Pancreatitis

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EDUCATION GAPS

1. Fluid management in acute pancreatitis is evolving to include lactated Ringer solution, although more pediatric research is needed.
2. Early enteral nutrition within 24 hours is recommended to avoid prolonged nil per os status and associated morbidity.
3. Prophylactic antibiotics are not recommended.

OBJECTIVES *After reading this article, readers should be able to:*

1. Know the classification of pediatric pancreatitis.
2. Understand the etiology, risk factors, clinical manifestations, approach to diagnosis, and treatment of pancreatitis in children.
3. Recognize current consensus guidelines on early enteral nutrition and aggressive fluid management.
4. Know the complications of pancreatitis in children and their appropriate diagnostic and therapeutic strategies.

INTRODUCTION

Pancreatitis is an inflammatory process of the pancreas presenting as a spectrum of clinical disease. Acute pancreatitis (AP) is a reversible process, but it may progress to acute recurrent pancreatitis (ARP). This increases the risk of developing chronic pancreatitis (CP), which carries higher morbidity due to irreversible pancreatic duct strictures, exocrine pancreatic insufficiency, insulin-dependent diabetes mellitus, and chronic pain. Pancreatitis is occurring at an increasing rate in children, which is troubling given the paucity of research in pediatric patients. Historically, management recommendations for pediatric pancreatitis have evolved based on consensus conferences and research in the adult population. In 2018, consensus guidelines for the management of AP were published for both pediatrics (1)(2)(3) and adult medicine. (4)

CLASSIFICATION OF PEDIATRIC PANCREATITIS

Per the INSPPIRE (INternational Study Group of Pediatric Pancreatitis: In search for a cuRE), the 3 categories of pancreatitis are AP, ARP, and CP.

AP in pediatric patients requires at least 2 of the following 3 criteria: 1) abdominal pain suggestive of AP, such as acute onset and epigastric in origin; 2)

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ABBREVIATIONS

AIP	autoimmune pancreatitis
AP	acute pancreatitis
ARP	acute recurrent pancreatitis
CP	chronic pancreatitis
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasound ultrasonography
IL	interleukin
LR	lactated Ringer solution
MRCP	magnetic resonance cholangiopancreatography
SIRS	systemic inflammatory response syndrome
TPN	total parenteral nutrition
TUS	transabdominal ultrasonography

serum amylase and/or lipase levels at least 3 times the upper limit of normal; and 3) imaging findings consistent with AP. (5) ARP is defined by at least 2 acute attacks within a year, with interval resolution of pain or normalization of serum pancreatic enzyme levels, or by more than 3 lifetime episodes without evidence of CP. (5)(6) CP requires the presence of exocrine or endocrine insufficiency and histologic and morphologic changes that are irreversible, including fibrosis, islet cell loss, inflammatory cell infiltrates, and intraductal calculi. (5)

AP IN PEDIATRICS

Epidemiology

The incidence of pediatric AP has increased in the past 2 decades, (7) ranging from 0.78 to 13.2 pediatric cases per 100,000 annually in the United Kingdom (8) and the United States, (9) respectively. This increase in incidence is multifactorial, having been linked to heightened awareness, appropriate biochemical testing, increasing multisystem disorders, and the rising prevalence of obesity. (10)(11)

Pathophysiology

The damage associated with pancreatitis occurs after inflammatory cytokine-mediated induction of systemic inflammatory response syndrome (SIRS). (12) Specifically, the initial trigger results in excessive intracellular calcium signals in a few pancreatic acinar cells (Fig 1). (13) This intracellular hypercalcemia prematurely activates intra-acinar pancreatic trypsinogen to trypsin, which then activates other digestive proenzymes and together mediates acinar cell injury via autodigestion. (14) This process is exacerbated by inflammatory cytokines such as tumor necrosis factor α, interleukin (IL)-1β, IL-6, and IL-8. Histamine, kallikrein, and bradykinin also contribute to the progression and severity of illness by liberating additional proteases and amplifying the SIRS cycle that causes damage to acinar cells. Oxygen free radicals are thought to be involved in the direct attack of unsaturated phospholipids of the cell membrane, leading to accumulation of lipid degradation products (eg, malonaldehyde and 4-hydroxynonenol) and resulting in increased membrane permeability, protease intracellular leakage, and Ca^{2+} influx. (15)

Protective mechanisms such as autodegradation of trypsin and inhibition of trypsin by pancreatic secretory trypsin inhibitor, alpha-1 antitrypsin, and α2-macroglobulin can negate the initial triggering events. Other defense mechanisms, such as the compensatory anti-inflammatory response syndrome, can offset SIRS via the production of anti-inflammatory cytokines, including IL-4, IL-10, and IL-1ra. (14)(16) However, when the balance shifts toward SIRS, pancreatic necrosis and/or multiple organ failure ensues.

Etiology

The causes of AP in children can be broadly categorized into biliary disorders, systemic conditions, infections, trauma, medications, structural abnormalities, metabolic diseases, genetic mutations, autoimmune disorders, and idiopathic etiologies (Table 1). Furthermore, any of these conditions could lead to ARP or CP.

BILIARY DISORDERS. Gallstones, microlithiasis, sludge, and pancreaticobiliary anomalies are common etiologies of pancreatitis in the pediatric population, accounting for 3% to 30% of cases. (19) In particular, pancreatitis should be suspected if the presentation includes transaminitis and/or direct hyperbilirubinemia. Pancreaticobiliary anomalies

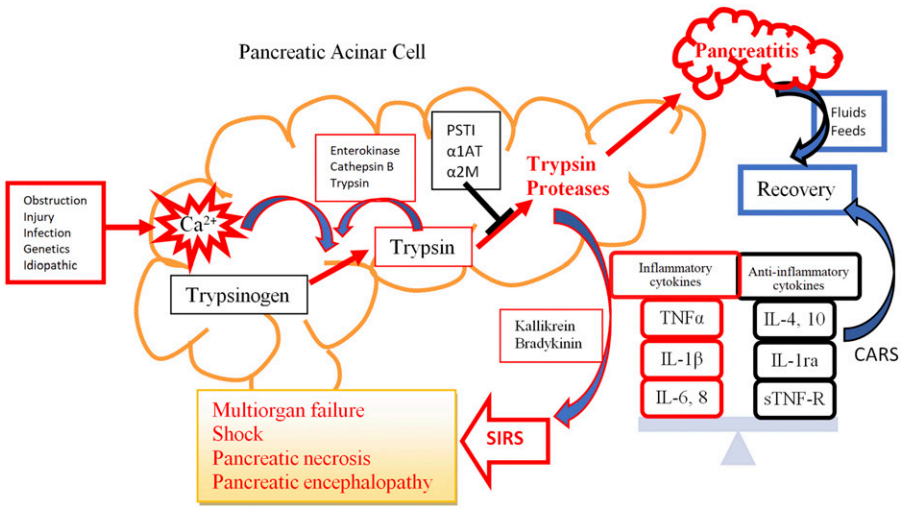

Figure 1. Pancreatic acinar cell. The diagram shows the initial insult, which leads to an inappropriate rise in intracellular calcium that triggers the activation of trypsin and other digestive proenzymes, which in turn stimulate inflammatory cytokines, leading to systemic inflammatory response syndrome (SIRS) and pancreatitis. Protective mechanisms include the inhibitory factors, including pancreatic secretory trypsin inhibitor (PSTI), alpha-1 antitrypsin (α1AT), α2-macroglobulin (α2M), and compensatory anti-inflammatory response syndrome (CARS). IL=interleukin, TNF=tumor necrosis factor.

Table 1. Etiology of Pancreatitis in Children and Adolescents

COMMON BILIARY DISORDERS	LESS COMMON INFECTIONS	RARE AUTOIMMUNE
- Cholelithiasis	- Viral: mumps, measles, coxsackievirus, echovirus, influenza, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, hepatitis A, varicella zoster virus	- Type 1 autoimmune pancreatitis
- Biliary sludge	- Bacterial: *Mycoplasma pneumoniae*, *Salmonella* spp, gram-negative bacteria	- Type 2 autoimmune pancreatitis
- Choledochal cyst		- Primary sclerosing cholangitis
- Caroli disease (rare)		
Systemic conditions	Metabolic disorders (17)	Anatomical
- Sepsis/shock	- Diabetic ketoacidosis	- Pancreaticobiliary junction malunion
- Hemolytic uremic syndrome	- Hyperlipidemia	- Annular pancreas
- Inflammatory bowel disease	- Organic acidemia	- Pancreas divisum
- Systemic lupus erythematosus	- Hypercalcemia	- Sphincter of Oddi dysfunction
- Juvenile idiopathic arthritis	- Alpha-1 antitrypsin deficiency	
- Polyarteritis nodosa	- Long-term total parenteral nutrition	
- Henoch-Schonlein purpura		
- Kawasaki disease		
- Cystic fibrosis		
- Celiac disease		
Medications (8)(18)	Genetic/hereditary disorders: 34 gene mutations	Nutrition
- L-asparaginase/cytarabine/vincristine	- *CFTR*	- Malnutrition
- Valproic acid/carbamazepine	- *SPINK1*	- Vitamin A and D deficiency
- Azathioprine/6-mercaptopurine	- *PRSS1*	
- Mesalamine	- *CTRC*	
- Sulfamethoxazole/trimethoprim	- *CASR, CEL, CLDN2, CPA1, SBDS, UBR1*	
- Calcium carbonate		
- Indomethacin		
- Isoniazid		
- Estrogen/corticosteroid		
- Furosemide		
Trauma		
- Blunt injury		
- Child abuse		
- Endoscopic retrograde cholangiopancreatography		
Idiopathic		

increase the risk of pancreatitis, such as pancreas divisum, (19)(20) choledochocyst, or, rarely, Caroli disease, which is characterized by cystic dilation of hepatic bile ducts.

IDIOPATHIC. Approximately 13% to 34% of pancreatitis cases are reported as idiopathic. However, this statistic continues to decrease as genetic data for previously diagnosed idiopathic cases emerge. (21)

SYSTEMIC CONDITIONS. The reported case association between AP and systemic illness ranges from 3.5% to 48%. (22) Commonly described systemic conditions associated with an increased risk include sepsis, shock, hemolytic uremic syndrome, systemic lupus erythematosus, juvenile idiopathic arthritis, celiac disease, and inflammatory bowel disease, especially with the association of primary sclerosing

cholangitis. (23) Cystic fibrosis, leading to inspissated bile and pancreatic fluids in pancreaticobiliary ducts, may present with pancreatitis. Vasculitides such as polyarteritis nodosum, Henoch-Schonlein purpura, and Kawasaki disease have also been linked to pancreatitis.

MEDICATIONS. Drug-induced pancreatitis is due to different mechanisms depending on the medication, including immunologic reactions (eg, 6-mercaptopurine, amino salicylates), accumulation of toxic metabolites, ischemia (eg, diuretics), intravascular thrombosis (eg, estrogen), and increased viscosity of a pancreatic juice (eg, glucocorticoids). (8)(18)

TRAUMA. Trauma should always be considered as an etiology for AP. Examples of trauma associated with pancreatitis include blunt injury, child abuse, and instrumentation of the pancreaticobiliary junction and pancreatic ducts via endoscopic retrograde cholangiopancreatography (ERCP).

INFECTIONS. Many infections have been associated with pancreatitis, including viruses such as mumps, measles, coxsackievirus, echovirus, influenza, hepatitis A, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and varicella zoster virus. Bacterial etiologies for pancreatitis include *Mycoplasma pneumoniae*, *Salmonella*, and gram-negative bacteria.

METABOLIC DISEASES. Several metabolic diseases are associated with AP. A few etiologies include diabetic ketoacidosis, hyperlipidemia, organic acidemias such as methylmalonic academia, hypercalcemia, and alpha-1 antitrypsin deficiency. (17) Prolonged total parenteral nutrition (TPN) may not only predispose children to AP but also trigger acute episodes in patients with CP.

GENETIC DISORDERS. With advancements in gene sequencing, genetic variants associated with pancreatitis are becoming increasingly important factors for understanding the pathophysiology of pediatric pancreatitis. (24) Studies have identified mutations in genes involved in premature intrapancreatic activation of trypsin (*CFTR, PRSS1, PRSS2, SPINK1, CTRC, CTSB, KRT8, CASR*), in calcium signaling and zymogen exocytosis (*ATP2C2, STIM, TRPV6, DMBT1, TRP*), in pancreatic secretion and ion homeostasis (*CLPS, F2RL1, SLC4A2, RAP27B, CPB1, SLC4A4, SLC26A3, TMPRSS15, UBR1, SBDS*), and in the autophagy pathway (*HSP90AA1, LAMP2, MAP1LC3B*). Other newly discovered potential pancreatitis susceptibility genes include *CPA1,* (25) *CLDN2,* (26) and *CEL.* (27) Although up to 34 gene mutations have been associated with ARP and CP, mutations of *CFTR* and *PRSS1* occur at the highest rate in idiopathic ARP and CP, respectively. (21)(28)(29)(30) As specific mutations predispose an individual to ARP and CP, genetic testing is recommended for recurrent AP and/or an isolated AP event in the setting of family history of AP or CP. Initial screenings should focus on the most common pathogenic variants, which include *PRSS1, SPINK1, CTRC, CPA1, CFTR,* and the *CEL* hybrid. Genetic findings aid in long-term prognosis, especially since hereditary pancreatitis associated with *PRSS1* mutations have been linked to increased risk of pancreatic adenocarcinoma. (31)

AUTOIMMUNE PANCREATITIS. Autoimmune pancreatitis (AIP), a rare cause of pediatric pancreatitis, is defined by pancreatic parenchymal changes that are clinically responsive to corticosteroids. (32) AIP occurs as either type 1 or type 2. Type 1 is associated with elevated immunoglobulin G4 levels, diffuse narrowing of the main pancreatic duct, segmental enlargement of the pancreas, and/or strictures of the lower bile duct. (33) However, normal immunoglobulin G4 levels do not rule out AIP. Type 2 is more common in children and is associated with inflammatory bowel disease and other autoimmune processes. (34)

ANATOMICAL. The pancreas may be predisposed to pancreatitis due to congenital anatomical abnormalities such as pancreaticobiliary junction malunion, which creates an environment causing poor flow of the pancreatic fluids in the abnormal duct. Annular pancreas is a congenital anomaly that may increase the risk of pancreatitis. Pancreas divisum and sphincter of Oddi dysfunction can result in inadequate pancreatic secretion drainage, resulting in pancreatitis.

Diagnosis

SYMPTOM CRITERIA. In pediatrics, 68% to 95% of patients with AP present with abdominal pain, (14)(35) 62% to 89% are localized to the epigastric region, and 1.6% to 5.6% have associated radiating back pain. (36)(37) In contrast, infants and toddlers present more commonly with irritability and vomiting. (22) The pain associated with pancreatitis stems from multiple mechanisms, including stimulation of visceral pancreatic and somatic peritoneal pain receptors by inflammatory cytokines. (38) Elevated pressures in the pancreatic system leading to ischemia and activation of primary sensory neurons are other mechanisms for abdominal pain during pancreatitis. (39)

BIOCHEMICAL CRITERIA. Although amylase and/or lipase levels are used to diagnose pancreatitis, an elevated serum lipase level is more sensitive than amylase level for diagnosis. (6)(14) Serum amylase and lipase levels are elevated in 50% to 85% and 77% to 100% of pediatric patients, respectively. (19)(22)(35)(37)(40) Serum amylase levels rise within 6 to 12 hours and fall within 3 to 5 days. The differential diagnosis for hyperamylasemia includes salivary gland conditions, intestinal etiologies such as obstruction,

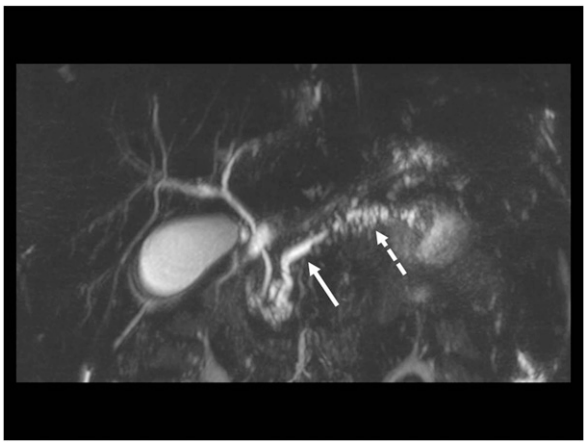

Figure 2. Three-dimensional maximum-intensity projection from a magnetic resonance cholangiopancreatography examination in an 11-year-old patient with chronic pancreatitis. The main pancreatic duct is dilated (solid white arrow), with significant irregularity. The irregularity is most pronounced in the area of the pancreatic tail (dashed arrow), where there are also multiple dilated side branch ducts.

peptic ulcers, appendicitis, celiac disease, gastroenteritis, and eating disorders. Conversely, an elevated serum lipase level can be seen as early as day 1 of illness, persists for 14 days, and is pancreatic specific. Serum triglyceride and calcium levels should be measured with the first episode of AP to rule out hypertriglyceridemia or hypercalcemia as potential etiologies. (1)

IMAGING. The diagnostic features of AP on imaging studies include evidence of biliary obstruction, parenchymal changes, and peripancreatic fluid collections. Controlled trials on the use of imaging tools have yet to be performed in children. (1) Transabdominal ultrasonography (TUS) is the recommended initial imaging study for suspected AP, with an effectiveness rate of 56% to 84% in pediatric patients with AP. (41) TUS is advantageous because it lacks ionizing radiation, is effective for the identification of gallstones and pancreatic fluid collections, and comparatively costs less than other modalities.

Although not yet widely used in children due to its availability, endoscopic ultrasonography (EUS) is an effective tool to recognize biliary pancreatitis or pseudocysts in children greater than 5 years old. (42) In a study looking at 11,000 pediatric EUS procedures, indications, and outcomes, the authors underscored that EUS indications in children are comparable with those in adults. Furthermore, the findings significantly contributed to the diagnosis and treatment of pediatric pancreaticobiliary disease. (43)

Magnetic resonance cholangiopancreatography (MRCP) is the imaging method of choice for diagnostic evaluation of the pancreaticobiliary system in children and is recommended by the INSPPIRE consensus when TUS is suggestive of AIP (32) or in pediatric ARP and CP. (5) It carries less risk than ERCP and is highly sensitive in detecting congenital ductal abnormalities, choledocholithiasis, strictures, pancreas divisum, and pancreatic and biliary tumors. (44)(45) Figures 2 and 3 present MRCP images from an 11-year-old with CP due to *PRSS1* mutation demonstrating pancreatic duct stricture with intermittent dilation, so-called beading, of the duct.

Contrast-enhanced abdominal computed tomography is not first-line imaging due to radiation exposure but is best suited for situations of diagnostic uncertainty and clinical deterioration, such as necrosis and bleeding in clinically severe AP. The optimal timing for detecting inflammatory changes surrounding the pancreas by computed tomography is at least 72 to 96 hours after initial AP presentation. (46)

ERCP is available in some pediatric centers and may be combined with EUS where available. (47)(48) ERCP should be used only for therapeutic purposes due to the risks associated with ERCP, such as bleeding, perforation, and pancreatitis. In particular, the risk of pancreatitis after ERCP was reported to be 9.7%. (47)(48)

Management

FLUID RESUSCITATION. Aggressive fluid resuscitation is a mainstay in the acute management of AP. It addresses hypovolemia, increases pancreatic perfusion, improves microcirculation, and reduces the risk of necrosis. Both normal saline and lactated Ringer solution (LR) have been studied. In an adult study, compared with normal saline, LR was shown to significantly decrease the incidence of SIRS (49) and the development of post-ERCP pancreatitis. (50) However, another study found no difference between LR and normal

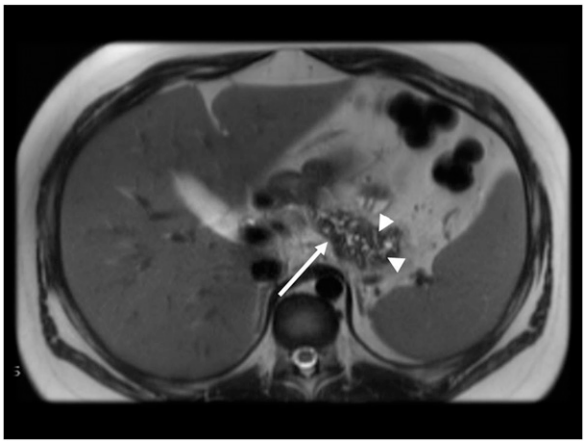

Figure 3. Axial T2 HASTE (half-Fourier acquired single-shot turbo spin-echo) image at the level of the pancreatic tail demonstrating significant atrophy of the pancreatic parenchyma (solid white arrow) along with multiple dilated side branch ducts (arrowheads).

Table 2. Management Recommendation Summary

PAIN	FLUIDS	NUTRITION	ANTIBIOTICS
Acetaminophen	LR or D5W NS at 1.5 to 2× maintenance rate	Oral feeding within 24–48 h of admission	Only indicated for cholangitis or necrotizing pancreatitis
Ibuprofen	Initiate within 24 h of presentation	Nasogastric/nasojejunal feedings if not tolerating oral feeds	Carbapenems, quinolones, or metronidazole
Opioids	Monitor BUN/creatinine and urine output for 24–48 h	Parenteral nutrition if not tolerating enteral feeds	
		Feed normal diet if eating	
		Polymeric formula (if no food allergies)	

BUN=blood urea nitrogen, D5W=dextrose 5% in water, LR=lactated Ringer solution, NS=normal saline.

saline when looking at mortality and duration of hospital stay. (51) Current recommendations are for initiation of therapy with dextrose-containing crystalloids (1) or LR (2) at 1.5 to 2 times maintenance within 24 hours (Table 2). (47) Notably, pediatric studies have demonstrated an association between aggressive fluid administration and fewer ICU admissions, shortened hospital stays, and higher rates of clinical recovery. (52)(53)

PAIN. There is no specific pain management guideline for pediatric AP or quality data on differences between analgesics. Acetaminophen and ibuprofen are the first-line agents for mild pain, and opioids are indicated for severe pain. Although opioids increase the sphincter of Oddi tone, clinical studies do not correlate this with poor outcomes. A Cochrane review assessing the efficacy and safety of opioid use found that it is appropriate in the treatment of pain related to AP and that its use may decrease the need for supplementary analgesia. (54) However, a retrospective review of 211 pediatric patients with AP at the Boston Children's Hospital Emergency Department found that opioid analgesia was more frequently prescribed than nonopioid alternatives, time to analgesia was shorter in opioid-receiving patients, and they required more doses of analgesics. (55)

Procaine, a local anesthetic that is administered systemically, has been considered for basic analgesia for AP. One controlled trial showed the effectiveness of systemic administration of procaine in pancreatitis, with accelerated postoperative recovery, improved cognitive function, and overall shortened hospital stay. (56) Epidural anesthesia, used as a sympathetic nerve block that redistributes blood flow to nonperfused pancreatic regions, has shown improved pancreatic perfusion, decreased AP pain, and the need for necrosectomy. (57)

NUTRITION. Guidelines for pediatrics have been extrapolated from adult data and consensus from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee. (2)(3) Enteral feeding within 24 to 48 hours of pancreatitis onset is recommended. Multiple studies support early feeding with a regular diet in mild AP because early feeding can reduce the length of stay. (2)(3) Remaining nil per os or on a clear liquid diet does not improve abdominal pain. If a patient cannot tolerate an oral diet, nasogastric or nasojejunal enteral formula feeding is recommended. Initiation of feedings is not dependent on the severity of pancreatitis, and studies have not demonstrated a difference between nasogastric and nasojejunal feedings. Likewise, polymeric formula is appropriate first-line nutrition. TPN is reserved for when enteral nutrition cannot be tolerated, such as pancreatic fistulae, perforated pancreatic duct, ileus, or abdominal compartment syndrome. The risks of central line infections secondary to bacterial translocation increase with TPN in the setting of AP. (1)

ANTIBIOTICS. Prophylactic antibiotics are not recommended in AP, even in the presence of severe AP or existing necrosis, because most are sterile. Indications for antibiotics include systemic infectious complications, cholangitis, and suspected infected pancreatic necrosis. In the setting of persistent systemic inflammatory response beyond the first week of symptom onset, ultrasonography-guided fine-needle aspiration could differentiate infected and sterile pancreatic necroses. Imipenem, meropenem, fluoroquinolones, and metronidazole exhibit effective tissue penetration and bactericidal properties for infected pancreatic necrosis and prevention of septic complications. (58)(59) Antibiotics ideally are used in conjunction with surgical or percutaneous drainage.

BILIARY AP MANAGEMENT. ERCP is indicated in the setting of choledocholithiasis, biliary duct sludge causing biliary pancreatitis, cholangitis, and biliary or pancreatic duct obstruction (Fig 4). Procedures performed with ERCP in pediatric patients include biliary or pancreatic sphincterotomy, stent placement, stricture dilation, and transmural drainage of cysts. One study showed that therapeutic ERCP is

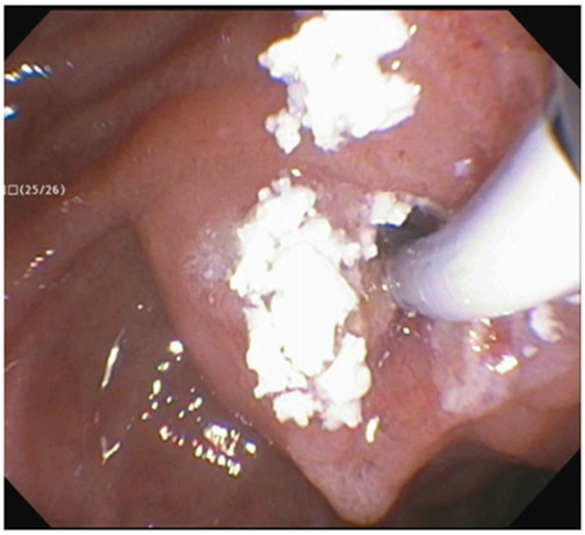

Figure 4. Multiple pancreatic duct stones extracted during endoscopic retrograde cholangiopancreatography after sphincterotomy in an 11-year-old patient with chronic hereditary pancreatitis.

frequently used in children with ARP or CP because both are associated with pancreaticobiliary obstruction. (60) ERCP should be completed within 24 hours in patients with severe cholangitis. Pancreatic fluid collection and pseudocysts are common complications of AP, occurring in approximately 58% and 38% of children with AP, respectively. (61) Interventional EUS is used for visualization to drain pancreatic pseudocysts. (62)(63)

Complications

Localized complications include the development of pseudocysts, pancreatic necrosis, and abscesses. A pseudocyst is a homogenous collection of amylase-rich pancreatic fluid surrounded by granulation tissue. The cysts take approximately 30 days to develop and can be complicated by infection or hemorrhage, resulting in pancreatic ascites. Of note, if compensatory anti-inflammatory response syndrome is excessive in the inflammatory cascade, inhibition of new cytokine production can lead to increased susceptibility to sepsis, infectious necrosis, and pancreatic abscess.

The systemic complications are vast, can be devastating in pancreatitis, and may include multiorgan system failure, shock, gastrointestinal bleeding, splenic artery pseudoaneurysms, splenic infarction, intestinal obstruction, and perforation. In addition, cardiorespiratory, metabolic, and renal complications may occur, including acute respiratory distress syndrome, pleural effusion, pericardial effusion, myocardial dysfunction, acute renal failure, hypermetabolic state, hypocalcemia, disseminated intravascular coagulation, and ascites.

ACUTE RECURRENT PANCREATITIS

There is a 10% to 35% chance of AP recurrence after the initial episode. (35) Risk factors play a major role in the development of ARP and CP. Identified risk factors, similar to AP, include genetic mutations, obstructions, toxic/metabolic disorders, and autoimmune processes (Table 1).

Previously, Giefer et al (64)(65) detected pancreatitis-associated genetic mutations (*PRSS1*, *CFTR*, *SPINK1*, or *CTRC*) in 71% of children with early-onset pancreatitis, which is defined as occurring before 6 years of age. Meanwhile, a smaller percentage of such mutations was detected in children12 years and older with ARP or CP. These differences in age suggest external triggers, such as hypertriglyceridemia, autoimmune diseases, metabolic diseases, or medications as more likely etiologies for ARP in older children. (64)(65)

CHRONIC PANCREATITIS

CP is an irreversible inflammatory process that results in morphologic changes, such as stricture, atrophy, and pseudocysts, or impaired exocrine or endocrine pancreas function as a consequence of ARP. (5) CP is most often diagnosed clinically with the aid of laboratory and imaging studies rather than by histopathologic analysis. Genetic etiologies are common for pediatric CP, although recurrent or prolonged obstruction, trauma, chronic toxins such as TPN, and systemic diseases such as AIP are all possible etiologies. A sweat chloride test should be performed as part of the diagnostic evaluation of CP to rule out cystic fibrosis. AP in the setting of CP is treated essentially the same, with aggressive fluid management, pain control, and early feeding. If the patient demonstrates pancreatic exocrine insufficiency, then pancreatic enzyme replacement therapy may be used with enteral feeding for improved absorption.

In pediatric patients with CP, a normal diet is recommended, consisting of 35% to 40% fat, 20% protein, and 40% to 45% carbohydrates, between acute episodes. Patients with CP should be evaluated for pancreatic exocrine insufficiency and fat malabsorption via fecal pancreatic elastase-1 or 72-hour fecal fat test. Every 6 to 12 months they should have their weight, height, body mass index, and fat-soluble vitamins A, D 25-OH, E, and K measured. If supplementation is required, repeated levels should be drawn after 3 months. There is no evidence supporting routine monitoring of trace elements or water-soluble vitamins. Although there are no data on bone mineral density in children, the consensus recommendation is that bone mineral density should be assessed in children with CP presenting with low vitamin D 25-OH levels, fractures, or malnutrition.

Pain control should be managed with nonopioid therapies while also ruling out continued injury if there is an acute exacerbation of pain. The use of pancreatic enzyme replacement therapy for pain control is controversial, with a recent systematic review in adults showing it to be ineffective. (66) In CP, pain control is aimed at treating the neuropathic nature of the pancreatic pain. In particular, the current literature supports the use of selective serotonin reuptake inhibitors, pregabalin, or gabapentin; however, no studies have evaluated the efficacy of these medications in children with CP. (67)

The scope of this review is not sufficient to fully explore the surgical options. Surgery is indicated in patients with chronic debilitating pain, chronic malnutrition due to pancreatic exocrine insufficiency, malabsorption despite nutritional rehabilitation, and/or diabetes. In addition to the traditional surgical options to provide pancreatic drainage, there is growing evidence for management of pediatric CP with pancreatectomy and islet cell autotransplant, with favorable results for pain resolution and nutritional outcomes. (68)

Summary

With the advent of the INSPPIRE collaborative, improved imaging, increased numbers of pediatric interventional endoscopists trained in ERCP and EUS, and increased genetic testing, much has changed in the field of pediatric pancreatitis in the past several years. However, further research is desperately needed regarding the specific etiologies and the optimal fluid, nutrition, and interventional management of pediatric pancreatitis. At this time, the key changes to management include early enteral nutrition within 24 hours and avoidance of nil per os/TPN due to decreased morbidity associated with enteral nutrition. Nutrition may be oral, nasogastric, or nasojejunal depending on the clinical scenario. IV fluid management with LR may be superior to normal saline, but studies in children are lacking. Prophylactic antibiotics are not warranted for pancreatitis, including severe or necrotic AP unless the pancreas is proved to be infected via convincing clinical evidence or diagnostic tests. Finally, additional studies are needed to assess pain management to identify the optimal minimal opioid therapy.

Suggested Quality Improvement Projects

- Methods to reduce length of stay in patients with pancreatitis.
- Evaluation of efficacy of LR versus normal saline in pediatric pancreatitis.
- Role of diet or dietary supplements in recurrent attacks of pancreatitis.
- Monitoring practices to identify risk factors and detect early growth and nutritional deficiencies in CP.
- Prospective analysis of AP pain management with objective measures to help curb the opioid epidemic.

References for this article can be found at http://pedsinreview.aappublications.org/content/41/No. 10/511.

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1. You are asked to do a consultation of a previously healthy 16-year-old boy with acute abdominal pain. His pain is localized to the epigastric region and has worsened over the past 2 days. He experienced 1 episode of nonbilious, nonbloody emesis. No fever or change in stool pattern was noted. He takes no medications. He denies alcohol use. Family history is negative for any chronic conditions. He is an A and B student and plays offensive tackle for his high school football team. On physical examination he appears uncomfortable but is in no distress. His BMI is at the 95th percentile. Abdominal examination shows tenderness over the epigastric region, with soft and nontender lower quadrants and no organomegaly. Results of laboratory studies, including a complete blood cell count and a complete metabolic panel, are normal except for an amylase level of 1,240 U/L (20.7 μkat/L) and a lipase level of 860 U/L (14.4 μkat/L). Abdominal ultrasonography findings are normal. He is diagnosed as having acute pancreatitis. This is the third case you have seen in the past 6 months. After 22 years in practice, you are curious why you are seeing more cases of this condition. Which one of the following factors has been linked to the increasing prevalence of acute pancreatitis in the past 2 decades?

   A. Binge drinking.
   B. E-cigarette use.
   C. Lead exposure.
   D. Obesity.
   E. Vegetarian diet.

2. You are asked to see a 12-year-old girl presenting with her third episode of acute pancreatitis in the past 8 months. Previous testing for her first episode of acute pancreatitis included normal liver function test results, lipid profile, immunoglobulin subclasses, and abdominal ultrasonography. She presents with acute abdominal pain, intermittent vomiting, and biochemical features similar to her previous presentations. On physical examination she appears uncomfortable and is frustrated that this is happening again. Her BMI is at the 50th percentile and she appears well nourished. She experienced no interval weight loss since her last episodes of pancreatitis. Abdominal ultrasonography and magnetic resonance cholangiopancreatography (MRCP) are normal. Which one of the following is the most appropriate test to obtain to help identify the cause predisposing this patient to recurrent pancreatitis?

   A. Endoscopic retrograde cholangiopancreatography (ERCP).
   B. Fecal elastase.
   C. Genetic testing.
   D. Ultrasonography-guided pancreatic needle biopsy.
   E. Urine drug screen.

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3. An 8-year-old boy is admitted with his second episode of acute pancreatitis. Similar to the first episode, he experienced 3 days of increasing abdominal pain and intermittent nonbloody, nonbilious emesis. On physical examination he is uncomfortable but in no distress. He is not jaundiced and there are no excoriations to suggest pruritus. The epigastric area is tender to palpation, but the lower quadrants are soft. Laboratory values are as follows: hemoglobin, 14.8 g/dL (148 g/L); white blood cell count (WBC), 16,300 (16.3×10^9/L); sodium, 140 mEq/L (140 mmol/L); carbon dioxide, 21 mEq/L (21 mmol/L); blood urea nitrogen (BUN), 16 mg/dL (5.7 mmol/L); creatinine, 0.9 mg/dL (79.6 μmol/L); total bilirubin, 2.8 mg/dL (47.9 μmol/L); conjugated bilirubin, 0.2 mg/dL (3.4 μmol/L); aspartate aminotransferase (AST), 53 U/L (0.89 μkat/L); alanine aminotransferase (ALT), 82 U/L (1.37 μkat/L); γ-glutamyltransferase (GGT), 115 U/L (1.92 μkat/L); amylase, 940 U/L (15.7 μkat/L); and lipase, 1,020 U/L (17.03 μkat/L). Ultrasonography findings are normal. Which one of the following is the next best imaging test recommended to be performed to evaluate the pancreaticobiliary system in this patient?

   A. Contrast-enhanced computed tomography.
   B. Exploratory laparoscopy.
   C. Endoscopic ultrasonography.
   D. Hepatobiliary scintigraphy.
   E. MRCP.

4. You are seeing a 15-year-old boy in your office for emergency department follow-up. He presents with a 5-day history of increasing abdominal discomfort and nausea without vomiting. There has been no change in his stool pattern, but he is not urinating as frequently as normal. He was seen in the emergency department 2 days ago, where laboratory studies included a normal complete blood cell count and urinalysis findings. A comprehensive metabolic panel included normal electrolyte, BUN, and creatinine levels, but the AST and ALT levels were 62 U/L (1.04 μkat/L) and 86 U/L (1.44 μkat/L), respectively. A trial of over-the-counter antacid therapy did not relieve the discomfort. On physical examination he is mildly tachycardic and appears uncomfortable and tired. Mucous membranes are tacky. Capillary refill is less than 2 seconds. There is no jaundice or scleral icterus. The epigastric area is tender, but there is no organomegaly and the lower quadrants are soft. You decide to admit him to the hospital for further evaluation and management. Laboratory studies showed the following values: hemoglobin, 17 g/dL (170 g/L); WBC, 12,400 (12.4×10^9/L); sodium, 145 mEq/L (145 mmol/L); carbon dioxide, 19 mEq/L (19 mmol/L); BUN, 25 mg/dL (8.9 mmol/L); creatinine, 1.2 mg/dL (106.1 μmol/L); triglycerides, 120 mg/dL (1.36 mmol/L); cholesterol, 60 mg/dL (1.55 mmol/L); AST, 80 U/L (1.34 μkat/L); ALT, 95 U/L (1.59 μkat/L); GGT, 66 U/L (1.10 μkat/L); amylase, 1,430 U/L (23.88 μkat/L); and lipase, 1,080 U/L (18.04 μkat/L). On urinalysis the specific gravity was 1.021; pH 6.5; and negative for white or red blood cells, leukocyte esterase. Abdominal ultrasonography findings are normal. After he received 10 mL/kg of normal saline, lactated Ringer solution at twice his maintenance fluid rate was given overnight. The next morning he reports that he is feeling better but continues to experience significant epigastric abdominal pain despite analgesics. Liver tests, amylase, lipase, BUN, and creatinine levels are decreasing. Which one of the following is the best recommendation to address his nutritional needs for the day?

   A. Clear liquids.
   B. Mechanically soft diet.
   C. Nothing by mouth.
   D. Regular diet.
   E. Total parenteral nutrition.

5. A 14-year-old girl is admitted to the hospital with her fourth episode of acute pancreatitis in 2 years. Results of diagnostic studies, including magnetic resonance imaging, ERCP, a lipid panel, autoimmune markers, sweat chloride test, genetic testing, and immunoglobulin subclasses, have been negative or normal. You are concerned that she now may have chronic pancreatitis. Which one of the following study results is most likely to support the diagnosis of chronic pancreatitis?

   A. Elevated amylase and lipase levels.
   B. Elevated erythrocyte sedimentation rate.
   C. Elevated fecal alpha-1 antitrypsin level.
   D. Low fecal pancreatic elastase-1 level.
   E. Low serum ionized calcium level.

Pancreatitis

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