An Update on Pediatric Pancreatitis

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ABSTRACT

There has been a rise in the incidence and number of admissions of children with pancreatitis over the past 20 years. Current management practices for pancreatitis in children are adapted from standards of care for adults, and there are a lack of multicenter, prospective research studies on pancreatitis in children. There are inherent differences in the clinical presentation and natural course of pancreatitis between adults and children. This review focuses on the current understanding of the epidemiology, etiologies, evaluation, and management of children with pancreatitis.

Pancreatitis in children has been diagnosed more frequently in the past few decades, possibly due to an increase in health care provider awareness and etiologies of pancreatitis being identified, as well as more thorough evaluations of children. In the United States, the incidence of acute pancreatitis over the past decade was estimated to be 13.2 cases per 100,000 people annually, meaning that approximately 11,000 children were diagnosed each year. This increase in pancreatitis in children has created a significant health and economic burden, with hospitalization costs nearing approximately $200 million annually.

CLASSIFICATION SYSTEMS

There are various proposed methods of classification of pancreatitis in children among pediatric gastroenterologists, but all of them were extrapolated from adult studies. Lack of a uniform classification system has impeded the comparative study of outcomes between various centers. The International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium is the first global, multicenter collaboration established to systematically define pediatric pancreatitis and develop a standardized approach to diagnosis and management.

Three categories of pancreatitis have been defined: acute pancreatitis (AP), acute recurrent pancreatitis (ARP), and chronic pancreatitis (CP). AP is defined as a reversible inflammatory process of the pancreas that may be self-limited or cause multisystemic organ dysfunction. ARP and CP are characterized by irreversible damage to the pancreatic tissue, such as fibrosis and necrosis, which may lead to pancreatic endocrine or exocrine insufficiencies. ARP is defined as two or more separate episodes of AP with interim return to baseline. The diagnosis of CP requires recurrent episodes of pancreatitis with exocrine or endocrine insufficiency and characteristic imaging findings. These findings include pancreatic calcifications, ductal dilatation, fluid collections, and, in advanced cases, pancreatic fibrosis or atrophy.

CHANGING ETIOLOGIES

The leading causes of pancreatitis in adults are calculous gall bladder disease and alcohol abuse. This contrasts with the leading causes of pancreatitis in children, which are biliary system abnormalities, medications, systemic diseases (eg, sepsis, cystic fibrosis, inflammatory bowel disease, hemolytic uremic syndrome), and blunt abdominal trauma. Up to 30% of cases of AP in children can be attributed to gallstones that cause obstruction of the pancreatic duct. Drug-induced pancreatitis (DIP) has been estimated to account for 13% of cases of pediatric AP. However, the actual incidence and prevalence of DIP appears to be underestimated due to underreporting. The three drugs most commonly associated with DIP include valproic acid, L-aspariginase, and prednisone. Both accidental and nonaccidental trauma account for 10% to 40% of AP cases in children. Less common but other known causes of AP include infections and metabolic disorders (Table 1). AP has also been reported as...
TABLE 1.

Etiologies of Pancreatitis in Children

<table>
<thead>
<tr>
<th>Classification</th>
<th>Common Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary</td>
<td>Choledochal cyst, cholecystitis, gall stones, pancreas divisum, pancreatobiliary malunion, and tumor</td>
</tr>
<tr>
<td>Systemic</td>
<td>Shock, sepsis, systemic lupus erythematosus, juvenile idiopathic arthritis, hemolytic uremic syndrome, Kawasaki disease, inflammatory bowel disease, polyarteritis nodosa, organ transplantation, Henoch-Schonlein purpura, chronic total parenteral nutrition use</td>
</tr>
<tr>
<td>Medication</td>
<td>Azathioprine, mercaptopurine, prednisone, mesalamine, cytarabine, salicylic acid, indomethacin, tetracycline, chlorothiazide, isoniazid, anticoagulants, estrogen use</td>
</tr>
<tr>
<td>Trauma</td>
<td>Abdominal trauma, post-ERCP, perforated gastric or duodenal ulcer</td>
</tr>
<tr>
<td>Infections</td>
<td>Measles, mumps, coxsackievirus, echovirus, influenza, Epstein-Barr virus, mycoplasma, Salmonella, hepatitis A, and Escherichia coli</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hyperlipidemia, hypertriglyceridemia, cystic fibrosis, diabetes mellitus, hypercalcemia, Reye’s syndrome, renal disease, propionic acidemia, nutritional deficiency, and hereditary pancreatitis</td>
</tr>
</tbody>
</table>

Abbreviation: ERCP, endoscopic retrograde cholangiopancreatography.
Adapted from Werlin and Wilschanski.1

WHEN TO SUSPECT PANCREATITIS

All children who present with abdominal pain, nausea, and/or vomiting in combination or as isolated symptoms should be evaluated for pancreatitis in conjunction with a comprehensive history and physical examination. It is essential to inquire about history of nonaccidental abdominal trauma, medications, infections, gallstones, and dietary history.10 AP may be the initial extraintestinal manifestation of a systemic illness such as inflammatory bowel disease. A study conducted by Chen et al.11 found that AP preceded the diagnosis of IBD in more than 2% of patients.

HOW TO DIAGNOSE PANCREATITIS

The INSPPIRE initiative has established that a diagnosis of AP requires two of the following three criteria: (1) characteristic abdominal pain (epigastric or right upper quadrant with or without radiation to the back), (2) serum amylase and/or lipase values 3 or more times the upper limit of normal, and (3) imaging findings (ultrasound, magnetic resonance imaging, or computed tomography [CT]) compatible with AP. In the case of imaging, the use of contrast greatly enhances the diagnosis of pancreatitis, more clearly showing interstitial edema and areas of heterogeneous inflammation or necrosis within the pancreas. When pancreatitis is suspected, serum amylase and lipase should be measured, keeping in mind that lipase is more sensitive and specific than amylase. Measuring amylase level is useful when recurrent pancreatic inflammation in the setting of an acute episode is considered because amylase takes shorter time to reach a peak and has a shorter half-life. Additionally, other laboratory studies such as serum calcium, electrolytes, urea nitrogen, creatinine, albumin, transaminases, bilirubin, and triglycerides, as well as white blood cell count, will help identify the cause and possible complications of pancreatitis. Immunoglobulin G4 (IgG4) levels should be obtained in patients with CP, as autoimmune pancreatitis should be considered in the differential diagnosis. Hamano et al.12 reported that elevated IgG4 is a characteristic finding in cases of autoimmune pancreatitis (sensitivity 95% and specificity 97%) but is not diagnostic because elevation can also be observed in other autoimmune processes.

Ultrasound remains the most common imaging modality to aid in the diagnosis of pancreatitis due to its accessibility and safety profile, but the sensitivity of ultrasound (70%) is limited when compared to CT (90%).6 CT should be considered in patients when severe or complicated pancreatitis is suspected, or in patients with obese body habitus due to the limitations of ultrasound in detecting pancreatic tissue adequately beneath adipose tissue. In children, the greatest limitation of CT scans is radiation exposure. Magnetic resonance cholangiopancreatography (MRCP) is a valuable noninvasive imaging tool reserved to investigate etiologies of ARP and CP. MRCP is used to diagnose intrahepatic and pancreatic ductal abnormalities, common bile duct abnormalities, choledocholithiasis, strictures, pancreatic divisum, and pancreatic or biliary tumors.13 MRCP is favored over ERCP because it eliminates the risks of contrast and radiation to the patient. MRI/MRCP is a desirable imaging modality but access, cost, and time are limitations.

In cases of ARP, CP, or idiopathic pancreatitis (especially if the child is younger than age 3 years), certain hereditary disorders should be included in the diagnostic evaluation, including cat- ionic trypsinogen (PRSS1) gene mutation, serine protease inhibitor Kazal type I (SPINK1) gene mutation, cystic fibro-
sis transmembrane regulator gene abnormalities, chymotrypsin C, and calcium-sensing receptor genes, to decrease the proportion of cases labeled as “idiopathic.” Patients with PRSS1 or SPINK1 gene mutations (hereditary pancreatitis) are at higher risk of developing pancreatic exocrine insufficiency, diabetes mellitus type 1, and pancreatic cancer.

**ASSESSING SEVERITY**

The three most commonly used severity predictor scores in adults are Ranson’s Criteria for Pancreatitis Mortality, Glasgow Acute Pancreatitis Severity score, and Acute Physiology and Chronic Health Examination score. Unfortunately, none of these tests are sensitive nor specific, and none of them have been validated for use in children. In 2002, DeBanto et al. established a prognostic tool called the Pediatric Acute Pancreatitis Severity score (PAPS) for risk stratification. The parameters of the score include three of the following eight criteria: (1) age (<7 years), (2) weight (<23 kg), (3) white blood cell count at admission (>18,500 cells/mL), (4) lactate dehydrogenase at admission (>2,000 U/L), (5) 48-hour trough calcium (<8.3 mg/dL), (6) 48-hour trough albumin (<2.6 g/dL), (7) 48-hour fluid sequestration (>75 mL/kg per 48 hours), and (8) 48-hour rise in blood urea nitrogen (>5 mg/dL). This study reported PAPS sensitivity to be 70% compared to 30% for Ranson’s criteria and 35% for the Glasgow score. Current pancreatitis investigation practices vary due to a lack of consensus in pediatric literature. However, Coffey et al. recently proposed that obtaining lipase values within the first 24 hours of admission makes it an optimal marker of severity stratification early in hospital course compared to PAPS, Ranson, and Glasgow scores, which include markers identified at 48 hours of hospitalization. A lipase more than 7 times the upper limit of normal was found to have 85% sensitivity and a negative predictive value of 89% for predicting severe pancreatitis. Another added benefit is the availability and cost-effectiveness of obtaining this single parameter.

**COMPLICATIONS**

Complications of AP can be divided into early or late onset. Early systemic complications such as respiratory distress syndrome, pneumonia, pulmonary effusions, shock, or renal failure develop in fewer than 6% of children with AP. Fevers and signs of systemic illness presenting 2 weeks after the onset of pancreatitis should prompt evaluation for infectious complications. Late onset complications include pancreatic necrosis or pseudocysts. Approximately 10% to 20% of children, particularly those with traumatic pancreatitis, develop pancreatic pseudocysts 4 weeks after the onset of pancreatitis. Uncomplicated pseudocysts can be managed conservatively with serial monitoring by ultrasound. Complicated pseudocysts that bleed or become infected may require drainage and antibiotics. Approximately 15% to 35% of children with AP may have recurrence of pancreatitis. These patients should be assessed for biliary tract anomalies, metabolic disorders, hereditary pancreatitis, and hypertriglyceridemia. Mortality rates among children with pancreatitis range from 0% to 11%. The mortality rate remains lower than in adult patients, in whom alcohol is one of the leading causes of pancreatitis.

**CURRENT MANAGEMENT STRATEGIES**

**Nutrition**

Historically, management practices of pediatric AP have been adopted from adult literature, which emphasized pancreatic rest by maintaining patients nil per os and the early use of parenteral nutrition to limit stimulation of the pancreatic secretions and prevent starvation. These practices have been challenged by a systematic review of three randomized control trials that showed early enteral nutrition and avoidance of parenteral nutrition are associated with prevention of bacterial stasis in the gut, lower rates of infection, and decreased mortality.

Early feeding and nutrition should be a goal in management of AP. Unfortunately, surveys of pediatric management in AP estimated that only 3% of pediatric patients are initially given enteral feeds whereas 44% receive parenteral nutrition, despite the available evidence mentioned earlier. This staggering difference suggests possible unawareness of pediatric clinicians regarding current AP management.

Introduction of nutrition in mild AP should be patient directed when good appetite is achieved. If oral feeds are unsuccessful, consider nasogastric or nasojejunal semielemental feeds at one-fourth to one-eighth of total calorie requirement at a continuous slow rate, and then increase as tolerated. Parenteral feeds should be reserved for more severe cases of pancreatitis when enteric feeds are not tolerated or total caloric intake is not sufficiently met. Although there are no definitive guidelines on duration of low-fat diet after an episode of pancreatitis in the current pediatric literature, many clinicians encourage patients to adhere to a low-fat diet for 6 to 8 weeks after treatment.

**Intravenous Fluid Therapy**

Fluid resuscitation remains a critical aspect of management of AP in children. The inflammatory process in the pancreas results in dilation of pancreatic vasculature, promoting increased vascular permeability, extravasation of fluids into extrapancreatic tissue, and potential for ischemia and necrosis of the organ.
tissue causing “third-spacing” of fluids, leading to hypovolemia and shock. Aggressive fluid resuscitation within the first 24 hours of hospitalization is critical to maintain pancreatic perfusion and reduce the rate of cell lysis and further pancreatic enzyme diffusion into surrounding tissue. There are limited data in the pediatric literature to suggest an optimal fluid type and fluid rate. Crystalloid solutions such as normal saline (NS) and lactated ringer (LR) solution are more commonly used for initial volume replacement. Studies in adults have recently reported that LR may lead to a greater reduction in inflammatory response when compared to NS by creating a more optimal pH buffer. Current recommendations are to administer more than one-third of the estimated fluid volume requirement for the first 72-hour period within the first 24 hours of hospitalization to reduce the hospital complication rate.22

Pain Management

There is no evidence in the pediatric literature that shows optimal analgesics for control of abdominal pain in pediatric pancreatitis. Although the traditional thought has been that morphine may cause paradoxical spasm of sphincter of Oddi, more recent trials have clarified that the sphincter of Oddi is equally sensitive to all opiates but morphine provides more long-term relief than meperidine.23 In patients age 17 years and older, there is indication for treating moderate to severe pain using tramadol, a centrally acting synthetic opioid analgesic that acts via inhibition of ascending pain pathways due to its higher efficacy than morphine.24

Antioxidants

Antioxidants (eg, selenium, ascorbic acid, beta-carotene, alpha-tocopherol, and methionine) are frequently used as supplements and complementary therapy to provide pain relief and decrease the need for analgesics in patients with ARP and CP. Antioxidants inhibit oxidative and free radical stress caused to tissues by reactive oxygen and nitrogen released by inflamed pancreatic acinar cells. A recent study done by Bhardwaj et al.25 showed a reduction in the number of painful days per month in chronic pancreatitis patients by a mean of 4.15 days in the antioxidant group compared to the placebo group.

Pancreatic Enzyme Replacement Therapy

In patients with CP, fibrosis and destruction of acinar cells may lead to exocrine pancreatic insufficiency (when <10% of pancreatic function remains intact) requiring pancreatic enzyme replacement therapy. Typically, these patients present with features of steatorrhea, weight loss, and abdominal discomfort due to abnormal lipid digestion. Diagnosis of pancreatic exocrine insufficiency is made by 72-hour quantitative fecal fat test estimation, low fecal elastase, or abnormal secretin pancreozymin-stimulated pancreatic function tests during upper endoscopy. A new study also suggests pancreatic enzyme replacement as a form of pain control due to the negative feedback loop effect, by suppressing and down-regulating the secretion of cholecystokinin and, therefore, decreasing the pancreatic enzyme output.18 The results of the studies are variable because of the high rate of placebo response. Also, there is potential for the replacement enzymes to be inactivated by gastric acids before they effectively reach the pancreas.
Monitoring

Prior to patient discharge, it is important to ensure that dehydration and electrolyte abnormalities have been duly corrected, the patient has achieved adequate pain control on oral medications, and is tolerating an enteral diet. After discharge, routine follow-up with the primary care physician is needed to monitor for potential complications such as pseudocyst. If the patient presents with recurrent or worsening abdominal pain approximately 4 to 6 weeks after the initial event, pseudocyst should be considered and repeat lipase level and abdominal ultrasound should be used to assess for peripancreatic fluid collection. Currently there is no screening tool to detect the children who are at risk for developing pancreatitis so that primary prevention can be initiated. Secondary prevention of pancreatitis is specific to etiology. Cholecystectomy will prevent further attacks of gallstone pancreatitis, dietary modifications can prevent hypertriglyceridermia-induced pancreatitis, and avoiding certain medications (Table 1) can prevent recurrent episodes of drug-induced pancreatitis.

CONCLUSIONS

Pancreatitis in children has been diagnosed more frequently over the past 20 years; however, there are still multiple facets of management of pediatric pancreatitis that are modeled after adult studies. Further research is being conducted to fully understand its course, define optimal management, and create better outcomes in children.

Salient points to remember about pancreatitis in children are listed in Table 2.

REFERENCES