific safety questions in children.

Chronic pancreatitis with development of obstructing intraductal stones occurs in children as it does in adult patients (22,84,88). Endoscopic removal by means of PS and stone extraction using instruments such as an occlusion balloon or retrieval basket has been effective in ductal clearance (22,84,86,88) (Fig. 6). In cases in which recalcitrant stones are unable to be extracted by the conventional approach, successful use of extracorporeal shock wave lithotripsy (89–91) and more recently pancreatoscopy-guided lithotripsy have been described in adults and children (22,92–94). Nonendoscopic, intraoperative pancreatoscopy using a pediatric cystoscope was described by one group whereby PD stones were removed by irrigation alone (95).

ERCP can be both diagnostic and therapeutic for duct leaks and disruptions that are most often secondary to abdominal trauma. Based on more recent reports, in such scenarios PS and PD stenting via ERCP has been used successfully to manage duct leaks, although higher-grade injuries may still necessitate surgical intervention (96,97).

The benefits from endoscopic therapy remain unproven for some conditions in both children and adults. One such example is pancreas divisum in which minor papillotomy has shown mixed results in adult patients (98,99). Several small pediatric case series have been reported with successful endoscopic intervention, suggesting that ERCP should be considered for a child with ARP or CP with pancreas divisum (22,84,100,101). Future studies will be beneficial to elucidate whether a true benefit exists.

Endoscopic Ultrasonography-guided Tissue Sampling and Intervention

EUS offers diagnostic imaging, guided tissue sampling and advanced therapeutic interventions in a single procedure. Although the published pediatric experience remains modest, these advanced techniques are currently used with regularity in adult patients with pancreatic disease. One limitation to using EUS in children is the large outer diameter and bulky tips of typical echo-endoscopes that may make them difficult to maneuver through the oropharynx and around the duodenal sweep of smaller children. In addition, as most linear echo-endoscopes have an oblique field of view, maneuvering these relatively high-risk anatomical regions is done in a semiblind manner that can increase the risk for perforation. Although the application of traditional linear echo-endoscopes may be feasible in patients weighing at least 15 kg, data evaluating this modality in patients of this size are clearly limited (102). Until more experience is obtained with this equipment in small children, extreme care should be used to optimize safety. Use of inherently smaller (6.3–6.9 mm outer diameter) endobronchial ultrasound equipment in the GI tract has been described to perform diagnostic procedures and to guide tissue acquisition in children as young as 2 months of age with success (103).

The handful of pediatric series currently available suggest that EUS-guided pancreatic tissue sampling and other EUS-guided interventions can be performed with technical and clinical
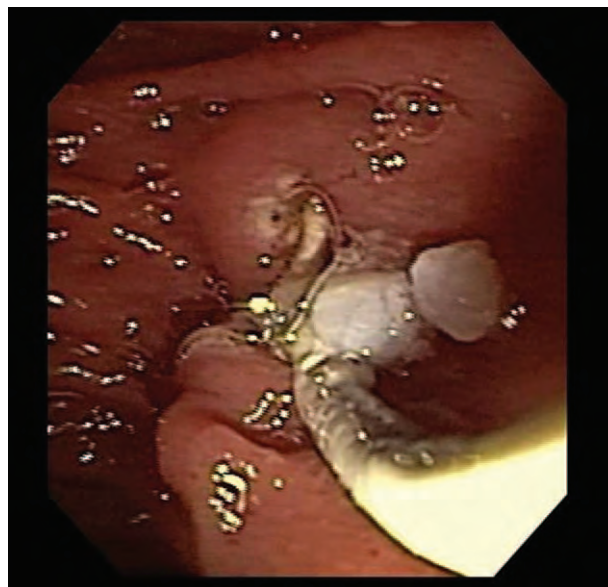

FIGURE 6. Interventional endoscopic retrograde cholangiopancreatography (ERCP): pancreatic duct stones extraction.

outcomes comparable with adults undergoing these procedures for similar indications (33–36,104–106). The 2 most commonly encountered clinical scenarios in which EUS-guided techniques are reported in the pediatric population include pancreatic tissue sampling in the setting of pancreatic mass or suspected AIP, and drainage of symptomatic pancreatic fluid collections.

EUS-guided tissue acquisition has emerged as a preferred technique to obtain pancreatic tissue (107). In the setting of evaluating a solid pancreatic mass, recent meta-analysis suggests that the procedure is technically successful in >95% of cases when performed by an experienced endoscopist with a sensitivity of 87% and a specificity approaching 100% (108). Based on the limited pediatric data, similar performance characteristics of EUS-guided tissue acquisition in the evaluation of solid pancreatic lesions would be expected, although further studies are needed for confirmation (32–34,106). The diagnostic yield of EUS-guided biopsy in the setting of suspected AIP has been reported to be 86% in a small pediatric case series (63). During pediatric EUS examinations, several adjuvant imaging techniques including strain elastography for the evaluation of tissue stiffness and contrast harmonic imaging for assessment of lesional perfusion have been described as being helpful in identifying pancreatic lesions that are more likely to be inflammatory in nature as seen in the setting of AIP. Experience with these advanced imaging techniques in pediatrics remains limited, thus their role is largely undefined (36).

For pancreatic fluid collections requiring therapy, endoscopic drainage has emerged as an attractive alternative to surgical and percutaneous approaches with favorable technical success shown in at least 2 randomized control trials involving adult patients (109,110). Pediatric experience with the technique is growing and suggests that it can be safely and effectively performed even in small children with similarly high rates of technical and clinical success (111,112) (Fig. 7). The variety of different endoscopic techniques used to treat pancreatic fluid collections have been well chronicled by several recent reviews (113,114). Frequently, EUS is used as part of these techniques to confirm adequate location and wall maturity of the fluid collection, and to help avoid vascular structures during the endoscopic cystostomy creation. High-frequency ultrasound probes have also been used in pediatric

FIGURE 7. Interventional endoscopic ultrasonography (EUS). Access needle in walled-off pancreatic necrosis as part of drainage procedure.

patients to assist with fluid collection evaluation before cystostomy creation (115). When necessary, endoscopic necrosectomy can be performed through appropriately created cystostomies, as recently described by Giefer et al (116) in an 11-year-old child.

Computed Tomography-guided Interventions

The deep location of the pancreas surrounded by vasculature and multiple organs, including the liver, spleen, kidneys, and GI tract, can make percutaneous tissue sampling or drainage of fluid collections a difficult endeavor. CT-guided percutaneous pancreas interventions are well-established techniques (117). Real-time imaging with low radiation dose CT fluoroscopy or intermittent CT image guidance can safely guide access needles to the appropriate location, often through small windows that may be less optimal for ultrasound guidance.

Acute peripancreatic fluid collections, postnecrotic fluid collections and pancreatic pseudocysts are primary reasons for undergoing CT-guided catheter drainage. The most appropriate timing of such intervention is, however, sometimes disputed. Despite the risk of infection, percutaneous drainage of sterile, larger peripancreatic fluid collections is a widely used and effective therapy (118). Although traditionally necrosectomy has been the primary treatment of postnecrotic fluid collections and walled-off pancreatic necrosis, studies have also demonstrated the efficacy of percutaneous catheter drainage in patients meeting select criteria (119). Large pseudocysts may cause significant pain or respiratory complications as a result of compression. In these patients, surgery or percutaneous drainage are both accepted forms of treatment. If significant communication exists with the ductal system, external drainage will, however, likely be unsuccessful, and surgery or endoscopic transpapillary drainage may be required for more definitive treatment (120). In addition to this, one specific concern with percutaneous drainage is the potential creation of a fistula between the cyst and skin.

Percutaneous FNA biopsy of a pancreatic mass is a safe and accurate method of tissue sampling. When a clear window to the lesion is absent, a transorgan, transintestinal, and/or transvenous route may be necessary in up to 40% of the cases requiring CT guidance (121). Although traversing the intestine is thought by some to increase the risk of pancreatic infection, older studies have reported a low risk of significant complication (122).

Benefits and Limitations of the Different Technologies

Table 1 provides a summary of the different imaging and procedural modalities available and some important benefits and limitations of these techniques.

Recommendations for Use

Based on the current available literature, we put forth the following recommendations:

1. TUS is a reasonable first imaging modality to use in suspected pediatric pancreatic abnormalities, particularly because of its noninvasive nature, accessibility, ease of use in children of all ages, and the absence of ionizing radiation exposure. TUS may also be used to evaluate for complications of pancreatitis (such as pseudocysts) and to follow-up after therapeutic interventions (including pseudocyst drainage).

2. Should more detailed imaging be needed, it is preferentially obtained by MRI/MRCP due to its avoidance of ionizing radiation and its detailed ability to evaluate both pancreatic parenchyma and ductal anatomy. Younger children (approximately 4–5 years of age and younger, with some variability based on developmental level and medical comorbidities) may require deep sedation or general anesthesia (123).

3. CT imaging may be useful particularly in the acute inflammatory setting when US is not sufficiently detailed, when MRI/MRCP is not readily available, for assessment of necrosis and other complications, for abdominal trauma, and when a short duration of imaging is desirable based on patient instability and/or tolerance. CT can be used for percutaneous pancreatic tissue sampling or drainage of pancreatic fluid collections based on anatomic location and local expertise/availability. Its most significant drawback is use of ionizing radiation. Younger pediatric patients may still require sedation or general anesthesia.

4. ERCP is infrequently indicated for the initial diagnostic evaluation for pancreatic abnormalities, but may be necessary for diagnosis of ductal variants or determining the continuity of the ducts in certain congenital lesions. The principal role of ERCP is in therapeutic interventions including sphincterotomy, stenting across strictures and obstructions, removal of pancreatic ductal stones, and draining communicating pancreatic fluid collections using a transpapillary approach. Pediatric patients must be sedated and fluoroscopy/radiation is used.

5. EUS is an emerging modality that provides detailed evaluation of the pancreatic parenchyma and ductal system. EUS enables the endoscopist to obtain FNA sampling or larger core tissue biopsies that may be beneficial in the diagnosis of certain pathologies such as neoplasms or AIP. It may also allow for sequential therapeutic ERCP if amenable ductal pathology is identified. Thus, it may offer an advantage over other purely diagnostic modalities such as MRCP if sedation is required to complete them. Pediatric patients must be sedated.

6. There needs to be greater dissemination of knowledge and skills in pediatric ERCP and EUS to optimize their benefits in pediatric pancreatology. If pediatric specialists are not available, a reasonable option is to involve adult endoscopists skilled in ERCP and EUS and comfortable performing procedures in children. The recent increase in pediatric gastroenterologists pursuing advanced endoscopic training in these modalities will lead to greater availability of these skills for the pediatric population and ongoing development of this field of study should be encouraged.

TABLE 1. Advantages and limitations of available pancreatic imaging and procedures in pediatrics

Imaging modality	General advantages and uses	General limitations/ drawbacks
TUS	Lack of ionizing radiation	Difficult to fully evaluate pancreas due to retroperitoneal location and elongated shape
	Affordable	Patient body habitus may affect visualization
	Portable	Limitations in differentiation of normal from abnormal parenchyma
	Lack of need for sedation	Limited assessment of ductal anatomy/pathology
	Widely available	Poor for neuroendocrine tumors
	Can easily repeat over time/ follow to ''resolution''	Little to no therapeutic indications in pediatric pancreatology
	Good for small structures	Operator dependent
	Assessment of vasculature possible with Doppler	
	Imaging of calcifications	
	Detection of most pediatric tumors (other than insulinomas) especially if cystic component	
CT (IV contrast-enhanced)	Short duration scan (seconds)	Ionizing radiation
	Use of IV contrast allowing great detail of pancreatic parenchyma	Suboptimal for delineating ductal anatomy and pathology, particularly in a nondilated ductal system
	Good to define solid masses	
	Good for calcifications	
	Preferred modality for traumatic injuries	
	Good for neuroendocrine tumors	
MRI/MRCP	Lack of ionizing radiation	Longer duration scan (30–60 minutes)
	Best for intrinsic tissue characterization	Need for sedation/ general anesthesia for younger children
	Best to image biliary and pancreatic ductal systems via MRCP	Poor for calcifications
	Good to evaluate cystic/fluid-filled lesions on T2 sequences	Susceptible to motion artifact
	Good for PD strictures and filling defects	Artifact from indwelling surgical hardware
	MRCP with secretin may increase details	
	Good for duct injuries	
	Good for neuroendocrine tumors	
EUS	Lack of ionizing radiation	Need for anesthesia/sedation for all ages
	Excellent for detailed anatomic evaluation of pancreas parenchyma	Limited availability of appropriately trained physicians
	Excellent evaluation of ductal system and anatomy	Careful equipment selection is needed particularly for smaller children.
	Assessment of vasculature possible with Doppler	Interobserver agreement can be limited/low in the setting of chronic pancreatitis
	Allows for FNA, biopsy, and drainage procedures to be performed when appropriate	
	Allows for sequential therapeutic ERCP when appropriate	
	Short recovery time	
	Less invasive than surgical procedures	
ERCP/ERP	Detailed evaluation of pancreatic ductal system	Ionizing radiation/fluoroscopy
	Sensitive in evaluation and definition of PD injuries	Need for anesthesia/sedation in all ages
	Less invasive than surgical procedures	Limited availability of appropriately trained physicians
	Ability to place remove stones, dilate stricture and place internal stents	Risk of PEP

CT = computed tomography; ERCP/ERP = endoscopic retrograde cholangiopancreatography/endoscopic retrograde pancreatography; EUS = endoscopic ultrasound; FNA = fine needle aspiration; IV = intravenous; MRI/MRCP = magnetic resonance imaging/magnetic resonance cholangiopancreatography; PD = pancreatic duct; PEP = post-ERCP pancreatitis; TUS = transabdominal ultrasound.

Recommendations for Future Directions

Ongoing refinement of use of these modalities: Significant advances in radiologic imaging (MRI/MRCP) as well as endoscopic innovations including EUS has decreased the use/reliance on more invasive procedures such as ERCP for diagnostic purposes. Radiation minimization practices should be considered in imaging choice without compromising diagnostic yield. Anesthesia risk must also be considered particularly for younger children.

Improved delineation of the role of ERCP in pediatrics: The role of ERCP in the subset of children with pancreas divisum remains unclear at this time. Only collective multicenter studies will be able to answer this question. A wider application of extracorporeal shock wave lithotripsy and perhaps a novel employment of endoscopic pancreatoscopy-assisted lithotripsy for intraductal stones in children will require further assessment to determine the safety and efficacy of these technologies for this age group. The optimal approach for prevention of PEP in

children (eg, temporary stent and/or rectal indomethacin) has not been established. Equipment size remains a limitation in younger children.

Improved delineation of the role of EUS in pediatrics: Therapeutic EUS maneuvers are increasingly being described in adult patients, including pancreaticobiliary access, oncologic interventions, pancreatic cyst ablation, and endosurgical interventions such as the creation of ductoluminal anastomoses. Technical reviews describe the adult experience with these techniques (124,125). Contrast-enhanced harmonic EUS and EUS elastography are 2 other emerging technologies. The potential applications of EUS in children should be better explored through multicenter prospective studies.

Comparative studies evaluating the diagnostic utility and cost-effectiveness of the various modalities reviewed in this article are needed to optimize the field of pediatric pancreatology.

CONCLUSIONS

Pediatric pancreatology is an emerging field, and pediatric experts must become knowledgeable in the technologies available to image, diagnose, and intervene in pancreatic conditions. Various imaging modalities may be used, but TUS and MRI/MRCP are favored, with CT and EUS offering certain advantages in select cases. ERCP should primarily be used for therapeutic interventions except for rare cases in which detailed assessment of ductal anatomy is required. Interventional maneuvers primarily involve use of ERCP and EUS, with CT having a more limited role. To improve outcomes, future research is necessary to optimize equipment for use in pediatrics, increase expertise and training within the pediatric workforce, and broaden indications for pancreatic imaging and procedures in children.

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